



ANDA 215503

ANDA APPROVAL

Hikma Pharmaceuticals USA, Inc.
703 Palomar Airport Road
Suite 280
Carlsbad, CA 92011
Attention: Jonathan Endo
Regulatory Affairs Manager

Dear Jonathan Endo:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the tentative approval letter issued by this office on June 21, 2024, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly the ANDA is **approved**, effective on the date of this letter. We have determined your Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Victoza Injection, 18 mg/3 mL (6 mg/mL), of Novo Nordisk, Inc. (Novo), NDA - 022341.

The RLD upon which you have based your ANDA, Novo's Victoza Injection, 18 mg/3 mL (6 mg/mL), is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
8,114,833 (the '833 patent)	February 13, 2026
9,265,893 (the '893 patent)	March 23, 2033
9,968,659 (the '659 patent)	July 9, 2037

Your ANDA contains paragraph IV certifications to the '833 and '893 patents, under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens, under this ANDA. You have notified the Agency that Hikma Pharmaceuticals USA, Inc, (Hikma) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Hikma for infringement of the '833 and '893 patents in the United States District Court for the District of Delaware [Novo Nordisk Inc. and Novo Nordisk A/S v. Hikma Pharmaceuticals USA Inc., Civil Action No. 21-01783]. You have also notified the Agency that this case was dismissed.

With respect to the '659 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the FD&C Act that this is a method-of-use patent that does not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as <https://www.uspnf.com/>.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas>.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Paul
Levine

Digitally signed by Paul Levine

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **LIRAGLUTIDE INJECTION** safely and effectively. See full prescribing information for **LIRAGLUTIDE INJECTION**.

LIRAGLUTIDE injection, for subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide injection causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **Liraglutide injection is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).**

RECENT MAJOR CHANGES

Warning and Precautions, Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.8).....11/2024

INDICATIONS AND USAGE

Liraglutide injection is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus (1).

Limitations of Use:

- Not for treatment of type 1 diabetes mellitus.
- Should not be coadministered with other liraglutide-containing products.

DOSAGE AND ADMINISTRATION

- **Adult Patients:** Initiate at 0.6 mg injected subcutaneously once daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose (2.1).
- **Pediatric Patients:** Initiate at 0.6 mg injected subcutaneously once daily for at least one week. If additional glycemic control is required increase the dose to 1.2 mg daily and if additional glycemic control is still required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose (2.1).
- Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles (2.3).
- Inject liraglutide injection subcutaneously once-daily at any time of day, independently of meals, in the abdomen, thigh or upper arm (2.3).
- When using liraglutide injection with insulin, administer as separate injections. Never mix. (2.3).

DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/mL solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (3).

CONTRAINDICATIONS

- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Patients with a serious hypersensitivity reaction to liraglutide or any of the excipients in liraglutide injection (4).

WARNINGS AND PRECAUTIONS

- **Pancreatitis:** Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- **Never share a liraglutide injection pen** between patients, even if the needle is changed (5.3).
- **Hypoglycemia:** Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with liraglutide injection regardless of insulin and/or metformin use. Reduction in the dose of insulin secretagogues or insulin may be necessary (5.4).
- **Acute Kidney Injury:** Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of liraglutide injection in patients with renal impairment (5.5).
- **Hypersensitivity Reactions:** Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue liraglutide injection and promptly seek medical advice (5.6).
- **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7).
- **Pulmonary Aspiration During General Anesthesia or Deep Sedation:** Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures (5.8).

ADVERSE REACTIONS

- Most common adverse reactions (incidence $\geq 5\%$) in clinical trials are nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1).
- Immunogenicity-related events, including urticaria, were more common among liraglutide injection-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (12.6).

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Effects of delayed gastric emptying on oral medications:** Liraglutide injection delays gastric emptying and may impact absorption of concomitantly administered oral medications (7).

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Liraglutide injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

Revised: 11/2024

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF THYROID C-CELL TUMORS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Recommendations Regarding Missed Dose
- 2.3 Important Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risk of Thyroid C-cell Tumors
- 5.2 Pancreatitis
- 5.3 Never Share a Liraglutide Injection Pen Between Patients
- 5.4 Hypoglycemia
- 5.5 Acute Kidney Injury
- 5.6 Hypersensitivity Reactions
- 5.7 Acute Gallbladder Disease
- 5.8 Pulmonary Aspiration During General Anesthesia or Deep Sedation

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Delayed Gastric Emptying on Oral Medications
- 7.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Gastroparesis

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus
- 14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Recommended Storage

**17 PATIENT COUNSELING INFORMATION
MEDICATION GUIDE**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide injection causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [see *Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].
- Liraglutide injection is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of liraglutide injection and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with liraglutide injection [see *Contraindications (4) and Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Liraglutide injection is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus

Limitations of Use:

Liraglutide injection should not be used in patients with type 1 diabetes mellitus.

Liraglutide injection contains liraglutide and should not be coadministered with other liraglutide-containing products.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Adult Patients

- The recommended starting dosage of liraglutide injection is 0.6 mg injected subcutaneously once daily for one week. The 0.6 mg once daily dosage is intended to reduce gastrointestinal symptoms [see *Adverse Reactions (6.1)*] during initial titration and is not effective for glycemic control in adults.
- After one week at the 0.6 mg once daily dosage, increase the dosage to 1.2 mg injected subcutaneously once daily.
- If additional glycemic control is required, increase the dosage to the maximum recommended dosage of 1.8 mg injected subcutaneously once daily after at least one week of treatment with the 1.2 mg once daily dosage.

Pediatric Patients Aged 10 Years and Older

- The recommended starting dosage of liraglutide injection is 0.6 mg injected subcutaneously once daily.
- If additional glycemic control is required, increase the dosage in 0.6 mg increments after at least one week on the current dosage.
- The maximum recommended dosage is 1.8 mg injected subcutaneously once daily.

2.2 Recommendations Regarding Missed Dose

- Instruct patients who miss a dose of liraglutide injection to resume the once -daily dosage regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.

- If more than 3 days have elapsed since the last liraglutide injection dose, reinstitute liraglutide injection at 0.6 mg once daily to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Upon reinitiation, liraglutide injection should be titrated at the discretion of the healthcare provider.

2.3 Important Administration Instructions

- Inspect visually prior to each injection. Only use if solution is clear, colorless, and contains no particles.
- Inject liraglutide injection subcutaneously once daily at any time of day, independently of meals.
- Inject liraglutide injection subcutaneously in the abdomen, thigh or upper arm. No dosage adjustment is needed if changing the injection site and/or timing.
- Rotate injection sites within the same region in order to reduce the risk of cutaneous amyloidosis [see *Adverse Reactions* (6.2)].
- When using liraglutide injection with insulin, administer as separate injections. Never mix. It is acceptable to inject liraglutide injection and insulin in the same body region but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg.

4 CONTRAINDICATIONS

Liraglutide injection is contraindicated in patients with a:

- personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see *Warnings and Precautions* (5.1)].
- serious hypersensitivity reaction to liraglutide or to any of the excipients in liraglutide injection. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide injection [see *Warnings and Precautions* (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice [see *Nonclinical Toxicology* (13.1)]. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether liraglutide injection will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide injection have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide injection use in humans.

Liraglutide injection is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of liraglutide injection and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with liraglutide injection. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is

measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide injection. After initiation of liraglutide injection, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, liraglutide injection should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, liraglutide injection should not be restarted.

In glycemic control trials of liraglutide injection, there have been 13 cases of pancreatitis among liraglutide injection-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1,000 patient-years). Nine of the 13 cases with liraglutide injection were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a liraglutide injection-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

Liraglutide injection has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on liraglutide injection.

5.3 Never Share a Liraglutide Injection Pen Between Patients

Liraglutide injection pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.4 Hypoglycemia

Adult patients receiving liraglutide injection in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with liraglutide injection regardless of insulin and/or metformin use. [*see Adverse Reactions (6.1), Drug Interactions (7.2)*].

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.5 Acute Kidney Injury

Liraglutide injection has not been found to be directly nephrotoxic in animal studies or clinical trials.

There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in liraglutide injection-treated patients [*see Adverse Reactions (6.2)*]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [*see Adverse Reactions (6.1)*]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide injection. Use caution when initiating or escalating doses of liraglutide injection in patients with renal impairment [*see Use in Specific Populations (8.6)*].

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide injection [see *Adverse Reactions* (6.2)]. If a hypersensitivity reaction occurs, discontinue liraglutide injection; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-receptor agonist because it is unknown whether such patients will be predisposed to these reactions with liraglutide injection. Liraglutide injection is contraindicated in patients who have had a serious hypersensitivity reaction to liraglutide or any of the excipients in liraglutide injection [see *Contraindications* (4)].

5.7 Acute Gallbladder Disease

Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated [see *Adverse Reactions* (6.1)].

5.8 Pulmonary Aspiration During General Anesthesia or Deep Sedation

Liraglutide injection delays gastric emptying [see *Clinical Pharmacology* (12.2)]. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking liraglutide injection, including whether modifying preoperative fasting recommendations or temporarily discontinuing liraglutide injection could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking liraglutide injection.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors [see *Warnings and Precautions* (5.1)]
- Pancreatitis [see *Warnings and Precautions* (5.2)]
- Hypoglycemia [see *Warnings and Precautions* (5.4)]
- Acute Kidney Injury [see *Warnings and Precautions* (5.5)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.6)]
- Acute Gallbladder Disease [see *Warnings and Precautions* (5.7)]
- Pulmonary Aspiration During General Anesthesia or Deep Sedation [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

The safety of liraglutide injection in patients with type 2 diabetes mellitus was evaluated in 5 glycemic control, placebo-controlled trials in adults and one trial of 52 weeks duration in pediatric patients 10 years of age and older [see *Clinical Studies* (14.1)]. The data in Table 1 reflect exposure of 1,673 adult patients to liraglutide injection and a mean duration of

exposure to liraglutide injection of 37.3 weeks. The mean age of adult patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9 years and a mean HbA_{1c} of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88% and moderately impaired in 12% of the pooled population.

Table 1 shows common adverse reactions in adults, excluding hypoglycemia, associated with the use of liraglutide injection for the treatment of type 2 diabetes mellitus. These adverse reactions occurred more commonly on liraglutide injection than on placebo and occurred in at least 5% of patients treated with liraglutide injection. Overall, the type, and severity of adverse reactions in pediatric patients 10 years of age and older and above were comparable to that observed in the adult population.

Table 1 Adverse reactions reported in $\geq 5\%$ of Adult Patients Treated with Liraglutide Injection for Type 2 Diabetes Mellitus

	Placebo N=661	Liraglutide 1.2 mg N= 645	Liraglutide 1.8 mg N= 1024
Adverse Reaction	(%)	(%)	(%)
Nausea	5	18	20
Diarrhea	4	10	12
Headache	7	11	10
Nasopharyngitis	8	9	10
Vomiting	2	6	9
Decreased appetite	1	10	9
Dyspepsia	1	4	7
Upper Respiratory Tract Infection	6	7	6
Constipation	1	5	5
Back Pain	3	4	5

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights.

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions

Gastrointestinal Adverse Reactions

In the pool of 5 glycemic control, placebo-controlled adult clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of liraglutide injection-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2 to 3 months of the trials.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of liraglutide injection-treated adult patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of liraglutide injection-treated patients discontinued due to injection site reactions.

Hypoglycemia

In 5 adult glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 liraglutide injection-treated patients (7.5 events per 1,000 patient-years). Of these 8 liraglutide injection-treated patients, 7 patients were concomitantly using a sulfonylurea.

Table 2 Adult Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials

	Placebo Comparator	Liraglutide Injection Treatment
Add-on to Metformin	Placebo + Metformin (N = 121)	Liraglutide Injection + Metformin (N = 724)
Patient not able to self-treat	0	0.1 (0.001)
Patient able to self-treat	2.5 (0.06)	3.6 (0.05)
Add-on to Glimepiride	Placebo + Glimepiride (N = 114)	Liraglutide Injection + Glimepiride (N = 695)
Patient not able to self-treat	0	0.1 (0.003)
Patient able to self-treat	2.6 (0.17)	7.5 (0.38)
Not classified	0	0.9 (0.05)
Add-on to Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone (N = 175)	Liraglutide Injection + Metformin + Rosiglitazone (N = 355)
Patient not able to self-treat	0	0
Patient able to self-treat	4.6 (0.15)	7.9 (0.49)
Not classified	1.1 (0.03)	0.6 (0.01)
Add-on to Metformin + Glimepiride	Placebo + Metformin + Glimepiride (N = 114)	Liraglutide Injection + Metformin + Glimepiride (N = 230)
Patient not able to self-treat	0	2.2 (0.06)
Patient able to self-treat	16.7 (0.95)	27.4 (1.16)
Not classified	0	0

“Patient not able to self-treat” is defined as an event requiring the assistance of another person for treatment.

In a 26-week placebo-controlled clinical trial in pediatric patients 10 years of age and older with a 26-week open-label extension, 21.2% of liraglutide injection-treated patients (mean age 14.6 years) with type 2 diabetes mellitus, had hypoglycemia with a blood glucose <54 mg/dL with or without symptoms (335 events per 1,000 patient years). No severe hypoglycemic episodes occurred in the liraglutide injection treatment group (severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions).

Papillary thyroid carcinoma

In adult glycemic control trials of liraglutide injection, there were 7 reported cases of papillary thyroid carcinoma in patients treated with liraglutide injection and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1,000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Cholelithiasis and cholecystitis

In adult glycemic control trials of liraglutide injection, the incidence of cholelithiasis was 0.3% in both liraglutide injection-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both liraglutide injection-treated and placebo-treated patients.

Laboratory Tests

Bilirubin

In the five adult glycemic control trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of liraglutide injection-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown.

Calcitonin

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the adult glycemic control trials, adjusted mean serum calcitonin concentrations were higher in liraglutide injection-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among adult patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of liraglutide injection-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown.

Lipase and Amylase

In one adult glycemic control trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for liraglutide injection-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%.

The clinical significance of elevations in lipase or amylase with liraglutide injection is unknown in the absence of other signs and symptoms of pancreatitis [see *Warnings and Precautions* (5.2)].

Vital signs

Liraglutide injection did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed in adult patients treated with liraglutide injection compared to placebo.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of liraglutide injection. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Gastrointestinal*: Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death, ileus
- *General Disorders and Administration Site Conditions*: Allergic reactions: rash and pruritus
- *Hepatobiliary*: Elevations of liver enzymes, hyperbilirubinemia, cholestasis, cholecystitis, cholelithiasis requiring cholecystectomy, hepatitis
- *Immune system*: Angioedema and anaphylactic reactions
- *Metabolism and nutrition*: Dehydration resulting from nausea, vomiting and diarrhea
- *Neoplasms*: Medullary thyroid carcinoma
- *Nervous system*: Dysgeusia, dizziness
- *Pulmonary*: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.
- *Renal and urinary*: Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis
- *Skin and subcutaneous tissue*: Cutaneous amyloidosis

7 DRUG INTERACTIONS

7.1 Effects of Delayed Gastric Emptying on Oral Medications

Liraglutide injection causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide injection did not affect the absorption of the tested orally administered medications to any clinically relevant degree [see *Clinical Pharmacology* (12.3)]. Nonetheless, caution should be exercised when oral medications are concomitantly administered with liraglutide injection.

7.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

Liraglutide injection stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving liraglutide injection in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. When initiating liraglutide injection, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia [see *Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to liraglutide injection during pregnancy. Liraglutide injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD [see *Animal Data*].

The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin A_{1C} >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A_{1C} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Animal Data

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum,

pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F₂ generation rats descended from liraglutide-treated rats compared to F₂ generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of liraglutide injection in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats [see Data].

Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for liraglutide injection and any potential adverse effects on the breastfed infant from liraglutide injection or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

The safety and effectiveness of liraglutide injection as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older. Use of liraglutide injection for this indication is supported by a 26-week placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with type 2 diabetes mellitus, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.1,14.2)*]. The risk of hypoglycemia was higher with liraglutide injection in pediatric patients regardless of insulin and/or metformin use [see *Adverse Reactions (6.1)*].

The safety and effectiveness of liraglutide injection have not been established in pediatric patients less than 10 years of age.

8.5 Geriatric Use

In the liraglutide injection treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over [see *Clinical Studies (14.1)*]. No overall differences in safety or effectiveness for liraglutide injection have been observed between patients 65 years of age and older and younger patients.

8.6 Renal Impairment

No dose adjustment of liraglutide injection is recommended for patients with renal impairment [see *Clinical Pharmacology (12.3)*]. The safety and efficacy of liraglutide injection was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²) [see *Clinical Studies (14.1)*].

There is limited experience with liraglutide injection in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [see *Warnings and Precautions (5.5)* and *Adverse Reactions (6.2)*]. Use caution in patients who experience dehydration.

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, liraglutide injection should be used with caution in this patient population. No dose adjustment of liraglutide injection is recommended for patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

8.8 Gastroparesis

Liraglutide injection slows gastric emptying. Liraglutide injection has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE

Overdoses have been reported in clinical trials and post-marketing use of liraglutide injection. Observed effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION

Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

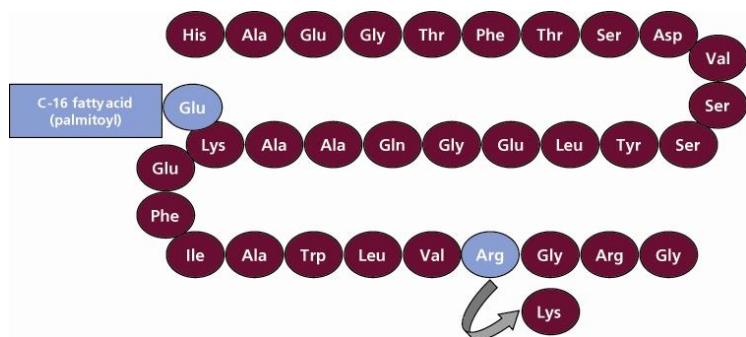


Figure 1 Structural Formula of liraglutide

Liraglutide Injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics

Liraglutide injection's pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as liraglutide injection lowered fasting, premeal and postprandial glucose throughout the day [see *Clinical Pharmacology* (12.3)].

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg liraglutide injection or placebo. Compared to placebo, the postprandial plasma glucose AUC_{0-300min} was 35% lower after liraglutide injection 1.2 mg and 38% lower after liraglutide injection 1.8 mg.

Glucose-dependent insulin secretion

The effect of a single dose of 7.5 mcg/kg (~ 0.7 mg) liraglutide injection on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes mellitus during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

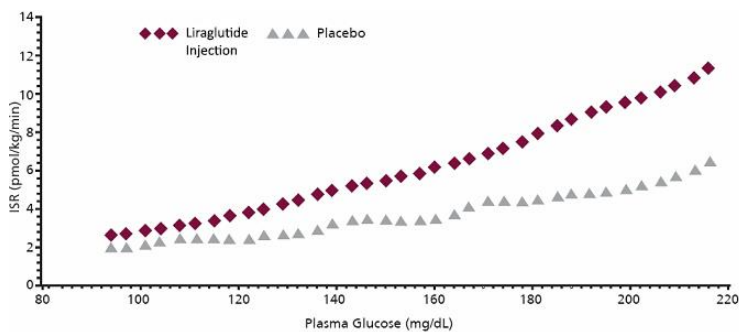


Figure 2 Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose Liraglutide Injection 7.5 mcg/kg (~ 0.7 mg) or Placebo in Patients with Type 2 Diabetes Mellitus (N=10) During Graded Glucose Infusion

Glucagon secretion

Liraglutide injection lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of liraglutide injection 7.5 mcg/kg (~ 0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying

Liraglutide injection causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)

The effect of liraglutide injection on cardiac repolarization was tested in a QTc study. Liraglutide injection at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8 to 12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg liraglutide injection, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. $AUC_{0-\infty}$ was equivalent between upper arm and abdomen, and between upper arm and thigh. $AUC_{0-\infty}$ from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution

The mean apparent volume of distribution after subcutaneous administration of liraglutide injection 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of liraglutide injection is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Elimination

The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours.

Metabolism

During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Excretion

Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6 to 8 days.

Specific Populations

Geriatric Patients

Age had no effect on the pharmacokinetics of liraglutide injection based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population pharmacokinetic analyses of patients 18 to 80 years of age [see *Use in Specific Populations* (8.5)].

Pediatric Patients

A population pharmacokinetic analysis was conducted for liraglutide injection using data from 72 pediatric patients (10 to 17 years of age) with type 2 diabetes mellitus. The pharmacokinetic profile of liraglutide injection in the pediatric patients was consistent with that in adults.

Male and Female Patients

Based on the results of population pharmacokinetic analyses, females have 25% lower weight-adjusted clearance of liraglutide injection compared to males.

Race or Ethnic Groups

Race and ethnicity had no effect on the pharmacokinetics of liraglutide injection based on the results of population pharmacokinetic analyses that included White, Black or African American, Asian and Hispanic or Latino/Non-Hispanic or Latino subjects.

Body Weight

Body weight significantly affects the pharmacokinetics of liraglutide injection based on results of population pharmacokinetic analyses. The exposure of liraglutide decreases with an increase in baseline body weight. However, the 1.2 mg and 1.8 mg daily doses of liraglutide injection provided adequate systemic exposures over the body weight range of 40 to 160 kg evaluated in the clinical trials. Liraglutide was not studied in patients with body weight >160 kg.

Patients with Renal Impairment

The single-dose pharmacokinetics of liraglutide injection were evaluated in patients with varying degrees of renal impairment. Patients with mild (estimated creatinine clearance 50 to 80 mL/min) to severe (estimated creatinine clearance <30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively [see *Use in Specific Populations (8.6)*].

Patients with Hepatic Impairment

The single-dose pharmacokinetics of liraglutide injection were evaluated in patients with varying degrees of hepatic impairment. Patients with mild (Child Pugh score 5 to 6) to severe (Child Pugh score > 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in patients with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively [see *Use in Specific Populations (8.7)*].

Drug Interaction Studies

In vitro assessment of drug-drug interactions

Liraglutide injection has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interactions

The drug-drug interaction studies were performed at steady state with liraglutide injection 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to reach the maximum dose of 1.8 mg/day. Administration of the interacting drugs was timed so that $C_{\max}$ of liraglutide injection (8 to 12 h) would coincide with the absorption peak of the co-administered drugs.

Digoxin

A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide injection at steady state. The concomitant administration with liraglutide injection resulted in a reduction of digoxin AUC by 16%; $C_{\max}$ decreased by 31%. Digoxin median time to maximal concentration ($T_{\max}$) was delayed from 1 h to 1.5 h.

Lisinopril

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide injection at steady state. The co-administration with liraglutide injection resulted in a reduction of lisinopril AUC by 15%; $C_{\max}$ decreased by 27%. Lisinopril median $T_{\max}$ was delayed from 6 h to 8 h with liraglutide injection.

Atorvastatin

Liraglutide injection did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide injection at steady state. Atorvastatin $C_{\max}$ was decreased by 38% and median $T_{\max}$ was delayed from 1 h to 3 h with liraglutide injection.

Acetaminophen

Liraglutide injection did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1,000 mg, administered 8 hours after the dose of liraglutide injection at steady state. Acetaminophen $C_{\max}$ was decreased by 31% and median $T_{\max}$ was delayed up to 15 minutes.

Griseofulvin

Liraglutide injection did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with liraglutide injection at steady state. Griseofulvin $C_{\max}$ increased by 37% while median $T_{\max}$ did not change.

Oral Contraceptives

A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide injection at steady state. Liraglutide injection lowered ethinylestradiol and levonorgestrel $C_{\max}$ by 12% and 13%, respectively. There was no effect of liraglutide injection on the overall exposure (AUC) of ethinylestradiol. Liraglutide injection increased the levonorgestrel $AUC_{0-\infty}$ by 18%. Liraglutide injection delayed $T_{\max}$ for both ethinylestradiol and levonorgestrel by 1.5 h.

Insulin Detemir

No pharmacokinetic interaction was observed between liraglutide injection and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and liraglutide injection 1.8 mg (steady state) were administered in patients with type 2 diabetes mellitus.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those with liraglutide injection or other liraglutide products.

A subset of liraglutide injection-treated patients (1,104 of 2,501, 44%) in five adult double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment [see *Clinical Studies (14.1)*] and 102/1,104 (9%) of liraglutide injection-treated patients developed anti-liraglutide antibodies. Of these 102 liraglutide injection-treated patients, 56 (5%) patients developed antibodies that cross-reacted with native GLP-1. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 12 (1%) of the liraglutide injection-treated patients. There was no identified clinically significant effect of anti-liraglutide antibodies on effectiveness of liraglutide injection.

In five double-blind adult glycemic control trials of liraglutide injection, events from a composite of adverse events potentially related to immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of liraglutide injection-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for liraglutide injection-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

In a clinical trial with pediatric patients aged 10 years and older [see *Clinical Studies (14.2)*], anti-liraglutide antibodies were detected in 1 (2%) liraglutide injection-treated patient at week 26 and 5 (9%) liraglutide injection-treated patients at week 53. None of the 5 patients had antibodies cross reactive to native GLP-1 or had neutralizing antibodies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies [see *Boxed Warning and Warnings and Precautions (5.1)*].

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11- times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

In glycemic control trials in adults, liraglutide injection has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin.

In each of the placebo controlled trials, treatment with liraglutide injection produced clinically and statistically significant improvements in hemoglobin A_{1c} and fasting plasma glucose (FPG) compared to placebo.

All liraglutide injection-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. Liraglutide injection 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance [see *Dosage and Administration (2)*].

Monotherapy

In this 52-week trial, 746 adult patients with type 2 diabetes mellitus were randomized to liraglutide injection 1.2 mg, liraglutide injection 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with liraglutide injection 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA_{1c} compared to glimepiride (Table 3). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the liraglutide injection 1.8 mg treatment group, 6.0% in the liraglutide injection 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American and 35.0% of Hispanic or Latino ethnicity. The mean BMI was 33.1 kg/m².

Table 3 Results of a 52-week Monotherapy Trial in Adults with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg	Liraglutide Injection 1.2 mg	Glimepiride 8 mg
Intent-to-Treat Population (N)	246	251	248
HbA_{1c} (%) (Mean)			
Baseline	8.2	8.2	8.2
Change from baseline (adjusted mean) ^b	-1.1	-0.8	-0.5
Difference from glimepiride arm (adjusted mean) ^b	-0.6**	-0.3*	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.1)	
Percentage of patients achieving HbA _{1c} <7%	51	43	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	172	168	172
Change from baseline (adjusted mean) ^b	-26	-15	-5
Difference from glimepiride arm (adjusted mean) ^b	-20**	-10*	
95% Confidence Interval	(-29, -12)	(-19, -1)	
Body Weight (kg) (Mean)			
Baseline	92.6	92.1	93.3
Change from baseline (adjusted mean) ^b	-2.5	-2.1	+1.1
Difference from glimepiride arm (adjusted mean) ^b	-3.6**	-3.2**	
95% Confidence Interval	(-4.3, -2.9)	(-3.9, -2.5)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

*p-value <0.05

**p-value <0.0001

Body Weight (kg) (Mean)				
Baseline	88.0	88.5	91.0	89.0
Change from baseline (adjusted mean) ^b	-2.8	-2.6	-1.5	+1.0
Difference from placebo + metformin arm (adjusted mean) ^b	-1.3*	-1.1*		
95% Confidence Interval	(-2.2, -0.4)	(-2.0, -0.2)		
Difference from glimepiride + metformin arm (adjusted mean) ^b	-3.8**	-3.5**		
95% Confidence Interval	(-4.5, -3.0)	(-4.3, -2.8)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†]For glimepiride, one-half of the maximal approved United States dose.

*p-value <0.05

**p-value <0.0001

Liraglutide Injection Compared to Sitagliptin, Both as Add-on to Metformin

In this 26-week, open-label trial, 665 adult patients with type 2 diabetes mellitus on a background of metformin $\geq 1,500$ mg per day were randomized to liraglutide injection 1.2 mg once daily, liraglutide injection 1.8 mg once daily or sitagliptin 100 mg once daily, all dosed according to approved labeling. Patients were to continue their current treatment on metformin at a stable, pre-trial dose level and dosing frequency.

The mean age of participants was 56 years, and the mean duration of diabetes was 6 years. Participants were 52.9% male, 86.6% White, 7.2% Black or African American and 16.2% of Hispanic or Latino ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA_{1c} from baseline to Week 26. Treatment with liraglutide injection 1.2 mg and liraglutide injection 1.8 mg resulted in statistically significant reductions in HbA_{1c} relative to sitagliptin 100 mg (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the liraglutide injection 1.2 mg group, 0.5% in the liraglutide injection 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group. From a mean baseline body weight of 94 kg, there was a mean reduction of 2.7 kg for liraglutide injection 1.2 mg, 3.3 kg for liraglutide injection 1.8 mg, and 0.8 kg for sitagliptin 100 mg.

Table 5 Results of a 26-week Open-label Trial of Liraglutide Injection Compared to Sitagliptin (both in combination with metformin) in Adults with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg + Metformin	Liraglutide Injection 1.2 mg + Metformin	Sitagliptin 100 mg+ Metformin
Intent-to-Treat Population (N)	218	221	219
HbA_{1c} (%) (Mean)			
Baseline	8.4	8.4	8.5
Change from baseline (adjusted mean)	-1.5	-1.2	-0.9
Difference from sitagliptin arm (adjusted mean) ^b	-0.6**	-0.3**	
95% Confidence Interval	(-0.8, -0.4)	(-0.5, -0.2)	
Percentage of patients achieving HbA _{1c} <7%	56	44	22
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	179	182	180
Change from baseline (adjusted mean)	-39	-34	-15
Difference from sitagliptin arm (adjusted mean) ^b	-24**	-19**	
95% Confidence Interval	(-31, -16)	(-26, -12)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

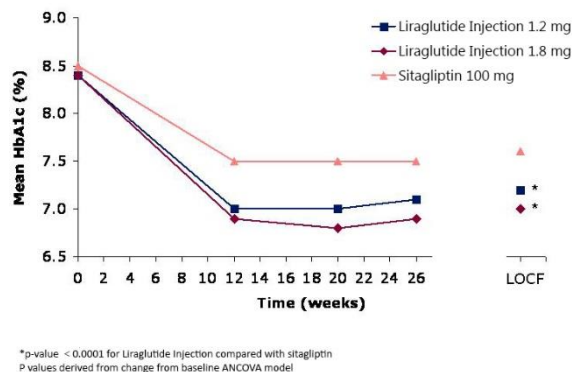


Figure 4 Mean HbA_{1c} for Adult Patients with Type 2 Diabetes Mellitus who Completed the 26-week Trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 26

Combination Therapy with Metformin and Insulin

This 26-week open-label trial enrolled 988 adult patients with type 2 diabetes mellitus with inadequate glycemic control (HbA_{1c} 7-10%) on metformin ($\geq 1,500$ mg/day) alone or inadequate glycemic control (HbA_{1c} 7-8.5%) on metformin ($\geq 1,500$ mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with liraglutide injection titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA_{1c} <7% with liraglutide injection 1.8 mg and metformin and continued treatment in a non-randomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions [see *Adverse Reactions* (6.1)]. The remaining 323 patients with HbA_{1c} $\geq 7\%$ (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily insulin detemir administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with liraglutide injection 1.8 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26 week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with liraglutide injection 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with insulin detemir.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic or Latino ethnicity. The mean BMI was 34.0 kg/m².

Treatment with insulin detemir as add-on to liraglutide injection 1.8 mg + metformin resulted in statistically significant reductions in HbA_{1c} and FPG compared to continued, unchanged treatment with liraglutide injection 1.8 mg + metformin alone (Table 6). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with liraglutide injection 1.8 mg + metformin alone.

Table 6 Results of a 26-week Open-label Trial of Insulin detemir as add on to Liraglutide Injection + Metformin Compared to Continued Treatment with Liraglutide Injection + Metformin alone in Adult Patients with Type 2 Diabetes Mellitus not Achieving HbA_{1c} < 7% after 12 weeks of Metformin and Liraglutide Injection^a

	Insulin detemir + Liraglutide Injection + Metformin	Liraglutide Injection + Metformin
Intent-to-Treat Population (N)	162	157
HbA_{1c} (%) (Mean)		
Baseline (week 0)	7.6	7.6
Change from baseline (adjusted mean)	-0.5	0
Difference from Liraglutide Injection + metformin arm (LS mean) ^b	-0.5**	
95% Confidence Interval	(-0.7, -0.4)	
Percentage of patients achieving HbA _{1c} <7%	43	17
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline (week 0)	166	159
Change from baseline (adjusted mean)	-39	-7
Difference from Liraglutide Injection + metformin arm (LS mean) ^b	-31**	
95% Confidence Interval	(-39, -23)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

Add-on to Sulfonylurea

In this 26-week trial, 1,041 adult patients with type 2 diabetes mellitus were randomized to liraglutide injection 0.6 mg, liraglutide injection 1.2 mg, liraglutide injection 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 56 years, and the mean duration of diabetes was 8 years. Participants were 49.4% male, 64.4% White and 2.8% Black or African American. The mean BMI was 29.9 kg/m².

Treatment with liraglutide injection 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to glimepiride (Table 7). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the liraglutide injection 1.8 mg + glimepiride treatment group, 3.5% in the liraglutide injection 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

Table 7 Results of a 26-week Trial of Liraglutide Injection as add-on to Sulfonylurea in Adult Patients with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg + Glimepiride	Liraglutide Injection 1.2 mg + Glimepiride	Placebo + Glimepiride	Rosiglitazone 4 mg[†] + Glimepiride
Intent-to-Treat Population (N)	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline (adjusted mean) ^b	-1.1	-1.1	+0.2	-0.4
Difference from placebo + glimepiride arm (adjusted mean) ^b	-1.4**	-1.3**		
95% Confidence Interval	(-1.6, -1.1)	(-1.5, -1.1)		
Percentage of patients achieving HbA _{1c} <7%	42	35	7	22
Fasting Plasma Glucose (mg/dL) (Mean)				

Baseline	174	177	171	179
Change from baseline (adjusted mean) ^b	-29	-28	+18	-16
Difference from placebo + glimepiride arm (adjusted mean) ^b	-47**	-46**		
95% Confidence Interval	(-58, -35)	(-58, -35)		
Body Weight (kg) (Mean)				
Baseline	83.0	80.0	81.9	80.6
Change from baseline (adjusted mean) ^b	-0.2	+0.3	-0.1	+2.1
Difference from placebo + glimepiride arm (adjusted mean) ^b	-0.1	0.4		
95% Confidence Interval	(-0.9, 0.6)	(-0.4, 1.2)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†]For rosiglitazone, one-half of the maximal approved United States dose.

**p-value <0.0001

Add-on to Metformin and Sulfonylurea

In this 26-week trial, 581 adult patients with type 2 diabetes mellitus were randomized to liraglutide injection 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2,000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to liraglutide injection 1.8 mg underwent a 2 week period of titration with liraglutide injection. During the trial, the liraglutide injection and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of ≤ 100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

The mean age of participants was 58 years, and the mean duration of diabetes was 9 years. Participants were 56.5% male, 75.0% White and 3.6% Black or African American. The mean BMI was 30.5 kg/m².

Treatment with liraglutide injection as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA_{1c} compared to placebo add-on to glimepiride and metformin (Table 8). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the liraglutide injection 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

Table 8 Results of a 26-week Trial of Liraglutide Injection as Add-on to Metformin and Sulfonylurea in Adult Patients with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride	Insulin glargine[†] + Metformin + Glimepiride
Intent-to-Treat Population (N)	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline (adjusted mean) ^b	-1.3	-0.2	-1.1
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-1.1**		
95% Confidence Interval	(-1.3, -0.9)		
Percentage of patients achieving HbA _{1c} <7%	53	15	46
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	165	170	164
Change from baseline (adjusted mean) ^b	-28	+10	-32

Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-38**		
95% Confidence Interval	(-46, -30)		
Body Weight (kg) (Mean)			
Baseline	85.8	85.4	85.2
Change from baseline (adjusted mean) ^b	-1.8	-0.4	1.6
Difference from placebo + metformin + glimepiride arm (adjusted mean) ^b	-1.4*		
95% Confidence Interval	(-2.1, -0.7)		

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

[†]For insulin glargine, optimal titration regimen was not achieved for 80% of patients.

*p-value <0.05

**p-value <0.0001

Liraglutide Injection Compared to Exenatide, Both as Add-on to Metformin and/or Sulfonylurea Therapy

In this 26-week, open-label trial, 464 adult patients with type 2 diabetes mellitus on a background of metformin monotherapy, sulfonylurea monotherapy or a combination of metformin and sulfonylurea were randomized to once daily liraglutide injection 1.8 mg or exenatide 10 mcg twice daily. Maximally tolerated doses of background therapy were to remain unchanged for the duration of the trial. Patients randomized to exenatide started on a dose of 5 mcg twice-daily for 4 weeks and then were escalated to 10 mcg twice daily.

The mean age of participants was 57 years, and the mean duration of diabetes was 8 years. Participants were 51.9% male, 91.8% White, 5.4% Black or African American and 12.3% of Hispanic or Latino ethnicity. The mean BMI was 32.9 kg/m².

Treatment with liraglutide injection 1.8 mg resulted in statistically significant reductions in HbA_{1c} and FPG relative to exenatide (Table 9). The percentage of patients who discontinued for ineffective therapy was 0.4% in the liraglutide injection treatment group and 0% in the exenatide treatment group. Both treatment groups had a mean decrease from baseline in body weight of approximately 3 kg.

Table 9 Results of a 26-week Open-label trial of Liraglutide Injection versus Exenatide (both in combination with metformin and/or sulfonylurea) in Adult Patients with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg once daily + metformin and/or sulfonylurea	Exenatide 10 mcg twice daily + metformin and/or sulfonylurea
Intent-to-Treat Population (N)	233	231
HbA_{1c} (%) (Mean)		
Baseline	8.2	8.1
Change from baseline (adjusted mean) ^b	-1.1	-0.8
Difference from exenatide arm (adjusted mean) ^b	-0.3**	
95% Confidence Interval	(-0.5, -0.2)	
Percentage of patients achieving HbA _{1c} <7%	54	43
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline	176	171
Change from baseline (adjusted mean) ^b	-29	-11
Difference from exenatide arm (adjusted mean) ^b	-18**	
95% Confidence Interval	(-25, -12)	

^aIntent-to-treat population using last observation carried forward

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

Add-on to Metformin and Thiazolidinedione

In this 26-week trial, 533 adult patients with type 2 diabetes mellitus were randomized to liraglutide injection 1.2 mg, liraglutide injection 1.8 mg or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2,000 mg). Patients

underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2,000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2,000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 61.6% male, 84.2% White, 10.2% Black or African American and 16.4% of Hispanic or Latino ethnicity. The mean BMI was 33.9 kg/m².

Treatment with liraglutide injection as add-on to metformin and rosiglitazone produced a statistically significant reduction in mean HbA_{1c} compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the liraglutide injection 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the liraglutide injection 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

Table 10 Results of a 26-week Trial of Liraglutide Injection as Add-on to Metformin and Thiazolidinedione in Adult Patients with Type 2 Diabetes Mellitus^a

	Liraglutide Injection 1.8 mg + Metformin + Rosiglitazone	Liraglutide Injection 1.2 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
Intent-to-Treat Population (N)	178	177	175
HbA_{1c} (%) (Mean)			
Baseline	8.6	8.5	8.4
Change from baseline (adjusted mean) ^b	-1.5	-1.5	-0.5
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) ^b	-0.9**	-0.9**	
95% Confidence Interval	(-1.1, -0.8)	(-1.1, -0.8)	
Percentage of patients achieving HbA _{1c} <7%	54	57	28
Fasting Plasma Glucose (mg/dL) (Mean)			
Baseline	185	181	179
Change from baseline (adjusted mean) ^b	-44	-40	-8
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) ^b	-36**	-32**	
95% Confidence Interval	(-44, -27)	(-41, -23)	
Body Weight (kg) (Mean)			
Baseline	94.9	95.3	98.5
Change from baseline (adjusted mean) ^b	-2.0	-1.0	+0.6
Difference from placebo + metformin + rosiglitazone arm (adjusted mean) ^b	-2.6**	-1.6**	
95% Confidence Interval	(-3.4, -1.8)	(-2.4, -1.0)	

^aIntent-to-treat population using last observation on study

^bLeast squares mean adjusted for baseline value

**p-value <0.0001

Liraglutide Injection Compared to Placebo Both With or Without metformin and/or Sulfonylurea and/or Pioglitazone and/or Basal or Premix insulin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial in adult patients with type 2 diabetes mellitus, 279 patients with moderate renal impairment, as per MDRD formula (eGFR 30-59 mL/min/1.73 m²), were randomized to liraglutide injection or placebo once daily. Liraglutide injection was added to the patient's stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of liraglutide injection was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline HbA_{1c} ≤ 8% and fixed until liraglutide dose escalation was complete. Dose

reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic or Latino ethnicity. The mean BMI was 33.9 kg/m². Approximately half of patients had an eGFR between 30 and <45mL/min/1.73 m².

Treatment with liraglutide injection resulted in a statistically significant reduction in HbA_{1c} from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of liraglutide injection.

Table 11 Results of a 26-week Trial of Liraglutide Injection Compared to Placebo in Adult Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment^a

	Liraglutide Injection 1.8 mg + insulin and/or OAD	Placebo + insulin and/or OAD
Intent to Treat Population (N)	140	137
HbA_{1c} (%)		
Baseline (mean)	8.1	8.0
Change from baseline (estimated mean) ^{b, c}	-0.9	-0.4
Difference from placebo ^{b, c}	-0.6*	
95% Confidence Interval	(-0.8, -0.3)	
Proportion achieving HbA _{1c} < 7% ^d	39.3	19.7
FPG (mg/dL)		
Baseline (mean)	171	167
Change from baseline (estimated mean) ^e	-22	-10
Difference from placebo ^e	-12**	
95% Confidence Interval	(-23, -0.8)	

^a Intent-to-treat population

^b Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit. Multiple imputation method modeled “wash out” of the treatment effect for patients having missing data who discontinued treatment.

^c Early treatment discontinuation, before week 26, occurred in 25% and 22% of liraglutide injection and placebo patients, respectively.

^d Based on the known number of subjects achieving HbA_{1c} < 7%. When applying the multiple imputation method described in b) above, the estimated percents achieving HbA_{1c} < 7% are 47.6% and 24.9% for liraglutide injection and placebo, respectively.

^e Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit.

*p-value <0.0001

**p-value <0.05

14.2 Glycemic Control Trial in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

Liraglutide injection was evaluated in a 26-week, double-blind, randomized, parallel group, placebo controlled multicenter trial (NCT01541215), in 134 pediatric patients with type 2 diabetes mellitus aged 10 years and older. Patients were randomized to liraglutide injection once-daily or placebo once-daily in combination with metformin with or without basal insulin treatment. All patients were on a metformin dose of 1,000 to 2,000 mg prior to randomization. The basal insulin dose was decreased by 20% at randomization and liraglutide injection was titrated weekly by 0.6 mg for 2 to 3 weeks based on tolerability and an average fasting plasma glucose goal of ≤110 mg/dL.

The mean age was 14.6 years: 29.9% were ages 10 to 14 years, and 70.1% were greater than 14 years of age. 38.1% were male, 64.9% were White, 13.4% were Asian, 11.9% were Black or African American; 29.1% were of Hispanic or Latino ethnicity. The mean BMI was 33.9 kg/m² and the mean BMI SDS was 2.9. 18.7% of patients were using basal insulin at baseline. The mean duration of diabetes was 1.9 years and the mean HbA_{1c} was 7.8%.

At week 26, treatment with liraglutide injection was superior in reducing HbA_{1c} from baseline versus placebo. The estimated treatment difference in HbA_{1c} reduction from baseline between liraglutide injection and placebo was -1.06% with a 95% confidence interval of [-1.65%; -0.46%] (see Table 12).

Table 12 Results at week 26 in a trial comparing Liraglutide Injection in combination with metformin with or without basal insulin versus Placebo in combination with metformin with or without basal insulin in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

	Liraglutide Injection + metformin ± basal insulin	Placebo + metformin ± basal insulin
N	66	68
HbA_{1c} (%)		
Baseline	7.9	7.7
End of 26 weeks	7.1	8.2
Adjusted mean change from baseline after 26 weeks ^a	-0.64	0.42
Treatment difference [95% CI] Liraglutide Injection vs Placebo	-1.06 [-1.65; -0.46]*	
Percentage of patients achieving HbA _{1c} <7% ^b	63.7	36.5
FPG (mg/dL)		
Baseline	157	147
End of 26 weeks	132	166
Adjusted mean change from baseline after 26 weeks ^a	-19.4	14.4
Treatment difference [95% CI] Liraglutide Injection vs Placebo	-33.83 [-55.74; -11.92]	

^a The change from baseline to end of treatment visit in HbA_{1c} and FPG was analyzed using a pattern mixture model with multiple imputation. Missing observations (10.6% in the liraglutide injection, 14.5% in the placebo) were imputed from the placebo arm based on multiple (x10,000) imputations. The data for week 26 was then analyzed with an ANCOVA model containing treatment, sex and age group as fixed effects and baseline value as covariate.

^b Categories are derived from continuous measurements of HbA_{1c} using a pattern mixture model with multiple imputation for missing observations.

* p-value <0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes:

2 x Liraglutide Injection pen NDC 0143-9144-02

3 x Liraglutide Injection pen NDC 0143-9144-03

16.2 Recommended Storage

Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen.

After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect

Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Thyroid C-cell Tumors

Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Pancreatitis

Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Liraglutide injection promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Never Share a Liraglutide Injection Pen Between Patients

Advise patients that they must never share a liraglutide injection pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.3)]*.

Hypoglycemia

Inform patients that hypoglycemia has been reported when liraglutide injection is used with insulin secretagogues or insulin and may occur in pediatric patients regardless of concomitant antidiabetic treatment. Educate patients or caregivers on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.4)]*.

Acute Kidney Injury

Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of liraglutide injection. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking liraglutide injection and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up *[see Warnings and Precautions (5.7)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that liraglutide injection may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking liraglutide injection *[see Warnings and Precautions (5.8)]*.

Missed Dose

Inform patients not to take an extra dose of liraglutide injection to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If more than 3 days have elapsed since

the last dose, advise the patient to reinitiate liraglutide injection at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. Liraglutide injection should be titrated at the discretion of the healthcare provider [see *Dosage and Administration (2.2)*].

Manufactured by:

Hybio Pharmaceutical Co., Ltd. (Pingshan Factory)

2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China

Distributed by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

Revised November 2024

Medication Guide

Liraglutide (lir-a-gloo-tide) Injection

(liraglutide) injection, for subcutaneous use

Read this Medication Guide before you start using liraglutide injection and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about liraglutide injection?

Liraglutide injection may cause serious side effects, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, liraglutide injection and medicines that work like liraglutide injection caused thyroid tumors, including thyroid cancer. It is not known if liraglutide injection will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use liraglutide injection if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is liraglutide injection?

Liraglutide injection is an injectable prescription medicine used:

- along with diet and exercise to lower blood sugar (glucose) in adults and children who are 10 years of age and older with type 2 diabetes mellitus.

Liraglutide injection is not for use in people with type 1 diabetes. It should not be used with other medicines that contain liraglutide. It is not known if liraglutide injection is safe and effective to lower blood sugar (glucose) in children under 10 years of age.

Who should not use liraglutide injection?

Do not use liraglutide injection if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a serious allergic reaction to liraglutide or any of the ingredients in liraglutide injection. See the end of this Medication Guide for a complete list of ingredients in liraglutide injection. Symptoms of a serious allergic reaction include:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - very rapid heartbeat

What should I tell my healthcare provider before using liraglutide injection?

Before using liraglutide injection, tell your healthcare provider if you have any other medical conditions, including if you:

- have or have had problems with your pancreas, kidneys, or liver.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- are scheduled to have surgery or other procedures that use anesthesia or deep sleepiness (deep sedation).
- are pregnant or plan to become pregnant. It is not known if liraglutide injection will harm your unborn baby. Tell your healthcare provider if you become pregnant while using liraglutide injection.
- are breastfeeding or plan to breastfeed. It is not known if liraglutide injection passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using liraglutide injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Liraglutide injection may affect the way some medicines work and some medicines may affect the way liraglutide injection works.

Before using liraglutide injection, talk to your healthcare provider about low blood sugar and how to manage it.

Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use liraglutide injection?

- Read the **Instructions for Use** that comes with liraglutide injection.
- Use liraglutide injection exactly as your healthcare provider tells you to.
- **Your healthcare provider should show you how to use liraglutide injection before you use it for the first time.**
- **Use liraglutide injection 1 time each day, at any time of the day.**
- Liraglutide injection may be taken with or without food.
- Liraglutide injection is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject liraglutide injection into a muscle (intramuscularly) or vein (intravenously).
- Change (rotate) your injection site within the area you choose with each injection to reduce your risk of getting lumps under the skin (cutaneous amyloidosis). **Do not** use the same site for each injection.
- **Do not** mix insulin and liraglutide injection together in the same injection.
- You may give an injection of liraglutide injection and insulin in the same body area (such as your stomach area), but not right next to each other.
- If you miss a dose of liraglutide injection, take the missed dose at the next scheduled dose. **Do not** take 2 doses of liraglutide injection at the same time.
- If you take too much liraglutide injection, call your healthcare provider right away. Taking too much liraglutide injection may cause severe nausea, severe vomiting, and low blood sugar (hypoglycemia).
- **Do not share your liraglutide injection pen with other people, even if the needle has been changed.** You may give other people a serious infection or get a serious infection from them.
- The liraglutide injection pen you are using should be thrown away 30 days after you start using it.

Your dose of liraglutide injection and other diabetes medicines may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of liraglutide injection?

Liraglutide injection may cause serious side effects, including:

- See “**What is the most important information I should know about liraglutide injection?**”
- **inflammation of your pancreas (pancreatitis).** Stop using liraglutide injection and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use liraglutide injection with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. In children who are 10 years of age and older, the risk for low blood sugar may be higher with liraglutide injection regardless of use with another medicine that can also lower blood sugar.

Signs and symptoms of low blood sugar may include:

- dizziness or light-headedness
- sweating
- confusion or drowsiness
- headache
- blurred vision
- slurred speech
- shakiness
- fast heartbeat
- anxiety, irritability, or mood changes
- hunger
- weakness
- feeling jittery

- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.
- **serious allergic reactions.** Stop using liraglutide injection and get medical help right away, if you have any symptoms of a serious allergic reaction including:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - very rapid heartbeat
- **gallbladder problems.** Gallbladder problems have happened in some people who take liraglutide injection. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
 - pain in your upper stomach (abdomen)
 - fever
 - yellowing of skin or eyes (jaundice)
 - clay-colored stools
- **food or liquid getting into the lungs during surgery or other procedures that use anesthesia or deep sleepiness (deep sedation).** Liraglutide injection may increase the chance of food getting into your lungs during surgery or other procedures. Tell all your healthcare providers that you are taking liraglutide injection before you are scheduled to have surgery or other procedures.

The most common side effects of liraglutide injection may include nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation.

Talk to your healthcare provider about any side effects that bothers you or does not go away. These are not all the possible side effects of liraglutide injection.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of liraglutide injection.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use liraglutide injection for a condition for which it was not prescribed. Do not give liraglutide injection to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about liraglutide injection that is written for health professionals.

What are the ingredients in liraglutide injection?

Active ingredient: liraglutide

Inactive ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection, hydrochloric acid or sodium hydroxide may be added to adjust pH

Manufactured by: Hybio Pharmaceutical Co. Ltd

Distributed by: Hikma Pharmaceuticals USA Inc.

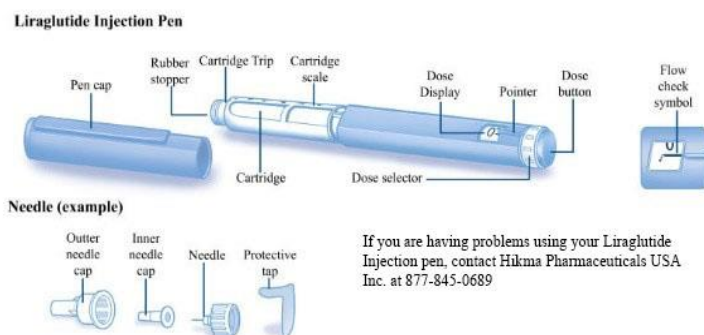
For more information, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 11/2024

INSTRUCTIONS FOR USE

Liraglutide Injection



First read the Medication Guide that comes with your liraglutide injection single-patient use pen and then read this Patient Instructions for Use for information about how to use your liraglutide injection pen the right way.

These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Do not share your liraglutide injection pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Your liraglutide injection pen is a disposable single-patient-use prefilled pen injector that contains 3 mL of liraglutide injection and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a liraglutide injection pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much liraglutide injection to take.

Liraglutide injection pen should be used with compatible disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your liraglutide injection pen.

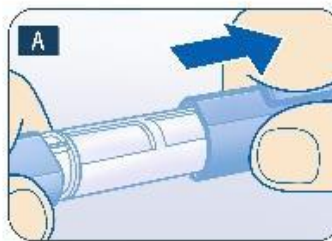
Important Information

- Δ Always use a new needle for each injection to prevent contamination.
- Δ Always remove the needle after each injection, and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of liraglutide, blocked needles and inaccurate dosing.
- Δ Keep your liraglutide injection pen and all medicines out of the reach of children.
- Δ If you drop your liraglutide injection pen, repeat “First Time Use For Each New Pen” (steps A through D).
- Δ Be careful not to bend or damage the needle.
- Δ Do not use the cartridge scale to measure how much liraglutide injection to inject.
- Δ Be careful when handling used needles to avoid needle stick injuries.
- Δ You can use your liraglutide injection pen for up to 30 days after you use it the first time.

First Time Use for Each New Pen

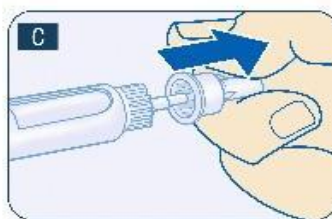
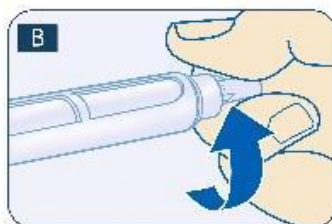
Step A. Check the Pen

- Take your new liraglutide injection pen out of the refrigerator.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your liraglutide injection pen.
- Pull off pen cap (See Figure A).
- Check liraglutide injection in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.



Step B. Attach the Needle

- Remove protective tab from outer needle cap (See Figure B).
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.
- Pull off outer needle cap (See Figure C). Do not throw away
- Pull off inner needle cap and throw away (See Figure D). A small drop of liquid may appear. This is normal.



Step C. Dial to the Flow Check Symbol

This step is done only **Once** for each new pen and is **Only** required the first time you use a new pen.

- Turn dose selector until the black line of flow check symbol () lines up with pointer (See Figure E). The flow check symbol does not administer the dose as prescribed by your healthcare provider.
- To select the dose prescribed by your healthcare provider, continue to Step G under “Routine Use”.



Step D. Prepare the Pen

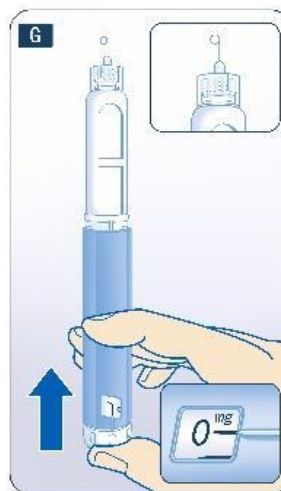
- Hold pen with needle pointing up.
- Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge (See Figure F).



- Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G). Repeat steps C and D, up to 6 times, until a drop of liraglutide injection appears at the needle tip.

If you still see no drop of liraglutide injection, use a new pen and contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689.

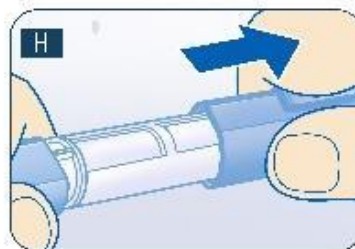
Continue to Step G under "Routine Use" →



Routine Use

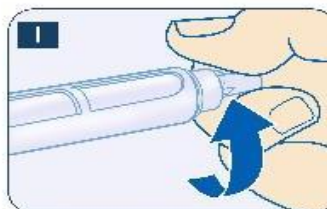
Step E. Check the Pen

- Take your liraglutide injection pen from where it is stored.
- Wash hands with soap and water before use.
- Check pen label before each use to make sure it is your liraglutide injection pen.
- Pull off pen cap (See Figure H).
- Check liraglutide injection in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
- Wipe the rubber stopper with an alcohol swab.

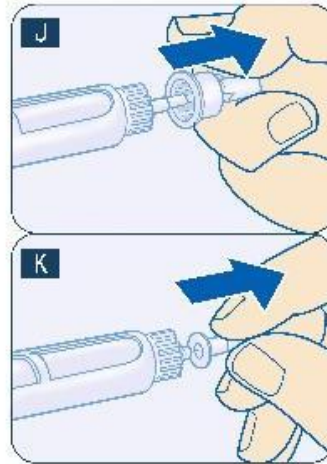


Step F. Attach the Needle

- Remove protective tab from outer needle cap.
- Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure (See Figure I).

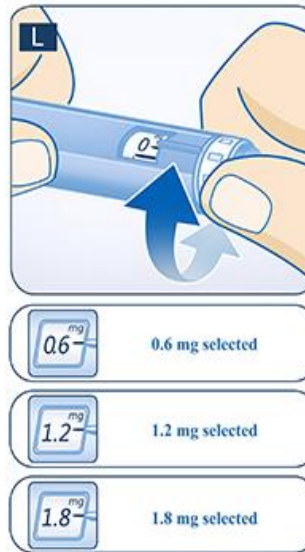


- Pull off outer needle cap. Do not throw away (See Figure J).
- Pull off inner needle cap and throw away (See Figure K). A small drop of liquid may appear. This is normal.



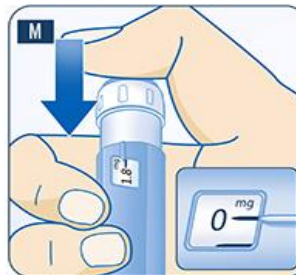
Step G. Dial the Dose

- Liraglutide injection pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of liraglutide injection that is prescribed for you.
- Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L).
- You will hear a "click" every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear.**
- If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause liraglutide injection to come out.

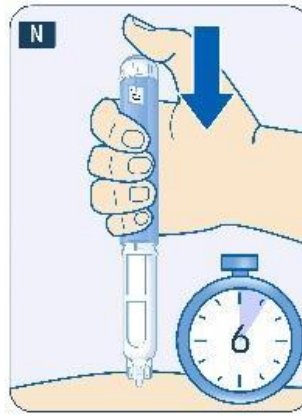


Step H. Injecting the Dose

- Insert needle into your skin in the stomach (abdomen), thigh or upper arm. Use the injection technique shown to you by your healthcare provider. **Do not inject liraglutide injection into a vein or muscle.**
- Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M).
- Be careful not to touch the dose display with your other fingers. This may block the injection.

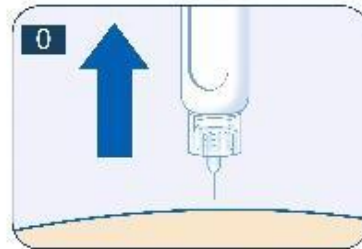


- Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin (See Figure N).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.



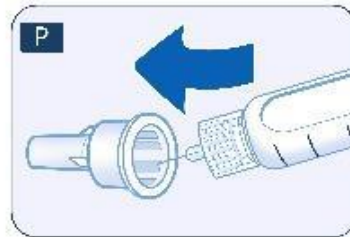
Step I. Withdraw Needle

- You may see a drop of liraglutide injection at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but **do not rub the area** (See Figure O).



Step J. Remove and Dispose of the Needle

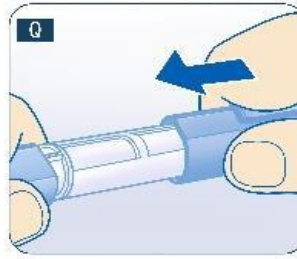
- Carefully put the outer needle cap over the needle (See Figure P). Unscrew the needle.
- Safely remove the needle from your liraglutide injection pen after each use.



- Put your used liraglutide injection pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - upright and stable during use
 - leak-resistant
 - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles with other people. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

Caring for your liraglutide injection pen

- After removing the needle, put the pen cap on your liraglutide injection pen and store your liraglutide injection pen without the needle attached (See Figure Q).
- Do not try to refill your liraglutide injection pen - it is prefilled and is disposable.
- Do not try to repair your pen or pull it apart.
- Keep your liraglutide injection pen away from dust, dirt and liquids.
- If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.



How should I store liraglutide injection?

Before use:

- Store your new, unused liraglutide injection pen in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If liraglutide injection is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze liraglutide injection or use liraglutide injection if it has been frozen. Do not store liraglutide injection near the refrigerator cooling element.

Pen in use:

- Use a liraglutide injection pen for only 30 days. Throw away a used liraglutide injection pen 30 days after you start using it, even if some medicine is left in the pen.
- Store your liraglutide injection pen at 59°F to 86°F (15°C to 30°C), or in a refrigerator at 36°F to 46°F (2°C to 8°C).
- When carrying the pen away from home, store the pen at a temperature between 59°F to 86°F (15°C to 30°C).
- If liraglutide injection has been exposed to temperatures above 86°F (30°C), it should be thrown away.
- Protect your liraglutide injection pen from heat and sunlight.
- Keep the pen cap on when your liraglutide injection pen is not in use.
- Always remove the needle after each injection and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage and inaccurate dosing.

Revised: November 2024

50 mm

66 mm

NDC 0143-9144-01

LIST XXXX

Rx Only

Discard pen 30 days after first use.

Liraglutide Injection

For Single Patient Use Only

18 mg/3 mL
(6 mg/mL)

Each prefilled pen contains 18 mg/3 mL (6 mg/mL) and will deliver 30 doses of 0.6 mg or 15 doses of 1.2 mg or 10 doses of 1.8 mg.

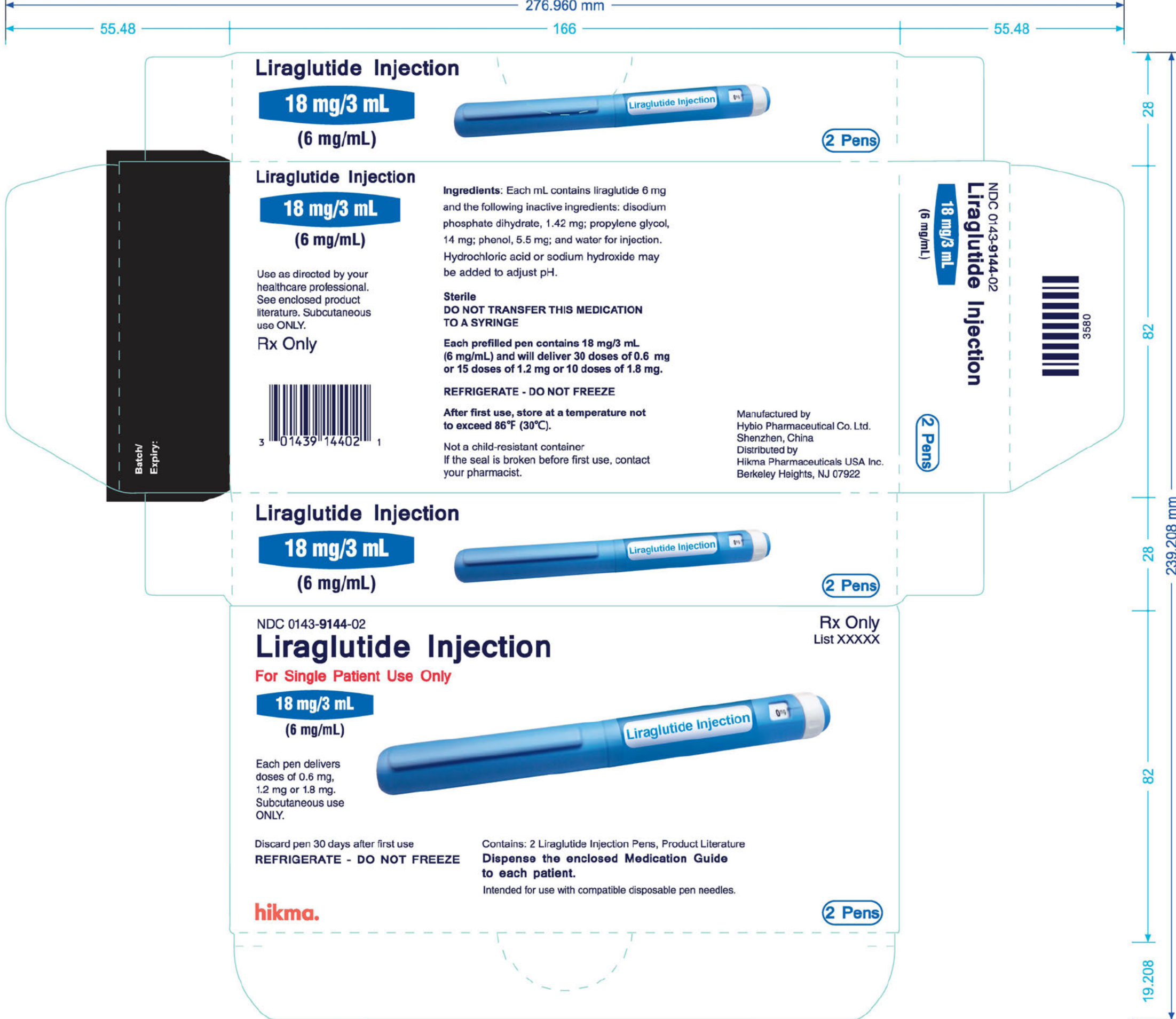
REFRIGERATE BEFORE
FIRST USE - DO NOT FREEZE

Expiry/
Batch:



Manufactured by
Hybio Pharmaceuticals Co. Ltd.
Distributed by
Hims Pharmaceuticals USA Inc.
86-0765-2656-xxx

08/2014



55.48

276.960 mm

166

55.48

Liraglutide Injection**18 mg/3 mL****(6 mg/mL)****3 Pens****Liraglutide Injection****18 mg/3 mL****(6 mg/mL)**

Use as directed by your healthcare professional. See enclosed product literature. Subcutaneous use ONLY.

Rx Only

3 01439 14403 8

Ingredients: Each mL contains liraglutide 6 mg and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

Sterile
DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

Each prefilled pen contains 18 mg/3 mL (6 mg/mL) and will deliver 30 doses of 0.6 mg or 15 doses of 1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE - DO NOT FREEZE

After first use, store at a temperature not to exceed 86°F (30°C).

Not a child-resistant container
If the seal is broken before first use, contact your pharmacist.

Manufactured by
Hybio Pharmaceutical Co. Ltd.
Shenzhen, China
Distributed by
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

NDC 0143-9144-03
Liraglutide Injection
18 mg/3 mL
(6 mg/mL)



4580

3 Pens**Liraglutide Injection****18 mg/3 mL****(6 mg/mL)****3 Pens**

NDC 0143-9144-03

Liraglutide Injection**For Single Patient Use Only****18 mg/3 mL****(6 mg/mL)**

Each pen delivers doses of 0.6 mg, 1.2 mg or 1.8 mg. Subcutaneous use ONLY.

Discard pen 30 days after first use

REFRIGERATE - DO NOT FREEZE**hikma.**

Contains: 3 Liraglutide Injection Pens, Product Literature
Dispense the enclosed Medication Guide to each patient.

Intended for use with compatible disposable pen needles.

Rx Only
List XXXXX**3 Pens**

28

82

28

82

19.208

239.208 mm

Clinical Review of Comparative Analyses
Division of Clinical Review (DCR)
Office of Safety and Clinical Evaluation (OCSE), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA	215503
Drug Product / Strength(s)	Liraglutide Injection, Solution for Subcutaneous Use 18 mg/3 mL (6 mg/mL)
ANDA Applicant	Hikma Pharmaceutical USA Inc.
RLD Product Name	Victoza (liraglutide recombinant) Injection, Solution for Subcutaneous Use, 18 mg/3 mL (6 mg/mL)
RLD # / Approval Date	NDA 022341, Approved 01/25/2010
RLD Sponsor	Novo Nordisk Inc.
Primary Reviewer	Denise Conti, PhD; DCR, OSCE Senior Staff Fellow
Secondary Reviewer	Amrita Ghosh, MD, PhD; DCR, OSCE Team Lead, Clinical Consult Team I
Tertiary Reviewer	Kimberly Witzmann, MD; DCR, OSCE Division Deputy Director (Acting)
Submission Date(s)	• <u>09/08/2021</u>: Comparative analyses report submitted in Module 5.3.5.4, Seq. 0001, ORIG-1. • <u>12/03/2021</u>: Product samples submitted in response to Clinical Information Request (IR) dated 11/16/2021; cover letter in Module 1.2, Seq. 0004, ORIG-1. • <u>01/13/2022</u>: Revised proposed labeling submitted in Module 1.14, Seq. 0005, ORIG-1, in response to Labeling Discipline Review Letter (DRL) dated 12/30/2021. • <u>03/11/2022</u>: Revised proposed labeling submitted in Module 1.14, Seq. 0009, ORIG-1, in response to Clinical IR dated 03/04/2022.
Date of Review	05/04/2022
GDUFA Goal Date	07/07/2022
Comparative Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences - Acceptable ☒ Other Design Differences ☒ Acceptable ☐ Not acceptable
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)
Recommendation (see Section 6)	Comments to the Applicant via: ☐ Complete Response Letter (CRL) ☒ None
	INTERNAL Comments to: ☐ Division of Labeling Review (DLR) ☐ Office of Pharmaceutical Quality (OPQ) ☒ None

1 INTRODUCTION AND BACKGROUND

This review evaluates the delivery device constituent part of the combination product intended to administer the drug product and any associated product labeling and packaging. This review focuses on the analysis of the user interface¹ for the drug-device combination product (drug and delivery device intended to administer a drug) comparing the proposed generic and the reference listed drug (RLD).

1.1 Summary of Drug Product Information Pertinent to Review

The RLD, Victoza (liraglutide recombinant) Injection, for Subcutaneous Use, Solution, 18 mg/3 mL (6 mg/mL), was approved on 01/25/2010 under NDA 022341; Applicant Holder: Novo Nordisk Inc.² Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated (i) as an adjunct to diet and exercise to improve glycemic control in **patients 10 years and older** with type 2 diabetes mellitus, and (ii) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. Victoza is supplied as a clear, colorless solution in a **prefilled, single-patient-use pen** that delivers doses of 0.6, 1.2 or 1.8 mg, it is available in two package sizes (2 pens or 3 pens, without pen needles) and it is intended for administration by patients or caregivers.³ Therefore, it is considered a drug-device combination product (type 2).⁴

The latest RLD labeling,³ approved on 11/20/2020, includes the Prescribing Information (PI). Full Prescribing Information contains a boxed warning stating RISK OF THYROID C-CELL TUMORS. The RLD labeling also includes Patient Counseling Information (Section 17 of PI), Medication Guide and Instructions for Use (IFU). Users are instructed to use the supplied prefilled pen to administer (via subcutaneous injection) the drug solution from the pen. Per RLD labeling, Victoza should be administered as follows:

- **Adult Dosage:** Initiate at 0.6 mg daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose.
- **Pediatric Dosage:** Initiate at 0.6 mg daily for at least one week. If additional glycemic control is required increase the dose to 1.2 mg daily and if additional glycemic control is still required, increase the dose to 1.8 mg daily after at least one week of treatment with the 1.2 mg daily dose.

Hikma Pharmaceuticals USA Inc. (the Applicant) submitted an abbreviated new drug application

¹ User interface refers to all components of the combination product with which a user interacts. See FDA draft guidance for industry, *Comparative analyses and Related Comparative Use Human Factors Studies for a Drug-Device Product Submitted in an ANDA* (January 2017).

² Per Orange Book, available at <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>, accessed 02/10/2022.

³ NDA 022341 Last Approved Labeling in DARRTS, approved on 11/20/2020 via Supplement-36: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805af7f4>. This supplement provides for the addition of information regarding severe hypoglycemia to Prescribing Information and Medication Guide.

⁴ FDA website *Combination Product Definition Combination Product Types* (<https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types>; current as of 02/15/2018, accessed 02/10/2022). A type 2 combination product is when “Drug is filled into or otherwise combined with the device AND the sole purpose of the device is to deliver drug.”

(ANDA) 215503 on 09/08/2021 for Liraglutide Injection, Solution for Subcutaneous Use, 18 mg/3 mL (6 mg/mL). The Applicant seeks approval for the following indication only: “as an adjunct to diet and exercise to improve glycemic control in **adult patients** with type 2 diabetes mellitus.”^{5,6} The proposed product is supplied as a clear, colorless solution in a **prefilled, single-patient-use pen** that delivers doses of 0.6, 1.2 or 1.8 mg, available in two package sizes (2 pens or 3 pens, without pen-needles),⁵ i.e., a drug-device combination product (type 2) similar to the RLD.⁷ There is no generic drug priority status granted for this application.⁷ On 11/16/2021, DCR sent a Clinical Information Request (IR) letter to the Applicant requesting Hikma to submit samples of the to-be-marketed proposed product (liraglutide injection) including the to-be-marketed labeling and samples of the RLD (Victoza Injection) for evaluation.⁸ DCR evaluated the samples and reviewed the comparative analyses report provided by the Applicant.⁹

1.2 Other Relevant Information

There are 11 pre-ANDA meeting packages and 102 valid controlled correspondences (CCs) for this drug product,¹⁰ of which 2 pre-ANDA meeting packages¹¹ and 13 CCs¹² have comparative analyses relevant to this review (see below for summary of these submissions).

- 13 CCs¹³ and 2 Pre-ANDA Meeting Packages¹⁴ – There were multiple **minor** design differences identified between the proposed pens and the RLD pen including color,

⁵ ANDA 215503 Draft Labeling Text in Module 1.14.1.3, Seq. 0005, received 01/13/2022, ORIG-1, available at [\\CDSESUB1\evsprod\anda215503\0005\m1\us\draft-labeling-text.pdf](https://cdsesub1\evsprod\anda215503\0005\m1\us\draft-labeling-text.pdf). The Applicant’s revised, proposed labeling was submitted in response to a Labeling DRL sent 12/30/2021, available at <https://panorama.fda.gov/task/view?ID=61cdbe0a00451fc2cfc1b9eb5d002a14>

⁶ This proposed labeling⁵ was revised by the Applicant according to the Labeling DRL dated 12/30/2021, available at <https://panorama.fda.gov/task/view?ID=61cdbe0a00451fc2cfc1b9eb5d002a14>, which requested, among other changes, to remove information related to new patient population exclusivities as noted in the Labeling Review C1 dated 11/23/2021, available at <https://panorama.fda.gov/task/view?ID=6139ff8d009943d1d11b2c72157e2861>.

⁷ ANDA 215503 Combination Product: 2-Prefilled Drug Delivery Device/System (syringe, patch, etc.) and Prioritization Factor: [None], available at <https://panorama.fda.gov/project/view?ID=6139ff8c00994050753f29ecca75b34a>

⁸ ANDA 215503 Clinical IR (A215503N000DCR InformationRequest01-PM11162021Samples.pdf) sent 11/16/2021, available at <https://panorama.fda.gov/task/view?ID=619320fc00102980c41f0a637bc26cdd>.

⁹ ANDA 215503 Threshold Analyses submitted in Module 5.3.5.4, Seq. 0001, received 09/08/2021, ORIG-1, available at [\\CDSESUB1\evsprod\anda215503\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-type-2-diabetes\5354-other-stud-rep\threshold-analyses-of-rlid-and-generic\report-body-ta.pdf](https://cdsesub1\evsprod\anda215503\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-type-2-diabetes\5354-other-stud-rep\threshold-analyses-of-rlid-and-generic\report-body-ta.pdf).

¹⁰ Per Controls Search Report from Palantir, accessed 02/08/2022, available at <https://analytics.fda.gov/workspace/report/ri.report.main.report.bafcd4b7-dd6d-4c22-8172-d52126bfe2ce>. DCR reviewer searched “22341” as the RLD parameter.

¹¹ Pre-ANDA meetings were filtered according to the following search parameters – Product Development: “PDEV” and Pre-Submission: “PSUB”.

¹² CCs were filtered according to the following search parameters – Valid Control: “Yes”, Discipline Category: “Device Evaluation” and Review Discipline: “ORS”.

¹³ These CCs are in Panorama: CC 2852928 (completed 04/14/2016), CC 15778065 (completed 08/18/2017), CC 23229961 (completed 07/23/2018), CC 24705957 (completed 09/17/2018), CC 03398 (completed 07/15/2019), CC 05390 (completed 12/16/2019), CC 05426 (completed 10/22/2019), CC 10691 (completed 06/04/2020), CC 13514 (completed 09/28/2020), CC 13751 (completed 10/09/2020), CC 19274 (completed 04/28/2021). These CCs are in Nexus: CC 00020926 (completed 07/09/2021), CC 00039034 (completed 09/10/2021).

¹⁴ [REDACTED] (b) (4)

dimensions, design of pen and components (e.g., cartridge holder, dose selector, dose button, dose display window, dose pointer), mechanism for needle attachment (e.g., threat and prints on extended dose selector plunger. In the pre-ANDA stage, firms were suggested to consider addressing the following **minor** design differences in their proposed pens to minimize differences from the RLD or provide adequate justification in their comparative analyses:

- [REDACTED] (b) (4)
- [REDACTED]

There were **other** design differences identified in CC 19274 (completed 04/28/2021) so that the proposed pen was found not eligible for an ANDA submission – [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]; (ii) [REDACTED] (b) (4); and (iii) [REDACTED] (b) (4)

There are currently **no** approved generic Liraglutide Injection, Solution for Subcutaneous Use, 18 mg/3 mL (6 mg/mL) per Orange Book.¹⁵ [REDACTED] (b) (4)

[REDACTED] All comparative analyses reviews completed by DCR have been reviewed (see table below for summary of relevant submissions).

[REDACTED TABLE CONTENTS] (b) (4)

¹⁵ Per Orange Book, available at <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>, accessed 02/19/2022.

¹⁶ [REDACTED] (b) (4)

¹⁷

There is currently one pending NDA supplement to modify the RLD labeling. If/when approved, this RLD labeling modification is not expected to impact this review.²⁰

2 COMPARATIVE ANALYSES REVIEW AND DISCUSSION

To evaluate if the proposed combination product is comparable with the RLD from a clinical use perspective, DCR conducted a review of the submitted comparative analyses of the user interface of the proposed generic combination product and its RLD, Victoza (liraglutide recombinant) Subcutaneous Injection, NDA 022341. DCR also evaluated relevant device-related information submitted in Module 3.2.P.7 (container closure system) and Module 1.14 (labeling).

2.1 Physical Comparison of the Proposed Product to the RLD

18

19

(b) (4)

²⁰ NDA 022341, DARRTS, COR-SNDAACK-02 (Acknowledge CBE Supplement), dated 12/23/2021: https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af806366fc&_afRedirect=495630998934692. Supplement-37, submitted as CBE on 12/13/2021, proposed a change to the PI according to the Supplement Request Letter (SRL) dated 10/29/2021, which requested addition of “hyperbilirubinemia” and “cholestasis” in Section 6.3 PostMarketing Experience.

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(b) (4) Therefore, this design difference does not affect the safety or risk profile of the proposed product when compared to the RLD; DCR considers this design difference is **acceptable**.

DCR classified the remaining physical design differences identified in Section 2.1 (e.g., color schemes, dimensions, size and shape of the pen and its parts) as **minor, acceptable** as they are unlikely to impact critical tasks for use of the proposed product when it is substituted for the RLD.

2.3 Labeling Comparison of Proposed Product to the RLD

The most current RLD labeling was approved on 11/20/2020 under Supplement-36.³ The RLD labeling includes Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU). The RLD labeling is available at <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805af7f4>.

For the labeling comparison of this drug-device combination product, DCR conducted a side-by-side, line-by-line comparison of the relevant sections of the labeling for the RLD and the proposed generic product that relates to the use of the device, specifically Dosage and Administration (Section 2 of PI), Dosage Forms and Strengths (Section 3 of PI), How Supplied / Storage and Handling (Section 16), IFU, container and carton labels. Except for the delivery device-related part of labeling, the review of the remainder of the labeling is deferred to the Division of Labeling Review (DLR).

²⁷ (b) (4)

²⁸ DCR reviewer notes that this physical design difference (i.e., needle connector design) was present in the proposed product submitted in separate ANDAs, but not assessed in the comparative analyses completed by DCR (Table 1).

²⁹ The website Victoza Liraglutide Injection is available at <https://www.victoza.com/faq/Using-the-Victoza-Pen.html>, accessed 02/23/2022.

The Applicant performed a labeling comparison³⁰ and concluded that the IFU for the proposed product is in accordance with that of the RLD.⁹

Below is presented the current status of Applicant's proposed labeling (Table 5) and a high-level overview of differences in labeling noted by DCR reviewer (Table 6). The following tables present a side-by-side comparison of the **labeling differences only**, including Reviewer's Comments under each table, where applicable.

Table 5: Applicant's Proposed Labeling Status (Current as of 02/14/2022).

Milestone for Division of Labeling Review (DLR)	Yes/No or N/A (if yes include date)
Was a DLR's Discipline Review Letter (DRL) / IR sent?	Yes (12/30/2021) ³¹
Applicant replied to DLR's DRL / IR with modified proposed labeling?	Yes (01/13/2022) ⁵
Submission date of proposed labeling used for this review	01/13/2022 ⁵

N/A = Not Applicable.

Table 6: Labeling Comparison – Proposed Product to the RLD.

Delivery Device-Related Labeling	Yes/No or N/A
(1) Any difference in the Dosage and Administration (Section 2 of PI) ?	Yes
(2) Any difference in the Dosage Forms and Strengths (Section 3 of PI) ?	No
(3) Any difference in the How Supplied/Storage and Handling (Section 16 of PI) ?	No
(4) Any differences in the IFU ?	Yes
(5) Any differences in the Container (Pen) Labeling ?	No
(6) Any differences in the Carton Labeling ?	Yes

N/A = Not Applicable.

Reviewer Comments:

(b) (4)

[Redacted Reviewer Comments]

Table 7 presents a side-by-side comparison of different figures in the IFU. For full IFU comparison, including the text (which is the same between the RLD and proposed product), see: <\\CDSESUB1\evsprod\anda215503\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-type-2-diabetes\5354-other-stud-rep\comparison-for-ifu\report-body-compifu.pdf>.

³⁰ ANDA 215503 Comparison for IFU submitted in Module 5.3.5.4, Seq. 0001, received 09/08/2021, ORIG-1, available at <\\CDSESUB1\evsprod\anda215503\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-type-2-diabetes\5354-other-stud-rep\comparison-for-ifu\report-body-compifu.pdf>.

³¹ ANDA 215503 Labeling DRL, approved on 12/30/2021, available at <https://panorama.fda.gov/task/view?ID=61cdbe0a00451fc2cfc1b9eb5d002a14>

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4 DESIGN DIFFERENCES SUMMARY

There are physical design differences, as well as differences in tasks and labeling, observed between the RLD and the proposed delivery device. The table below summarizes these differences and applicable reviewer classification and comments before (“Initial”) and after (“Final”) the assessment of Applicant’s response to clinical comparative analyses comments (see Section 3).

Table 10: Summary of Differences Between RLD and Proposed Product.

Differences	Applicant’s Classification (Minor/Other)	Initial Reviewer Classification (Minor/Other)	Final Reviewer Classification (Minor/Other)
1. Physical – Pen Body: color, dimensions	Minor	Minor	Minor
2. Physical – Cap: shape, color, dimensions, design of clip*	Minor	Minor	Minor
3. Physical – Cartridge Holder: shape, dimensions, color of surrounding of rubber stopper,* design of ridges (number and shape),* design of scale (thickness of lines and digits)*	Minor	Minor	Minor
4. Physical and Task – Cartridge Tip: needle connector design allows attachment of threaded screw-on needles only	Other (physical) Minor (task)	Minor	Minor
5. Physical – Dose Selector: color, (b) (4)	Minor	Minor	Minor
6. Physical – Dose Display: prints and background color scheme, area*	Minor	Minor	Minor
7. Physical – Dose Display: design of prints (b) (4)	No Difference	Minor	Minor
8. Physical – Pointer: (b) (4)*	Minor	Minor	Minor
9. Physical, Task and Labeling (IFU) – Dose Display: users need to line up the black line of dose digit with the pointer to perform related tasks including selection of dose	Not Identified	Other, Acceptable (b) (4)	Other, Acceptable
10. Physical and Task – (b) (4)	Not Identified	Other, Acceptable	Other, Acceptable
11. Labeling – IFU: figures show cartridge scale (b) (4)	Minor	Other, Not Acceptable	No Difference
12. Labeling – Carton: (b) (4)	Not Identified	Other, Not Acceptable	Minor

* Difference not identified by the Applicant in their comparative analyses report.⁹

5 CONCLUSION

From a clinical safety perspective, there are minor and other acceptable design differences between the RLD and the proposed drug delivery device (color, dimensions, shape of pen; design of pen

components - (b) (4)

Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a healthcare professional and/or without additional training prior to use of the generic combination product, and that the design differences as compared to RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug-device user interface for the proposed generic product acceptable.

6 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no recommendations/the following deficiencies:

- ☐ Major
- ☐ Minor
- ☒ N/A (Review is Adequate)

7 APPENDIX

Table A1: Task Analysis Comparison Provided by the Applicant
(differences in tasks between the proposed product compared to the RLD are highlighted in yellow by DCR reviewer).²²

Task	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
(b) (4)	Check the Pen	Check the Pen	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Take your new Victoza pen out of refrigerator.	Take your new Liraglutide injection pen out of refrigerator.	No difference	No use error	N/A	N/A	N/A	N/A
	Wash hands with soap and water before use.	Wash hands with soap and water before use.	No difference	Does not wash hands with soap	Microbial contamination	Low	Low	Warning has been specified clearly in label and is same as RLD
	Check pen label before each use to make sure it is your Victoza pen.	Check pen label before each use to make sure it is your Liraglutide injection pen.	No difference	Use the wrong pen	Medication Errors	Low	Low	The product information is specified clearly in label and is same as RLD
	Pull off pen cap	Pull off pen cap.	No difference	User has difficulty removing cap	No treatment, Delayed treatment	Low	Low	The cap attachment force is determined to not more than 9N.*
	Check Victoza in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.	Check Liraglutide injection pen in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.	No difference	Use does not check the cartridge or the liquid in cartridge	Microbial or foreign matter contamination; No treatment; Delayed treatment.	Low	Low	The pen holder and the cartridge are transparent, and warning has been specified clearly in label and is same as RLD.
	Wipe the rubber stopper with an alcohol swab.	Wipe the rubber stopper with an alcohol swab.	No difference	Does not wipe the rubber stopper	Microbial contamination	Low	Low	Warning has been specified clearly in label and is same as RLD

Task	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
(b) (4)	Attach the Needle (b) (4)	Attach the Needle (b) (4)	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Remove protective tab from outer needle cap.	Remove protective tab from outer needle cap.	No difference	No use error	N/A	N/A	N/A	N/A
	Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.	Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.	Minor design difference (b) (4)	User has difficulty attaching the needle	Dose delivery error.	Low	Low	The "twist-click" needle is not possible to be attached on the generic pen when user use "twist-click" needle to attach on the generic pen, in this case, it will not cause dose delivery error.
	Pull off outer needle cap. Do not throw away.	Pull off outer needle cap. Do not throw away.	No difference	No use error	N/A	N/A	N/A	N/A
	Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.	Pull off inner needle cap and throw away. A small drop of liquid may appear. This is normal.	No difference	No use error	N/A	N/A	N/A	N/A
	Dial to the Flow Check Symbol	Dial to the Flow Check Symbol	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
	This step is done only Once for each new pen and is Only required the first time you use a new pen.	This step is done only Once for each new pen and is Only required the first time you use a new pen.	No difference	Forget to prime or repeat operation of priming	The bubble is not expelled or the drug product is waste.	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Turn dose selector until flow check symbol (--) lines up with pointer. The flow check symbol does not administer the dose as prescribed by your healthcare provider.	Turn dose selector until flow check symbol (--) lines up with pointer. The flow check symbol does not administer the dose as prescribed by your healthcare provider.	No difference	The symbol (--) is taken as a dose.	Insufficient dose	Low	Low	Warning has been specified clearly in label and is same as RLD.
	To select the dose prescribed by your healthcare provider, continue to Step G under "Routine Use".	To select the dose prescribed by your healthcare provider, continue to Step G under "Routine Use".	No difference	Incorrect selection of dose	Insufficient dose or dose delivery error	Low	Low	The scale marking is clearly printed.
	Prepare the Pen	Prepare the Pen	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Hold pen with needle pointing up.	Hold pen with needle pointing up.	No difference	Forget to hold pen with needle pointing up	The bubble in liquid cannot float to the top.	Low	Low	Warning and the relevant picture have been specified clearly in label and is same as RLD.
	Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge.	Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge.	No difference	Forget to tap cartridge	The bubble in liquid cannot float to the top.	Low	Low	Warning has been specified clearly in label and is same as RLD.

Liraglutide Injection, Solution for Subcutaneous Use, 18 mg/3 mL (6 mg/mL)

Task	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
(b) (4)	Keep needle pointing up and press dose button until 0 mg lines up with pointer. Repeat steps C and D, up to 6 times, until a drop of Victoza appears at the needle tip.	Keep needle pointing up and press dose button until 0 mg lines up with pointer. Repeat steps C and D, up to 6 times, until a drop of Liraglutide injection appears at the needle tip.	No difference	Does not press dose button until 0 mg lines up with pointers.	The bubble in cartridge is not expelled and it cause insufficient dose.	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Dial the Dose	Dial the Dose	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Victoza pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza that is prescribed for you.	Liraglutide injection pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Liraglutide injection that is prescribed for you.	No difference	Incorrect selection of dose	Insufficient dose or overdose	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Turn the dose selector until your needed dose lines up with the pointer (0.6mg, 1.2 mg or 1.8 mg).	Turn the dose selector until your needed dose lines up with the pointer (0.6mg, 1.2 mg or 1.8 mg).	No difference	User has difficulty rotating the dose selection	No treatment, Delayed treatment	Low	Low	Dose selection torque has been verified. *
	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
	You will hear a "click" every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.	You will hear a "click" every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.	No difference	Cannot here a "click" or set dose by counting the number of clicks	Medication Errors	Low	Low	The "click" can be heard clearly. Warning has been specified clearly in label and is same as RLD.
	If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza to come out.	If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Liraglutide injection to come out.	No difference	No use error	N/A	N/A	N/A	N/A
	Injecting the Dose	Injecting the Dose	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Insert needle into your skin in the stomach, thigh or upper arm. Use the injection technique shown to you by your healthcare provider. Do not inject Victoza into a vein or muscle.	Insert needle into your skin in the stomach, thigh or upper arm. Use the injection technique shown to you by your healthcare provider. Do not inject Liraglutide injection into a vein or muscle.	No difference	User insert needle into vein or muscle.	Medication Errors	Low	Low	Warning has been specified clearly in label and is same as RLD.

Liraglutide Injection, Solution for Subcutaneous Use, 18 mg/3 mL (6 mg/mL)

Task	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
(b) (4)	Press down on the center of the dose button to inject until 0 mg lines up with the pointer.	Press down on the center of the dose button to inject until 0 mg lines up with the pointer.	No difference	User does not operate as per the labeling	Insufficient dose	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Be careful not to touch the dose display with your other fingers. This may block the injection.	Be careful not to touch the dose display with your other fingers. This may block the injection.	No difference	Users put their fingers to touch the dose display	Dose delivery error	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin.	Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin.	No difference	Not holding device to injection site for required time	Insufficient dose	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.	Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.	No difference	User use the same injection site for injection	Cause injury	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Withdraw Needle	Withdraw Needle	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
	You may see a drop of Victoza at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but do not rub the area.	You may see a drop of Liraglutide injection at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but do not rub the area.	No difference	No use error	N/A	N/A	N/A	N/A
	Remove and Dispose of the Needle	Remove and Dispose of the Needle	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows
	Carefully put the outer needle cap over the needle. Unscrew the needle.	Carefully put the outer needle cap over the needle. Unscrew the needle.	No difference	Improper disposal of pen needle	Injured by the needle	Low	Low	Warning has been specified clearly in label and is same as RLD.
	Safely remove the needle from your Victoza pen after each use.	Safely remove the needle from your Liraglutide injection pen after each use.	No difference					
	Put your used Victoza pen and needles in a FDA-cleared sharps disposal container right away after use.	Put your used Liraglutide injection pen and needles in a FDA-cleared sharps disposal container right away after use.	No difference					
	Caring for your Victoza pen	Caring for your Victoza pen	No difference	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows	Detailed as follows

Task (b) (4)	Description of Task of RLD pen	Description of Task of generic pen	Difference identified	Potential use errors	Potential hazard	Probability	Severity	Discussion and Justification
	After removing the needle, put the pen cap on your Victoza pen and store your Victoza pen without the needle attached.	After removing the needle, put the pen cap on your Liraglutide injection pen and store your Liraglutide injection pen without the needle attached.	No difference	No use error	N/A	N/A	N/A	N/A

Note: * Means the results adopted from design verification report from BD in [Topic 3.5.1](#) of Section 3.2.R.DEVICE.



Denise
Conti

Digitally signed by Denise Conti
Date: 5/04/2022 12:01:47PM
GUID: 5388e6e100067057841c5ddc44681318



Amrita
Ghosh

Digitally signed by Amrita Ghosh
Date: 5/04/2022 04:01:56PM
GUID: 5acd0ca50037b88ab9130ff063990dc9



Kimberly
Witzmann

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Date: 5/05/2022 08:06:09AM
GUID: 508da6ee0002782694c8988b30c071f3

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	November 6, 2024
ANDA Number(s)	215503
Review Number	5
Applicant Name	Hikma Pharmaceuticals USA Inc
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	NA
Submission Received Date	November 5, 2024
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Ellen Koo
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
<u>1.1</u>	<u>LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u>
<u>1.2</u>	<u>COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>1.3</u>	<u>POST-APPROVAL REVISIONS</u>
<u>2</u>	<u>INSTRUCTIONS FOR ASSESSMENT</u>
<u>3</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>
<u>4</u>	<u>LABELING REVIEW INFORMATION</u>
<u>4.1</u>	<u>REGULATORY INFORMATION</u>
<u>4.2</u>	<u>MODEL PRESCRIBING INFORMATION</u>
<u>4.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>4.4</u>	<u>UNITED STATES PHARMACOPEIA (USP)</u>
<u>4.5</u>	<u>MODEL CONTAINER LABELS</u>
<u>5</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
<u>5.1</u>	<u>QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
<u>5.1.1</u>	<u>DRUG PRODUCT REVIEW</u>
<u>5.1.2</u>	<u>DESCRIPTION</u>
<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>INJECTABLE PRODUCTS</u>
<u>5.2.1.1</u>	<u>CONTAINER LABEL FOR PARENTERAL SOLUTIONS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>MEDICATION GUIDE</u>
<u>5.6</u>	<u>OTHER PATIENT LABELING</u>

1 **LABELING COMMENTS (C5)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C5)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C5)**

The Division of Labeling has no further questions/comments at this time based on your labeling submission received November 5, 2024.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C5)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C5)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C5)

4 LABELING REVIEW INFORMATION(C5)

4.1 REGULATORY INFORMATION (C5)

4.2 MODEL PRESCRIBING INFORMATION (C5)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA022341 / S-043

Supplement Approval Date: 11/01/2024

Proprietary Name: Victoza

Established Name: liraglutide injection

Description of Supplement:

We also refer to our letter dated September 6, 2024, notifying you, under Section 505(c)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for glucagon-like peptide-1 receptor agonist (GLP-1 RA) products. This information pertains to the serious risk of pulmonary aspiration for patients undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

This sNDA provides for revisions to the labeling for Victoza consistent with our September 6, 2024, letter and October 11 and 16, 2024, email correspondence.

Link: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8077b8c4>

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments: C4 assessment: The currently submitted labeling is up to date with the current RLD/Model labeling identified in the Model labeling section above. C5 assessment: The labeling from the 11/5/2024 submission is provided to be in accordance with the current RLD/Model labeling identified in the Model labeling section above.		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C5)

The [Orange Book](#) was searched on 11/06/2024

Table 4 provides Orange Book patents for the Model Labeling (NDA022341) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	6268343	08/22/2022	U-968	A METHOD FOR IMPROVING	III	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
				GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS			
18 mg/3 mL (6mg/mL)	7762994	05/23/2024			IV	09/08/2021	Expired
18 mg/3 mL (6 mg/mL)	7762994*PED	11/23/2024			IV	09/08/2021	None
18 mg/3 mL (6 mg/mL)	8114833	08/13/2025			IV	09/08/2021	None
18 mg/3 mL (6 mg/mL)	8114833*PED	02/13/2026			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8579869	06/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8579869*PED	12/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618	06/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618*PED	12/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6 mg/mL)	9265893	09/23/2032			IV	09/08/2021	None
18 mg/3 mL (6 mg/mL)	9265893*PED	03/23/2033			IV	09/08/2021	None
18 mg/3 mL (6 mg/mL)	9968659	01/09/2037	U-2313	METHOD OF REDUCING THE RISK OF CARDIOVASCULAR DEATH, NON-FATAL MYOCARDIAL INFARCTION, AND/OR NON-FATAL STROKE IN ADULTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED CARDIOVASCULAR DISEASE BY ADMINISTERING LIRAGLUTIDE	viii	09/08/2021	Carve-out
18 mg/3 mL (6 mg/mL)	9968659*PED	07/09/2037			viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	RE41956	01/21/2021			II	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	RE41956*PED	07/21/2021			II	09/08/2021	Expired

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	NPP	06/17/2022	NEW PATIENT POPULATION	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	NPP PED	12/17/2022	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information	09/08/2021	Expired

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				associated with the listed exclusivities		

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments: Cycle #3: No change to patent certifications. The applicant provides the 12/19/2023 submission to provide a waiver granted by the sponsor of the RLD. Expired patents do not affect labeling. The 6/30/2023 submission is provided due to an RLD update (b) (4) C4 assessment: Expired patents do not affect labeling. C5 assessment: Expired patent '994 does not affect labeling.		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C5)

The [USP](#) was searched on 11/06/2024

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		

Deficiency	No Deficiency	
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: C4 assessment: No change noted C5 assessment: No change noted Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C5)

Model container/carton/blister labels (Source: NDA 022341/S-028 approval letter in DARRTS dated 4/25/2017)

Syringe label for 2 Pens/Carton

Expiry/
Batch:

8-9695-31-
205-7

NDC 0169-4060-12

LIST 406012

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.
REFRIGERATE BEFORE FIRST
USE - DO NOT FREEZE



Novo Nordisk Inc.
1-877-484-2869

1

Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only
Rx Only



01694 06012 8

Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dodecahydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile
**DO NOT TRANSFER THIS MEDICATION TO A
SYRINGE**

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE - DO NOT FREEZE

After first use, store at a temperature not to exceed
86°F (30°C).

Not a child-resistant container

If the seal is broken before first use, contact your
pharmacist.

PATENT Information: [http://novonordisk-
us.com/patients/products/product-patents.html](http://novonordisk-us.com/patients/products/product-patents.html)

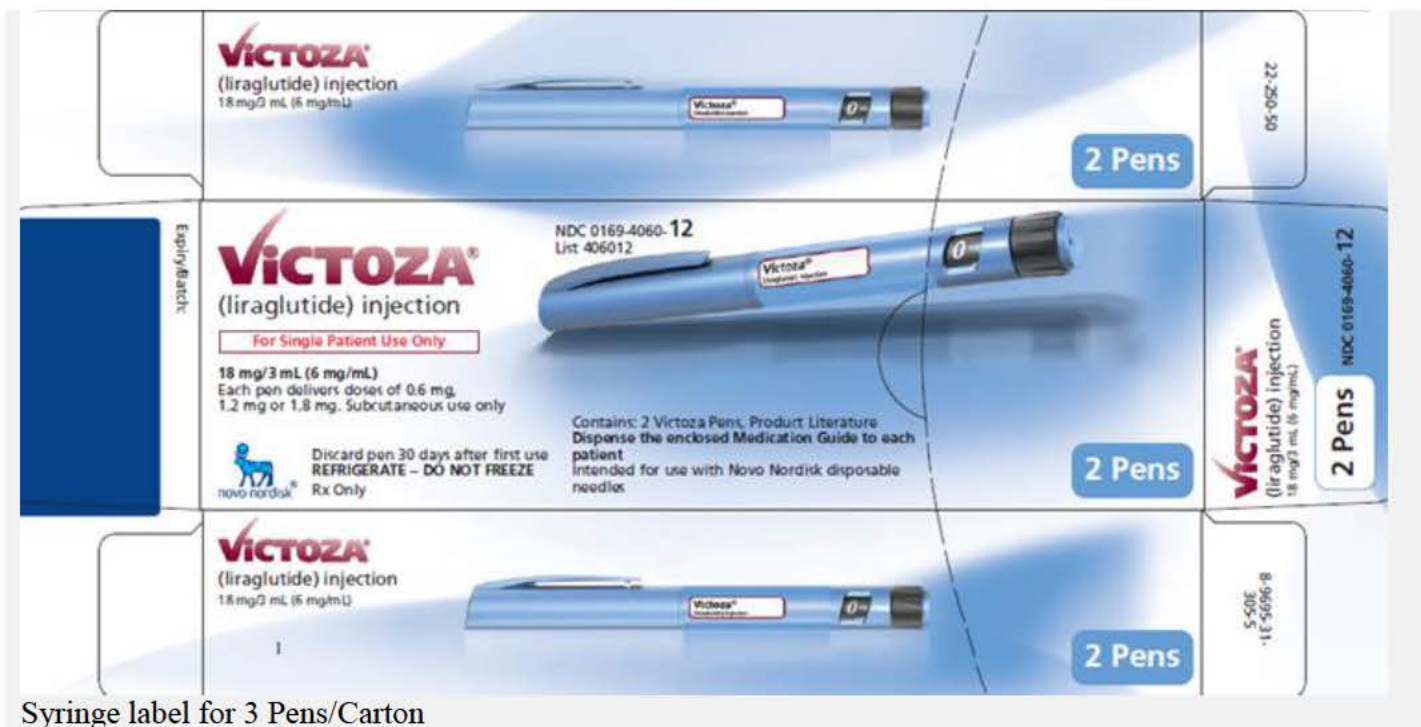
Victoza® is a registered
trademark of Novo Nordisk A/S.
© 2016 Novo Nordisk A/S

Novo Nordisk Inc.
Parsippany, NJ 08536
1-877-484-2869
(Se habla español)

www.victoza.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark





Syringe label for 3 Pens/Carton

Expiry/
Batch:

8-9695-31-
201-6

NDC 0169-4060-13

LIST 406013

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

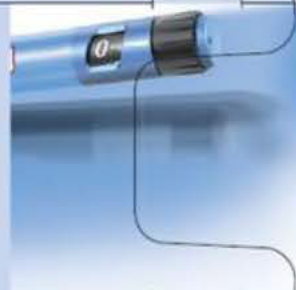
REFRIGERATE BEFORE FIRST
USE – DO NOT FREEZE



(01)10301694060132

Novo Nordisk Inc.
1-877-484-2869

1



Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only
Rx Only



01694 06013 3

Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE – DO NOT FREEZE

After first use, store at a temperature not to exceed
86°F (30°C).

Not a child-resistant container.
If the seal is broken before first use, contact your
pharmacist.

PATENT Information: [http://www.novonordisk-
us.com/patients/products/product-patents.html](http://www.novonordisk-us.com/patients/products/product-patents.html)

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Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark



Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

A215503 Drug Product R03-AQ (archived 6/11/2024)

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Deficiency #01 (CR dated 02/28/2024): In the Package Insert (PI) label, you stated

(b) (4)

please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34."

Summary of Applicant's Response (dated 03/21/2024): Hikma has confirmed with the DMF holder that Liraglutide is chemically synthesized. The package insert labeling has been revised in the Description section as requested. The following documents are provided in Module 1.14.

Reviewer's Assessment: Adequate

(b) (4)

The package insert labeling Description section was revised accordingly to state Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34." This is acceptable.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No," what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES (All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")

None

5.1.2 DESCRIPTION (C5)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).
Previous ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH.
Current ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Assessment: No change noted

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C5)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied VICTOZA Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x VICTOZA pen NDC 0169-4060-12 3 x VICTOZA pen NDC 0169-4060-13 16.2 Recommended Storage Prior to first use, VICTOZA should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen. After first use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an

Table 8: Comparison of Model Labeling to ANDA Labeling	
	injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Previous ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Current ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination. Assessment: No change noted

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C5)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan Factory) 2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan Factory) 2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922 Assessment: No change noted

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437].

Deficiency	No Deficiency	
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6)] or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure, cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The container label in in line with the RLD; however, we have comments for the applicant. Please refer to section 5.2.1.1 below. (b) (4)		
Assessment: The applicant has satisfactorily addressed all comment. Container labels are found acceptable. Previous labeling review:		

Currently proposed:



Cycle #3:

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

Additionally, the applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

From 6/30/2023 annotated SBS:



Container label is acceptable.

C4 assessment:

Container label was found acceptable in the C3 review.

Container label not submitted with the 3/21/2024 submission.

C5 assessment:

Container label was found acceptable in the C3 review.

Container label not submitted with the 11/5/2024 submission.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Product label states, "Discard unused portion" for single dose products.
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is NA . NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Cycle #3:

Container is acceptable.

C4 assessment:
 Container label was found acceptable in the C3 review.
 Container label not submitted with the 3/21/2024 submission.

C5 assessment:
 Container label was found acceptable in the C3 review.
 Container label not submitted with the 11/5/2024 submission.

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, strength per fraction of a milliliter is the only expression of strength.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 1 CFR 201.100(b)(5)(iii) .
☐	☒	Container label includes instructions for reconstitution if applicable.
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information.

Reviewer Comments:

The RLD does not list the total quantity per total volume followed by the concentration per mL; however, we will request the addition of this to be in line with USP General Chapter <7> labeling.
 Inactive ingredients are not listed on the container label but are listed on the carton labeling. This is in line with the RLD.

Cycle #3:

Container is acceptable

C4 assessment:
 Container label was found acceptable in the C3 review.
 Container label not submitted with the 3/21/2024 submission.

C5 assessment:
 Container label was found acceptable in the C3 review.
 Container label not submitted with the 11/5/2024 submission.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Unit-Dose Carton expression of strength appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Assessment:

The applicant provides carton labeling with the 1/13/2022 submission in response to the Labeling DRL and with the 3/11/2022 submission in response to a comment from DCR.

Comment to the applicant regarding carton labeling from DCR:

FDA Comment

Your proposed carton labeling states,

(b) (4)

We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

Response:

The proposed carton labeling has been revised with "Intended for use with compatible disposable pen needles" as requested.

The carton labeling from the 3/11/2022 submission supersedes the carton labeling from the 1/13/2022 submission.

Previous labeling review:

(b) (4)

Currently proposed:



The applicant satisfactorily addressed all comments. Carton labeling is found acceptable.

Cycle #3:

The applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

(b) (4)



(b) (4)

(b) (4) The RLD does not include this information on the carton labeling; however, this information is provided in the DESCRIPTION section of the PI and ingredients section of the MG. As the information is accurate, the inclusion is acceptable. Carton labeling is acceptable.

C4 assessment:

Carton labeling was found acceptable in the C3 review.

Carton labeling not submitted with the 3/21/2024 submission.

C5 assessment:

Carton labeling was found acceptable in the C3 review.

Carton labeling not submitted with the 11/5/2024 submission.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable:		

Deficiency	No Deficiency	
☐	☒	☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage form/strength carve out (RLD combined labeling): justification for retaining information for safety/efficacy.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		

(b) (4)

Assessment: The applicant has satisfactorily addressed all comments.

Cycle #3:

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

(b) (4)

PI is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises the DESCRIPTION section.

From the 3/21/2024 cover letter response:

Labeling

In the Package Insert (PI) label,

(b) (4)
(b) (4)

please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34."

(b) (4) The package insert labeling has been revised in the Description section as requested. The following documents are provided in Module 1.14.

- [Package Insert Rev. 03/2024 \(Word Version\)](#)
- [Package Insert Rev. 03/2024 \(PDF Version\)](#)
- [Side-by-Side Comparison of Previously Submitted vs Current Package Insert](#)
- SPL

No other revision to the PI, MG, or IFU noted. The DP review of the applicant's response is pending approval.

C5 assessment:

The 11/5/2024 submission is provided to be in accordance with a recent RLD update, NDA 022341/S-043 approved 11/1/2024.

The Prescribing Information is satisfactorily updated to be in accordance with the RLD.

Deficiency Comments:

5.5 MEDICATION GUIDE (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is up-to-date with model labeling.
☐	☒	Medication Guide meets content, format, and font size .
☐	☒	Phonetic spelling of the established/proprietary name is present and correct.
☐	☒	Description of child-resistant feature (if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	Revision date and approval statement appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a sufficient number of Medication Guides.
☐	☒	Applicant included the 1-800-FDA-1088 phone number.
☐	☒	Applicant included statement to print electronic Medication Guide if applicable.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

We have a comment regarding (b) (4). Please see below.

Assessment: The applicant satisfactorily addressed all comments.

Cycle #3:

The 6/30/2023 submission is provided due to an RLD update (b) (4) to the labeling.

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

MG is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises the DESCRIPTION section.

No revision to the MG or IFU noted.

C5 assessment:

The 11/5/2024 submission is provided to be in accordance with a recent RLD update, NDA 022341/S-043 approved 11/1/2024.

The Medication Guide is satisfactorily updated to be in accordance with the RLD.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C5)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The DCR review is pending.

Assessment:

The following IR was sent to the applicant on 3/4/2022 with regard to the IFU:

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product and we require additional information in order to complete our Clinical review.

1. We recommend that your proposed Instructions for Use (IFU) wording should reflect your proposed pen physical characteristics. We note that your proposed pen has a black line inside the dose display. In order for users to select the prescribed dose accurately using your proposed pen (and perform other tasks that rely upon the dose display) the black line needs to be lined up with the pointer by turning the dose selector. (b) (4)

IFU as follows:

- a. Revise Step C. Dial to the Flow Check Symbol to state, "Turn dose selector until the black line of flow check symbol [insert symbol] lines up with pointer (See Figure E)."
- b. Revise Step D. Prepare the Pen to state, "Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G)."
- c. Revise Step G. Dial the Dose to state:
 - i. "Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L)."
 - ii. "If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer."
- d. Revise Step H. (b) (4) to state, "Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M)."

2. (b) (4)

3. (b) (4) your proposed IFU states, "Liraglutide Injection pen should be used with compatible disposable needles." The labeling for your proposed product should provide clear information to help end users and pharmacists to identify pen needles that are compatible with your proposed pen. We recommend that you revise the carton labeling to state, "intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

4. Submit revised labeling to ensure that modifications in your proposed IFU and carton labeling are adequate based on the recommendations above. We refer you to the FDA Draft Guidance for Industry "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (January 2017).

The 3/11/2022 submission is in response to the DCR IR. The DCR review of the IR response is pending.

Cycle #3:

The DCR review (uploaded 5/22/2022) has no recommendations.

5 CONCLUSION

From a clinical safety perspective, there are minor and other acceptable design differences between the RLD and the proposed drug delivery device (color, dimensions, shape of pen; design of pen components - (b) (4)

Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a healthcare professional and/or without additional training prior to use of the generic combination product, and that the design differences as compared to RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug-device user interface for the proposed generic product acceptable.

6 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no recommendations/the following deficiencies:

- ☐ Major
☐ Minor
☒ N/A (Review is Adequate)

IFU is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises the DESCRIPTION section.

No revision to the MG or IFU noted.

C5 assessment:

No change is noted in the RLD's IFU with the most recent RLD update; therefore, no revision to subject ANDA's IFU is noted.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C5)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:



Esther
Kim

Digitally signed by Esther Kim
Date: 11/08/2024 11:11:53AM
GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo
Date: 11/08/2024 11:46:50AM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	April 9, 2024
ANDA Number(s)	215503
Review Number	4
Applicant Name	Hikma Pharmaceuticals USA Inc
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	NA
Submission Received Date	March 21, 2024
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
<u>1.1</u>	<u>LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u>
<u>1.2</u>	<u>COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>1.3</u>	<u>POST-APPROVAL REVISIONS</u>
<u>2</u>	<u>INSTRUCTIONS FOR ASSESSMENT</u>
<u>3</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>
<u>4</u>	<u>LABELING REVIEW INFORMATION</u>
<u>4.1</u>	<u>REGULATORY INFORMATION</u>
<u>4.2</u>	<u>MODEL PRESCRIBING INFORMATION</u>
<u>4.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>4.4</u>	<u>UNITED STATES PHARMACOPEIA (USP)</u>
<u>4.5</u>	<u>MODEL CONTAINER LABELS</u>
<u>5</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
<u>5.1</u>	<u>QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
<u>5.1.1</u>	<u>DRUG PRODUCT REVIEW</u>
<u>5.1.2</u>	<u>DESCRIPTION</u>
<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>INJECTABLE PRODUCTS</u>
<u>5.2.1.1</u>	<u>CONTAINER LABEL FOR PARENTERAL SOLUTIONS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>MEDICATION GUIDE</u>
<u>5.6</u>	<u>OTHER PATIENT LABELING</u>

1 **LABELING COMMENTS (C4)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)**

The Division of Labeling has no further questions/comments at this time based on your labeling submission received March 21, 2024.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C4)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C4)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA022341 / S-039

Supplement Approval Date: 07/05/2023

Proprietary Name: Victoza

Established Name: liraglutide injection

Description of Supplement:

This Prior Approval sNDA provides for the addition of "Nervous system disorders: dysgeusia" to section 6.2, Post-Marketing Experience, of the prescribing information (PI). During review of the supplement, the following additional changes were made:

- 'Ileus' was added to section 6.2 of the PI to align with other glucagon-like peptide (GLP) 1 products based on a Newly Identified Safety Signal (NISS) identified on June 15, 2022, for the risk of intestinal obstruction
- Dizziness was added to section 6.2
- Immunogenicity information was updated and relocated to section 12.6 to align with FDA guidance for industry, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format*

Link: <https://darts.fda.gov/darts/ViewDocument?documentId=090140af806dbe07>

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

S-040 is an approved CMC supplement that does not affect labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments: C4 assessment: The currently submitted labeling is up to date with the current RLD/Model labeling identified in the Model labeling section above.		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C4)

The [Orange Book](#) was searched on 04/09/2024

Table 4 provides Orange Book patents for the Model Labeling (NDA022341) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	6268343	08/22/2022	U-968	A METHOD FOR IMPROVING	III	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
				GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS			
18 mg/3 mL (6mg/mL)	7762994	05/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	7762994*PED	11/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833	08/13/2025			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833*PED	02/13/2026			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8579869	06/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8579869*PED	12/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618	06/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618*PED	12/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	9265893	09/23/2032			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9265893*PED	03/23/2033			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9968659	01/09/2037	U-2313	METHOD OF REDUCING THE RISK OF CARDIOVASCULAR DEATH, NON-FATAL MYOCARDIAL INFARCTION, AND/OR NON-FATAL STROKE IN ADULTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED CARDIOVASCULAR DISEASE BY ADMINISTERING LIRAGLUTIDE	viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	9968659*PED	07/09/2037			viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	RE41956	01/21/2021			II	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	RE41956*PED	07/21/2021			II	09/08/2021	Expired

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	NPP	06/17/2022	NEW PATIENT POPULATION	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	NPP PED	12/17/2022	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information	09/08/2021	Expired

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				associated with the listed exclusivities		

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments: Cycle #3: No change to patent certifications. The applicant provides the 12/19/2023 submission to provide a waiver granted by the sponsor of the RLD. Expired patents do not affect labeling. The 6/30/2023 submission is provided due to an RLD update (b) (4). C4 assessment: Expired patents do not affect labeling. Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)The [USP](#) was searched on 04/09/2024

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

C4 assessment:

No change noted

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: NDA 022341/S-028 approval letter in DARRTS dated 4/25/2017)

Syringe label for 2 Pens/Carton

Expiry/
Batch:

8-9695-31-
205-7

NDC 0169-4060-12

LIST 406012

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

REFRIGERATE BEFORE FIRST
USE – DO NOT FREEZE

Novo Nordisk Inc.
1-877-484-2869



1

Victoza®

(liraglutide) injection

18 mg/3 mL (6 mg/mL)

Use as directed by your healthcare professional.

See enclosed product literature.

Subcutaneous use only.

Rx Only



Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

**DO NOT TRANSFER THIS MEDICATION TO A
SYRINGE**

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE – DO NOT FREEZE

After first use, store at a temperature not to exceed

86°F (30°C).

Not a child-resistant container.

If the seal is broken before first use, contact your

pharmacist.

PATENT information: [http://novonordisk-](http://novonordisk-us.com/patients/products/product-patents.html)

[us.com/patients/products/product-patents.html](http://novonordisk-us.com/patients/products/product-patents.html)

Victoza® is a registered
trademark of Novo Nordisk A/S.
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Novo Nordisk Inc.

Plainsboro, NJ 08536

1-877-484-2869

(Se habla español)

www.victoza.com

Manufactured by:

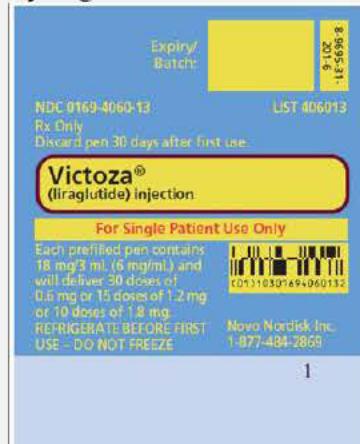
Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark





Syringe label for 3 Pens/Carton





5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

The screenshot of the labeling portion of the DP review is from the previously completed cycle. DP review to the CR response is pending.

A215503 Drug Product R02-IQ (archived 2/6/2024)

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☐ Yes ☒ No

If "No," explain.

(b) (4)

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES (All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")

1. In the Package Insert (PI) label, you stated (b) (4)

please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34."

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).
Previous ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH.
Current ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Assessment: No change noted

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16.1 How Supplied VICTOZA Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x VICTOZA pen NDC 0169-4060-12 3 x VICTOZA pen NDC 0169-4060-13 16.2 Recommended Storage Prior to first use, VICTOZA should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen. After first use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Previous ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03

Table 8: Comparison of Model Labeling to ANDA Labeling

	16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Current ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination. Assessment: No change noted

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan Factory) 2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan Factory) 2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922 Assessment: No change noted

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437].
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The container label is in line with the RLD; however, we have comments for the applicant. Please refer to section 5.2.1.1 below.

(b) (4)

Assessment: The applicant has satisfactorily addressed all comment. Container labels are found acceptable.
Previous labeling review:

(b) (4)

Currently proposed:



Cycle #3:

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

Additionally, the applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

From 6/30/2023 annotated SBS:

(b) (4)



(b) (4)

Container label is acceptable.

C4 assessment:
 Container label was found acceptable in the C3 review.
 Container label not submitted with the 3/21/2024 submission.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule over seal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is NA . NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Cycle #3:

Container is acceptable.

C4 assessment:

Container label was found acceptable in the C3 review.

Container label not submitted with the 3/21/2024 submission.

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, strength per fraction of a milliliter is the only expression of strength.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 1 CFR 201.100(b)(5)(iii) .
☐	☒	Container label includes instructions for reconstitution if applicable.
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information.

Reviewer Comments:

The RLD does not list the total quantity per total volume followed by the concentration per mL; however, we will request the addition of this to be in line with USP General Chapter <7> labeling.

Inactive ingredients are not listed on the container label but are listed on the carton labeling. This is in line with the RLD.

Cycle #3:

Container is acceptable

C4 assessment:

Container label was found acceptable in the C3 review.

Container label not submitted with the 3/21/2024 submission.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Unit-Dose Carton expression of strength appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Assessment:

The applicant provides carton labeling with the 1/13/2022 submission in response to the Labeling DRL and with the 3/11/2022 submission in response to a comment from DCR.

Comment to the applicant regarding carton labeling from DCR:

FDA Comment

Your proposed carton labeling states, (b) (4)

We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

Response:

The proposed carton labeling has been revised with "Intended for use with compatible disposable pen needles" as requested.

The carton labeling from the 3/11/2022 submission supersedes the carton labeling from the 1/13/2022 submission.

Previous labeling review:

1 Page has been withheld in full as b4 Draft Labeling

Liraglutide Injection

For Single Patient Use Only

18 mg/3 mL

(6 mg/mL)

Each pen delivers doses of 0.6 mg,
1.2 mg or 1.8 mg. Subcutaneous use only.

NDC 0143-9144-02
List XXXXX



Discard pen 30 days after first use
REFRIGERATE - DO NOT FREEZE
Rx only

Contains: 2 Liraglutide Injection Pens, Product Literature
Dispense the enclosed Medication Guide to each patient.
Intended for use with compatible disposable pen needles.

hikma.

(2 Pens)

Liraglutide Injection

For Single Patient Use Only

18 mg/3 mL

(6 mg/mL)

Each pen delivers doses of 0.6 mg,
1.2 mg or 1.8 mg. Subcutaneous use only.

NDC 0143-9144-03
List XXXXX



Discard pen 30 days after first use
REFRIGERATE - DO NOT FREEZE
Rx only

Contains: 3 Liraglutide Injection Pens, Product Literature
Dispense the enclosed Medication Guide to each patient.
Intended for use with compatible disposable pen needles.

hikma.

(3 Pens)

The applicant satisfactorily addressed all comments. Carton labeling is found acceptable.

Cycle #3:

The applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

(b) (4)



(b) (4)

(b) (4) The RLD does not include this information on the carton labeling; however, this information is provided in the DESCRIPTION section of the PI and ingredients section of the MG. As the information is accurate, the inclusion is acceptable. Carton labeling is acceptable.

C4 assessment:

Carton labeling was found acceptable in the C3 review.

Carton labeling not submitted with the 3/21/2024 submission.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20)

Deficiency	No Deficiency	
		☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		
Assessment: The applicant has satisfactorily addressed all comments.		
Cycle #3:		

(b) (4)

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

(b) (4)

(b) (4)

PI is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises the DESCRIPTION section.

From the 3/21/2024 cover letter response:

Labeling

In the Package Insert (PI) label,

(b) (4)
(b) (4)

please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34."

(b) (4) The package insert labeling has been revised in the Description section as requested. The following documents are provided in Module 1.14.

- [Package Insert Rev. 03/2024 \(Word Version\)](#)
- [Package Insert Rev. 03/2024 \(PDF Version\)](#)
- [Side-by-Side Comparison of Previously Submitted vs Current Package Insert](#)
- SPL

No other revision to the PI, MG, or IFU noted. The DP review of the applicant's response is pending approval.

Deficiency Comments:

5.5 MEDICATION GUIDE (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is up-to-date with model labeling.
☐	☒	Medication Guide meets content, format, and font size .
☐	☒	Phonetic spelling of the established/proprietary name is present and correct.
☐	☒	Description of child-resistant feature (if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	Revision date and approval statement appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a sufficient number of Medication Guides.
☐	☒	Applicant included the 1-800-FDA-1088 phone number.
☐	☒	Applicant included statement to print electronic Medication Guide if applicable.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4). Please see below.

Assessment: The applicant satisfactorily addressed all comments.

Cycle #3:

The 6/30/2023 submission is provided due to an RLD update (b) (4)

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

MG is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises (b) (4)

No revision to the MG or IFU noted.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The DCR review is pending.

Assessment:

The following IR was sent to the applicant on 3/4/2022 with regard to the IFU:

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product and we require additional information in order to complete our Clinical review.

1. We recommend that your proposed Instructions for Use (IFU) wording should reflect your proposed pen physical characteristics. We note that your proposed pen has a black line inside the dose display. In order for users to select the prescribed dose accurately using your proposed pen (and perform other tasks that rely upon the dose display) the black line needs to be lined up with the pointer by turning the dose selector. (b) (4)

We recommend that you revise the wording in your proposed IFU as follows:

- a. Revise Step C. Dial to the Flow Check Symbol to state, "Turn dose selector until the black line of flow check symbol [insert symbol] lines up with pointer (See Figure E)."
- b. Revise Step D. Prepare the Pen to state, "Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G)."
- c. Revise Step G. Dial the Dose to state,
 - i. "Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L)."
 - ii. "If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer."
- d. Revise Step H. (b) (4) to state, "Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M)."

2. (b) (4)

3. (b) (4)
your proposed IFU states, "Liraglutide Injection pen should be used with compatible disposable needles." The labeling for your proposed product should provide clear information to help end users and pharmacists to identify pen needles that are compatible with your proposed pen. We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

4. Submit revised labeling to ensure that modifications in your proposed IFU and carton labeling are adequate based on the recommendations above. We refer you to the FDA Draft Guidance for Industry "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (January 2017).

The 3/11/2022 submission is in response to the DCR IR. The DCR review of the IR response is pending.

Cycle #3:

The DCR review (uploaded 5/22/2022) has no recommendations.

5 CONCLUSION

From a clinical safety perspective, there are minor and other acceptable design differences between the RLD and the proposed drug delivery device (color, dimensions, shape of pen; design of pen components (b) (4)

Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a healthcare professional and/or without additional training prior to use of the generic combination product, and that the design differences as compared to RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug-device user interface for the proposed generic product acceptable.

6 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no recommendations/the following deficiencies:

- ☐ Major
☐ Minor
☒ N/A (Review is Adequate)

IFU is acceptable.

C4 assessment:

The 3/21/2024 submission is provided in response to CR and the applicant revises the DESCRIPTION section.

No revision to the MG or IFU noted.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other
Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)	
Reviewer Comments:	
Deficiency Comments:	



Esther
Kim

Digitally signed by Esther Kim
Date: 4/22/2024 03:58:19PM
GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo
Date: 4/22/2024 04:13:52PM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	January 4, 2024
ANDA Number(s)	215503
Review Number	3
Applicant Name	Hikma Pharmaceuticals USA Inc
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	NA
Submission Received Date	June 30, 2023, September 20, 2023
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
<u>1.1</u>	<u>LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u>
<u>1.2</u>	<u>COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>1.3</u>	<u>POST-APPROVAL REVISIONS</u>
<u>2</u>	<u>INSTRUCTIONS FOR ASSESSMENT</u>
<u>3</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>
<u>4</u>	<u>LABELING REVIEW INFORMATION</u>
<u>4.1</u>	<u>REGULATORY INFORMATION</u>
<u>4.2</u>	<u>MODEL PRESCRIBING INFORMATION</u>
<u>4.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>4.4</u>	<u>UNITED STATES PHARMACOPEIA (USP)</u>
<u>4.5</u>	<u>MODEL CONTAINER LABELS</u>
<u>5</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
<u>5.1</u>	<u>QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
<u>5.1.1</u>	<u>DRUG PRODUCT REVIEW</u>
<u>5.1.2</u>	<u>DESCRIPTION</u>
<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>INJECTABLE PRODUCTS</u>
<u>5.2.1.1</u>	<u>CONTAINER LABEL FOR PARENTERAL SOLUTIONS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>MEDICATION GUIDE</u>
<u>5.6</u>	<u>OTHER PATIENT LABELING</u>

1 **LABELING COMMENTS (C3)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)**

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received June 30, 2023, September 20, 2023.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C3)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C3)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA022341 / S-039

Supplement Approval Date: 07/05/2023

Proprietary Name: Victoza

Established Name: liraglutide injection

Description of Supplement:

This Prior Approval sNDA provides for the addition of "Nervous system disorders: dysgeusia" to section 6.2, Post-Marketing Experience, of the prescribing information (PI). During review of the supplement, the following additional changes were made:

- 'Ileus' was added to section 6.2 of the PI to align with other glucagon-like peptide (GLP) 1 products based on a Newly Identified Safety Signal (NISS) identified on June 15, 2022, for the risk of intestinal obstruction
- Dizziness was added to section 6.2
- Immunogenicity information was updated and relocated to section 12.6 to align with FDA guidance for industry, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling--Content and Format*

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=5202552_4802369_090140af806dbe07_NDA022341_3580446

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

S-040 is an approved CMC supplement that does not affect labeling.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C3)

The [Orange Book](#) was searched on 01/04/2024

Table 4 provides Orange Book patents for the Model Labeling (NDA022341) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	6268343	08/22/2022	U-968	A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH	III	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
				TYPE 2 DIABETES MELLITUS			
18 mg/3 mL (6 mg/mL)	6268343*PED	02/22/2023			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	7762994	05/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	7762994*PED	11/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833	08/13/2025			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833*PED	02/13/2026			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8579869	06/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8579869*PED	12/30/2023			IV	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618	06/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	8846618*PED	12/27/2022			III	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	9265893	09/23/2032			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9265893*PED	03/23/2033			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9968659	01/09/2037	U-2313	METHOD OF REDUCING THE RISK OF CARDIOVASCULAR DEATH, NON-FATAL MYOCARDIAL INFARCTION, AND/OR NON-FATAL STROKE IN ADULTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED CARDIOVASCULAR DISEASE BY ADMINISTERING LIRAGLUTIDE	viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	9968659*PED	07/09/2037			viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	RE41956	01/21/2021			II	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	RE41956*PED	07/21/2021			II	09/08/2021	Expired

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	NPP	06/17/2022	NEW PATIENT POPULATION	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Expired
18 mg/3 mL (6mg/mL)	NPP PED	12/17/2022	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Expired

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments: Cycle #3: No change to patent certifications. The applicant provides the 12/19/2023 submission to provide a waiver granted by the sponsor of the RLD. Expired patents do not affect labeling. The 6/30/2023 submission is provided due to an RLD update (b) (4)		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The [USP](#) was searched on 01/04/2024

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments:		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C3)

Model container/carton/blister labels (Source: NDA 022341/S-028 approval letter in DARRTS dated 4/25/2017)

Syringe label for 2 Pens/Carton

Expiry/
Batch:

8-9695-31-
205-7

NDC 0169-4060-12

LIST 406012

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

REFRIGERATE BEFORE FIRST
USE - DO NOT FREEZE



Novo Nordisk Inc.
1-877-484-2869

1

Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only.
Rx Only



Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

**DO NOT TRANSFER THIS MEDICATION TO A
SYRINGE**

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE - DO NOT FREEZE

After first use, store at a temperature not to exceed
86°F (30°C).

Not a child-resistant container.
If the seal is broken before first use, contact your
pharmacist.

PATENT information: [http://novonordisk-
us.com/patients/product/product-patents.html](http://novonordisk-us.com/patients/product/product-patents.html)

Victoza® is a registered
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Novo Nordisk Inc.
Plainsboro, NJ 08536
1-877-484-2869
(Se habla español)

www.victoza.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark





Syringe label for 3 Pens/Carton

Expiry/
Batch:

8-9695-31-
201-6

NDC 0169-4060-13

LIST 406013

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

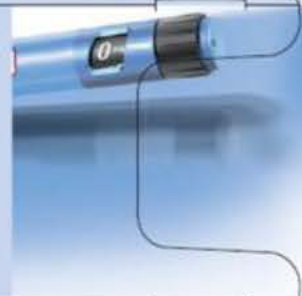
Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

REFRIGERATE BEFORE FIRST
USE – DO NOT FREEZE



Novo Nordisk Inc.
1-877-484-2869

1



Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only.
Rx Only



Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE – DO NOT FREEZE

After first use, store at a temperature not to exceed
96°F (30°C).

Not a child-resistant container.
If the seal is broken before first use, contact your
pharmacist.

PATENT Information: <http://novonordisk-us.com/patients/products/product-patents.html>
Victoza® is a registered
trademark of Novo Nordisk A/S.

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Novo Nordisk Inc.
Plainsboro, NJ 08536
1-877-484-2869
(Se habla español)

www.victoza.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark





5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

The screenshot of the labeling portion of the DP review is from the previously completed cycle. DP review to the CR response is pending.

A215503 Drug Product R01a-IQ

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

(b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☐ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: NA

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).
Previous ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH.
Current ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Assessment: No change noted

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16.1 How Supplied VICTOZA Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x VICTOZA pen NDC 0169-4060-12 3 x VICTOZA pen NDC 0169-4060-13 16.2 Recommended Storage Prior to first use, VICTOZA should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen. After first use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Previous ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02

Table 8: Comparison of Model Labeling to ANDA Labeling	
	3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Current ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination. Assessment: No change noted

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C3)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China. Distributed by: Hikma Pharmaceuticals USA Inc.

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	Berkeley Heights, NJ 07922
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan Factory) 2nd Ruhui Rd. Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922 Assessment: No change noted

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	Manufactured for	Distributed by	Distributed for

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.].
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		

Deficiency	No Deficiency	
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure, cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The container label in in line with the RLD; however, we have comments for the applicant. Please refer to section 5.2.1.1 below. (b) (4)		
Assessment: The applicant has satisfactorily addressed all comment. Container labels are found acceptable. Previous labeling review: (b) (4)		
Currently proposed:		



Cycle #3:

The 6/30/2023 submission is provided due to an RLD update (b) (4)

Additionally, the applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

From 6/30/2023 annotated SBS:

(b) (4)



Container label is acceptable.

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is NA . NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.
Reviewer Comments: Cycle #3: Container is acceptable. Deficiency Comments:		

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, strength per fraction of a milliliter is the only expression of strength.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 1 CFR 201.100(b)(5)(iii) .
☐	☒	Container label includes instructions for reconstitution if applicable.
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information.
Reviewer Comments: The RLD does not list the total quantity per total volume followed by the concentration per mL; however, we will request the addition of this to be in line with USP General Chapter <7> labeling. Inactive ingredients are not listed on the container label but are listed on the carton labeling. This is in line with the RLD. Cycle #3: Container is acceptable Deficiency Comments:		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Unit-Dose Carton expression of strength appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: Assessment: The applicant provides carton labeling with the 1/13/2022 submission in response to the Labeling DRL and with the 3/11/2022 submission in response to a comment from DCR. Comment to the applicant regarding carton labeling from DCR:		

FDA Comment

Your proposed carton labeling states,

(b) (4)

We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

Response:

The proposed carton labeling has been revised with "Intended for use with compatible disposable pen needles" as requested.

The carton labeling from the 3/11/2022 submission supersedes the carton labeling from the 1/13/2022 submission.

Previous labeling review:

(b) (4)

Currently proposed:

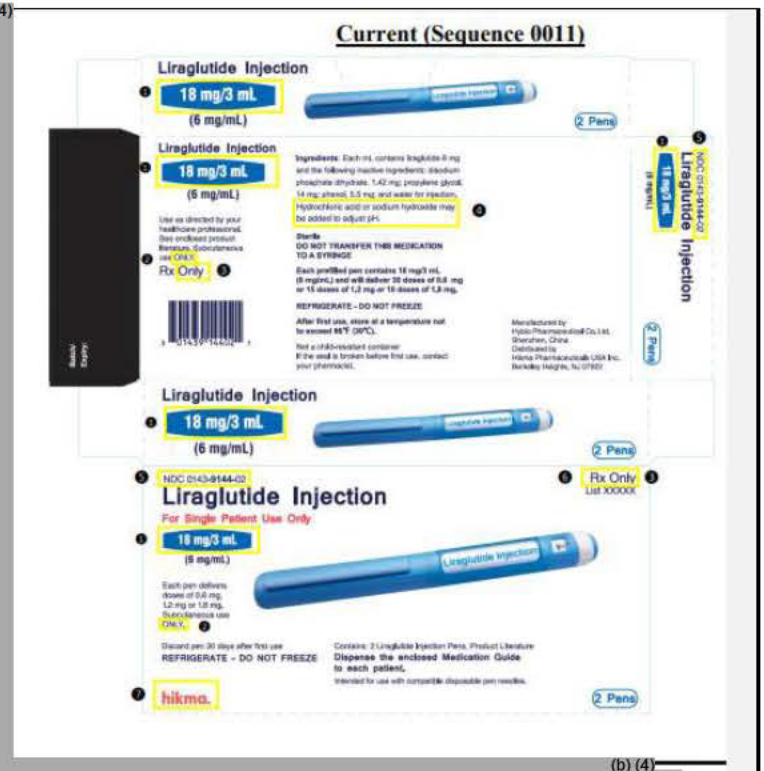


The applicant satisfactorily addressed all comments. Carton labeling is found acceptable.

Cycle #3:

The applicant updates the container and carton labeling to "align with current RLD labeling and current Hikma trade dress."

(b) (4)



(b) (4)

(b) (4). The RLD does not include this information on the carton labeling; however, this information is provided in the DESCRIPTION section of the PI and ingredients section of the MG. As the information is accurate, the inclusion is acceptable. Carton labeling is acceptable.

Deficiency Comments:

5.4 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].

Deficiency	No Deficiency	
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4)

Assessment: The applicant has satisfactorily addressed all comments.

Cycle #3:

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

(b) (4)

(b) (4)

PI is acceptable.

Deficiency Comments:
Deficiency # 1

Created in C1

Prescribing Information

(b) (4)

Response / Assessment:

Addressed

5.5 MEDICATION GUIDE (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is up-to-date with model labeling.
☐	☒	Medication Guide meets content, format, and font size .
☐	☒	Phonetic spelling of the established/proprietary name is present and correct.
☐	☒	Description of child-resistant feature (if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	Revision date and approval statement appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a sufficient number of Medication Guides.
☐	☒	Applicant included the 1-800-FDA-1088 phone number.
☐	☒	Applicant included statement to print electronic Medication Guide if applicable.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4) . Please see below.

Assessment: The applicant satisfactorily addressed all comments.

Cycle #3:

The 6/30/2023 submission is provided due to an RLD update

(b) (4)

The 9/20/2023 submission is provided due to RLD update, NDA 022341/S-039. The PI, MG, and IFU from this submission supersedes the PI, MG, and IFU from the 6/30/2023 submission.

MG is acceptable.

Deficiency Comments:

5.6 OTHER PATIENT LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The DCR review is pending.

Assessment:

The following IR was sent to the applicant on 3/4/2022 with regard to the IFU:

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product and we require additional information in order to complete our Clinical review.

1. We recommend that your proposed Instructions for Use (IFU) wording should reflect your proposed pen physical characteristics. We note that your proposed pen has a black line inside the dose display. In order for users to select the prescribed dose accurately using your proposed pen (and perform other tasks that rely upon the dose display) the black line needs to be lined up with the pointer by turning the dose selector. (b) (4)

L I

We recommend that you revise the wording in your proposed IFU as follows:

- a. Revise Step C. Dial to the Flow Check Symbol to state, "Turn dose selector until the black line of flow check symbol [insert symbol] lines up with pointer (See Figure E)."
 - b. Revise Step D. Prepare the Pen to state, "Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G)."
 - c. Revise Step G. Dial the Dose to state,
 - i. "Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L)."
 - ii. "If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer."
 - d. Revise Step H. (b) (4) to state, "Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M)."
2. (b) (4)
 3. (b) (4) your proposed IFU states, "Liraglutide Injection pen should be used with compatible disposable needles." The labeling for your proposed product should provide clear information to help end users and pharmacists to identify pen needles that are compatible with your proposed pen. We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.
 4. Submit revised labeling to ensure that modifications in your proposed IFU and carton labeling are adequate based on the recommendations above. We refer you to the FDA Draft Guidance for Industry "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (January 2017).

The 3/11/2022 submission is in response to the DCR IR. The DCR review of the IR response is pending.

Cycle #3:

The DCR review (uploaded 5/22/2022) has no recommendations.

5 CONCLUSION

From a clinical safety perspective, there are minor and other acceptable design differences between the RLD and the proposed drug delivery device (color, dimensions, shape of pen; design of pen components - (b) (4)

Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a healthcare professional and/or without additional training prior to use of the generic combination product, and that the design differences as compared to RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug-device user interface for the proposed generic product acceptable.

6 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative analyses and has no recommendations/the following deficiencies:

- ☐ Major
☐ Minor
☒ N/A (Review is Adequate)

IFU is acceptable.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:



Esther
Kim

Digitally signed by Esther Kim
Date: 1/05/2024 12:47:13PM
GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo
Date: 1/19/2024 08:20:16AM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/07/2022
ANDA Number(s)	215503
Review Number	2
Applicant Name	Hikma Pharmaceuticals USA Inc
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens
Proposed Proprietary Name	NA
Submission Received Date	January 13, 2022, March 11, 2022
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
<u>1.1</u>	<u>LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u>
<u>1.2</u>	<u>COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>1.3</u>	<u>POST-APPROVAL REVISIONS</u>
<u>2</u>	<u>INSTRUCTIONS FOR ASSESSMENT</u>
<u>3</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>
<u>4</u>	<u>LABELING REVIEW INFORMATION</u>
<u>4.1</u>	<u>REGULATORY INFORMATION</u>
<u>4.2</u>	<u>MODEL PRESCRIBING INFORMATION</u>
<u>4.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>4.4</u>	<u>UNITED STATES PHARMACOPEIA (USP)</u>
<u>4.5</u>	<u>MODEL CONTAINER LABELS</u>
<u>5</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
<u>5.1</u>	<u>QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
<u>5.1.1</u>	<u>DRUG PRODUCT REVIEW</u>
<u>5.1.2</u>	<u>DESCRIPTION</u>
<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>INJECTABLE PRODUCTS</u>
<u>5.2.1.1</u>	<u>CONTAINER LABEL FOR PARENTERAL SOLUTIONS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>MEDICATION GUIDE</u>
<u>5.6</u>	<u>OTHER PATIENT LABELING</u>

1 **LABELING COMMENTS (C2)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)**

The Division of Labeling has no further questions/comments at this time based on your labeling submissions received January 13, 2022 and March 11, 2022.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C2)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C2)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

Deficiency Comments:

Creation Cycle	Category	Deficiency	Response/Assessment	Post Approval
OT	Quality	Normal Text A B C D E F G H I J	Response/Assessment	Post Approval

[Add Deficiency](#)

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	6 mg/mL – 3 mL Prefilled Pen	1/13/2022	Satisfactory
Blister	N/A	N/A		
Carton	Final	Carton of 2 Prefilled Pens Carton of 3 Prefilled Pens	3/11/2022	Satisfactory
Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 03/2022	3/11/2022	Satisfactory
Medication Guide	Draft	Revised: March 2022	3/11/2022	Satisfactory
Patient Information	N/A	NA		
Instructions for Use	Draft	Revised: March 2022	3/11/2022	Satisfactory
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? Controlled Correspondence: (b) (4) Completed
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? (b) (5)

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA022341 / S-036

Supplement Approval Date: 11/20/2020

Proprietary Name: Victoza

Established Name: liraglutide injection

Description of Supplement:

This Prior Approval sNDA provides for the addition of information regarding severe hypoglycemia to Sections 5, 10, and 17, of the Prescribing Information and to the Medication Guide.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4705241_4293882_090140af805af7f4_NDA022341_3108918

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

BPCA template (b) (4) (based on NDA 022341/S-031 approved 6/17/2019).

S-037 is a pending labeling supplement that proposes changes to the approved labeling in accordance with the requests below:

In the last bullet of section 6.3 Postmarketing Experience, add the text underlined below:

- Hepatobiliary disorders: hyperbilirubinemia, elevations of liver enzymes, cholestasis, hepatitis

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C2)

The [Orange Book](#) was searched on 04/07/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA022341) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	6268343	08/22/2022	U-968	A METHOD FOR IMPROVING GLYCEMIC CONTROL IN	III	09/08/2021	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
				ADULTS WITH TYPE 2 DIABETES MELLITUS			
18 mg/3 mL (6 mg/mL)	6268343*PED	02/22/2023			III	09/08/2021	None
18 mg/3 mL (6mg/mL)	7762994	05/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	7762994*PED	11/23/2024			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833	08/13/2025			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8114833*PED	02/13/2026			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8579869	06/30/2023			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8579869*PED	12/30/2023			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	8846618	06/27/2022			III	09/08/2021	None
18 mg/3 mL (6mg/mL)	8846618*PED	12/27/2022			III	09/08/2021	None
18 mg/3 mL (6mg/mL)	9265893	09/23/2032			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9265893*PED	03/23/2033			IV	09/08/2021	None
18 mg/3 mL (6mg/mL)	9968659	01/09/2037	U-2313	METHOD OF REDUCING THE RISK OF CARDIOVASCULAR DEATH, NON-FATAL MYOCARDIAL INFARCTION, AND/OR NON-FATAL STROKE IN ADULTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED CARDIOVASCULAR DISEASE BY ADMINISTERING LIRAGLUTIDE	viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	9968659*PED	07/09/2037			viii	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	RE41956	01/21/2021			II	09/08/2021	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	RE41956*PED	07/21/2021			II	09/08/2021	Expired

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
18 mg/3 mL (6mg/mL)	NPP	06/17/2022	NEW PATIENT POPULATION	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	NPP PED	12/17/2022	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information	09/08/2021	Carve-out

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
				associated with the listed exclusivities		

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments:		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The [USP](#) was searched on 04/08/2022

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments:		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: NDA 022341/S-028 approval letter in DARRTS dated 4/25/2017)

Syringe label for 2 Pens/Carton

Expiry/
Batch:

8-9695-31-
205-7

NDC 0169-4060-12

LIST 406012

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

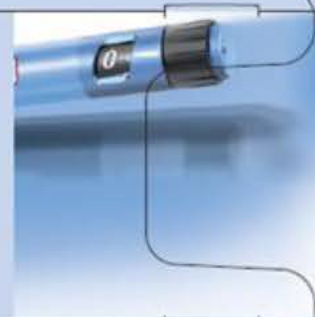
REFRIGERATE BEFORE FIRST
USE – DO NOT FREEZE



(01)10301694060125

Novo Nordisk Inc.
1-877-484-2869

1



Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only
Rx Only



01694 06012 8

Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

**DO NOT TRANSFER THIS MEDICATION TO A
SYRINGE**

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE – DO NOT FREEZE

After first use, store at a temperature not to exceed
86°F (30°C).

Not a child-resistant container
If the seal is broken before first use, contact your
pharmacist.

PATENT Information: [http://novonordisk-
us.com/patients/products/product-patents.html](http://novonordisk-us.com/patients/products/product-patents.html)

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Novo Nordisk Inc.
Plainsboro, NJ 08536

1-877-484-2869
(Se habla español)

www.victoza.com

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark



00 | - |



Syringe label for 3 Pens/Carton

Expiry/
Batch:

8-9695-31-
201-6

NDC 0169-4060-13

LIST 406013

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.

REFRIGERATE BEFORE FIRST
USE - DO NOT FREEZE

Novo Nordisk Inc.
1-877-484-2869



1

Victoza®
(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only.
Rx Only



Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: disodium
phosphate dihydrate, 1.42 mg; propylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.

Sterile

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE

Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE - DO NOT FREEZE

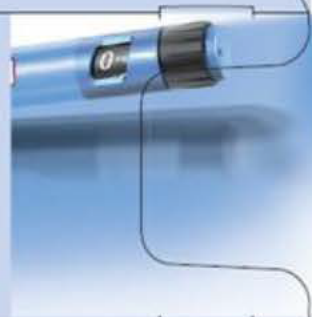
After first use, store at a temperature not to exceed
96°F (30°C).

Not a child-resistant container.
If the seal is broken before first use, contact your
pharmacist.

PATENT information: <http://novonordisk-us.com/patients/products/product-patents.html>

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Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark





5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

A215503 Drug Product R01-IQ (pending approval)

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in
DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for
Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No," what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent
compatibility studies)? ☒ Yes ☐ No ☐ N/A

(b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC
products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☐ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial
batch(es): NA

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling Assessor through the Platform with a list of
quality-related labeling deficiencies and also record reference number or link
for all the issues: NA

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).
Previous ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous).
Current ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous). Assessment: No change noted

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16.1 How Supplied VICTOZA Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x VICTOZA pen NDC 0169-4060-12 3 x VICTOZA pen NDC 0169-4060-13 16.2 Recommended Storage Prior to first use, VICTOZA should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen. After first use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Previous ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-XXXX-02

Table 8: Comparison of Model Labeling to ANDA Labeling	
	3 x Liraglutide Injection pen NDC 0143-XXXX-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Current ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-9144-02 3 x Liraglutide Injection pen NDC 0143-9144-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination. Assessment: NDC numbers are provided. Acceptable

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China. (b) (4) Distributed by:

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

	Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China. Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922 (b) (4) . Acceptable

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437].
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.

Deficiency	No Deficiency	
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6)] or 21 CFR 201.1(i)] .
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The container label in in line with the RLD; however, we have comments for the applicant. Please refer to section 5.2.1.1 below. (b) (4)		
Assessment: The applicant has satisfactorily addressed all comment. Container labels are found acceptable. Previous labeling review: (b) (4)		
Currently proposed:		



Deficiency Comments:

Deficiency # 1

Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).

Created in C1

Container Label

Response / Assessment:

Addressed

Deficiency # 2

Created in C1

General Comments

Response / Assessment:

Addressed on container, carton , and PI.

Deficiency # 3

Provide the revised container label and carton labeling in higher resolution.

Created in C1

General Comments

Response / Assessment:

Addressed

5.2.1 INJECTABLE PRODUCTS (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is NA . NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, strength per fraction of a milliliter is the only expression of strength.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 1 CFR 201.100(b)(5)(iii) .
☐	☒	Container label includes instructions for reconstitution if applicable.
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information.

Reviewer Comments:

The RLD does not list the total quantity per total volume followed by the concentration per mL; however, we will request the addition of this to be in line with USP General Chapter <7> labeling.

Inactive ingredients are not listed on the container label but are listed on the carton labeling. This is in line with the RLD.

Deficiency Comments:

Deficiency # 1

Created in C1

Container Label

Include the strength statement such that the total strength per total volume is the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses, as described in the USP, General Chapter <7> Labeling. For example:

18 mg/3 mL

(6 mg/mL)

Response / Assessment:

Addressed

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Assessment:

The applicant provides carton labeling with the 1/13/2022 submission in response to the Labeling DRL and with the 3/11/2022 submission in response to a comment from DCR.

Comment to the applicant regarding carton labeling from DCR:

FDA Comment

Your proposed carton labeling states,

(b) (4)

We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.

Response:

The proposed carton labeling has been revised with "Intended for use with compatible disposable pen needles" as requested.

The carton labeling from the 3/11/2022 submission supersedes the carton labeling from the 1/13/2022 submission.

Previous labeling review:

(b) (4)

Currently proposed:

Liraglutide Injection For Single Patient Use Only 18 mg/3 mL (6 mg/mL) Each pen delivers doses of 0.6 mg, 1.2 mg or 1.8 mg. Subcutaneous use only.  Discard pen 30 days after first use REFRIGERATE - DO NOT FREEZE Rx only Contains: 2 Liraglutide Injection Pens, Product Literature Dispense the enclosed Medication Guide to each patient. Intended for use with compatible disposable pen needles. hikma. 2 Pens	NDC 0143-9144-02 List XXXXX
Liraglutide Injection For Single Patient Use Only 18 mg/3 mL (6 mg/mL) Each pen delivers doses of 0.6 mg, 1.2 mg or 1.8 mg. Subcutaneous use only.  Discard pen 30 days after first use REFRIGERATE - DO NOT FREEZE Rx only Contains: 3 Liraglutide Injection Pens, Product Literature Dispense the enclosed Medication Guide to each patient. Intended for use with compatible disposable pen needles. hikma. 3 Pens	NDC 0143-9144-03 List XXXXX
The applicant satisfactorily addressed all comments. Carton labeling is found acceptable.	
Deficiency Comments: Deficiency # 1 Created in C1 Carton Labeling Response / Assessment:	Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Addressed
Deficiency # 2 Created in C1 Carton Labeling Response / Assessment:	We recommend revising the "For Single Patient Use Only" statement on the PDP to use red font to be in accordance with the RLD. Addressed
Deficiency # 3 Created in C1 Carton Labeling Response / Assessment:	Strength statement: We recommend increasing the prominence of "18 mg/3 mL" on the PDP. Addressed

5.4 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at end of HIGHLIGHTS section.
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	Dosage form and route of administration properly listed [21 CFR 201.57(c)(12)(B)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4)

Assessment: The applicant has satisfactorily addressed all comments.

Deficiency Comments:

Deficiency # 1

Created in C1

Prescribing Information

Response / Assessment:

Addressed

(b) (4)

Deficiency # 2

Created in C1

Prescribing Information

Response / Assessment:

HIGHLIGHTS/INDICATIONS AND USAGE, first bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (1)."

Addressed

Deficiency # 3

Created in C1

Prescribing Information

Response / Assessment:

HIGHLIGHTS: Revise (b) (4) to read "See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide."

Addressed

Deficiency # 4

Created in C1

Prescribing Information

Response / Assessment:

Addressed

(b) (4)

Deficiency # 5

Created in C1

Prescribing Information

Response / Assessment:

1 INDICATIONS AND USAGE:

- Bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus".
- (b) (4)

Deficiency # 6

Created in C1

Prescribing Information

Response / Assessment:

Addressed

(b) (4)

Deficiency # 7

Created in C1

Prescribing Information

6.1 Clinical Trials Experience:
Common Adverse Reactions

- First paragraph, first sentence: Revise to read, "The safety of Liraglutide Injection in subjects with type 2 diabetes was evaluated in 5 glycemic control, placebo-controlled trials in adults [see Clinical Studies (14.1)].

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

(b) (4)

Response / Assessment:

Addressed

Deficiency # 8

Created in C1

Prescribing Information

(b) (4)

Response / Assessment:

Addressed

Deficiency # 9	(b) (4) Immunogenicity:
Created in C1	(b) (4)
Prescribing Information	
	Of the 11 Liraglutide Injection-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1. In a clinical trial with pediatric patients 10 to 17 years [see Clinical Studies (14.2)], anti-liraglutide antibodies were detected in 1 (1.5%) Liraglutide Injection treated patient at week 26 and 5 (8.5%) Liraglutide Injection treated patients at week 53. None of the 5 had antibodies cross reactive to native GLP-1 or had neutralizing antibodies. " (b) (4)
Response / Assessment:	Addressed
Deficiency # 10	(b) (4)
Created in C1	
Prescribing Information	
Response / Assessment:	Addressed
Deficiency # 11	(b) (4)
Created in C1	
Prescribing Information	
Response / Assessment:	Addressed
Deficiency # 12	14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus, Table 3: Revise (b) (4) to read "-0.3*" and (b) (4) to read "-10*" in the "Liraglutide Injection 1.2 (b) (4)" column, (b) (4)
Created in C1	
Prescribing Information	
Response / Assessment:	Addressed
Deficiency # 13	(b) (4)
Created in C1	
Prescribing Information	
Response / Assessment:	Addressed

Deficiency # 14	HIGHLIGHTS/Title: Revise to read " LIRAGLUTIDE injection, for subcutaneous use ".
Created in C1	
Prescribing Information Response / Assessment:	Addressed
Deficiency # 15	(b) (4)
Created in C1	
Prescribing Information Response / Assessment:	Addressed
Deficiency # 16	(b) (4)
Created in C1	
Prescribing Information Response / Assessment:	Addressed
Deficiency # 17	(b) (4)
Created in C1	
Prescribing Information Response / Assessment:	Addressed
Deficiency # 18	(b) (4)
Created in C1	
Prescribing Information Response / Assessment:	Addressed
Deficiency # 19	(b) (4)
Created in C1	
Prescribing Information	
Response / Assessment:	Addressed
Deficiency # 20	(b) (4)
Created in C1	
Prescribing Information	

		(b) (4)
Response / Assessment:	Addressed	
Deficiency # 21	16 HOW SUPPLIED/ STORAGE AND HANDLING: Include the NDC numbers. If the NDC numbers are not available at the time of approval, consider stating "NDC numbers pending". We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.	
Created in C1		
Prescribing Information		
Response / Assessment:	Addressed	

5.5 MEDICATION GUIDE (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is up-to-date with model labeling.
☐	☒	Medication Guide meets content, format, and font size .
☐	☒	Phonetic spelling of the established/proprietary name is present and correct.
☐	☒	Description of child-resistant feature (if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	Revision date and approval statement appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a sufficient number of Medication Guides.
☐	☒	Applicant included the 1-800-FDA-1088 phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4) Please see below.

Assessment: The applicant satisfactorily addressed all comments.

Deficiency Comments:

Deficiency # 1 Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).

Created in C1

Medication Guide

Response / Assessment: Addressed

Deficiency # 2

Created in C1

Medication Guide

Response / Assessment: Addressed

Deficiency # 3	(b) (4)
Created in C1	
General Comments	
Response / Assessment:	Addressed

Deficiency # 4	(b) (4)
Created in C1	
Medication Guide	
Response / Assessment:	Addressed

Deficiency # 5	(b) (4)
Created in C1	
Medication Guide	
Response / Assessment:	Addressed

5.6 OTHER PATIENT LABELING (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

The DCR review is pending.

Assessment:

The following IR was sent to the applicant on 3/4/2022 with regard to the IFU:

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product and we require additional information in order to complete our Clinical review.

1. We recommend that your proposed Instructions for Use (IFU) wording should reflect your proposed pen physical characteristics. We note that your proposed pen has a black line inside the dose display. In order for users to select the prescribed dose accurately using your proposed pen (and perform other tasks that rely upon the dose display) the black line needs to be lined up with the pointer by turning the dose selector. (b) (4)

(b) (4)

We recommend that you revise the wording in your proposed IFU as follows:

- a. Revise Step C. Dial to the Flow Check Symbol to state, "Turn dose selector until the black line of flow check symbol [insert symbol] lines up with pointer (See Figure E)."
- b. Revise Step D. Prepare the Pen to state, "Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G)."
- c. Revise Step G. Dial the Dose to state,
 - i. "Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L)."
 - ii. "If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer."
- d. Revise Step H. (b) (4) to state, "Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M)."

2. (b) (4)

3. (b) (4)
 your proposed IFU states, "Liraglutide Injection pen should be used with compatible disposable needles." The labeling for your proposed product should provide clear information to help end users and pharmacists to identify pen needles that are compatible with your proposed pen. We recommend that you revise the carton labeling to state, "Intended for use with compatible disposable pen needles" to be consistent with your proposed IFU.
4. Submit revised labeling to ensure that modifications in your proposed IFU and carton labeling are adequate based on the recommendations above. We refer you to the FDA Draft Guidance for Industry "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (January 2017).

The 3/11/2022 submission is in response to the DCR IR. The DCR review of the IR response is pending.

Deficiency Comments:

Deficiency # 1

Created in C1

Instructions for use

Response / Assessment:

Addressed

Deficiency # 2

Add the revision date to the end of the Instructions for Use.

Created in C1

Instructions for use

Response / Assessment:

Addressed

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)

☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other
Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)	
Reviewer Comments:	
Deficiency Comments:	



Esther
Kim

Digitally signed by Esther Kim
Date: 4/08/2022 12:18:51PM
GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo
Date: 5/09/2022 08:44:07PM
GUID: 508da73d0002b687dfbf9b3859d80789

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	11/05/2021
ANDA Number(s)	215503
Review Number	1
Applicant Name	Hikma Pharmaceuticals USA Inc
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Prefilled Pens
Proposed Proprietary Name	NA
Submission Received Date	September 08, 2021
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Ellen Koo
Review Conclusion ☐ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
<u>1.1</u>	<u>LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u>
<u>1.2</u>	<u>COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>1.3</u>	<u>POST-APPROVAL REVISIONS</u>
<u>2</u>	<u>INSTRUCTIONS FOR ASSESSMENT</u>
<u>3</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>
<u>4</u>	<u>LABELING REVIEW INFORMATION</u>
<u>4.1</u>	<u>REGULATORY INFORMATION</u>
<u>4.2</u>	<u>MODEL PRESCRIBING INFORMATION</u>
<u>4.3</u>	<u>PATENTS AND EXCLUSIVITIES</u>
<u>4.4</u>	<u>UNITED STATES PHARMACOPEIA (USP)</u>
<u>4.5</u>	<u>MODEL CONTAINER LABELS</u>
<u>5</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
<u>5.1</u>	<u>QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
<u>5.1.1</u>	<u>DRUG PRODUCT REVIEW</u>
<u>5.1.2</u>	<u>DESCRIPTION</u>
<u>5.1.3</u>	<u>HOW SUPPLIED/STORAGE AND HANDLING</u>
<u>5.1.4</u>	<u>MANUFACTURER, DISTRIBUTOR, AND/OR PACKER</u>
<u>5.2</u>	<u>CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)</u>
<u>5.2.1</u>	<u>INJECTABLE PRODUCTS</u>
<u>5.2.1.1</u>	<u>CONTAINER LABEL FOR PARENTERAL SOLUTIONS</u>
<u>5.3</u>	<u>CARTON (OUTER OR SECONDARY PACKAGING) LABELING</u>
<u>5.4</u>	<u>PRESCRIBING INFORMATION</u>
<u>5.5</u>	<u>MEDICATION GUIDE</u>
<u>5.6</u>	<u>OTHER PATIENT LABELING</u>

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling deficiencies based on your submission received September 8, 2021:

1. GENERAL COMMENTS

a. Provide the revised container label and carton labeling in higher resolution.

b. [REDACTED] (b) (4)

c. [REDACTED] (b) (4)

2. CONTAINER LABEL

a. Include the strength statement such that the total strength per total volume is the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses, as described in the USP, General Chapter <7> Labeling. For example:

18 mg/3 mL

(6 mg/mL)

b. Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).

3. CARTON LABELING

a. Strength statement: We recommend increasing the prominence of "18 mg/3 mL" on the PDP.

b. We recommend revising the "For Single Patient Use Only" statement on the PDP to use red font to be in accordance with the RLD.

c. Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).

4. PRESCRIBING INFORMATION

a. HIGHLIGHTS OF PRESCRIBING INFORMATION

i. Title: Revise to read "**LIRAGLUTIDE injection, for subcutaneous use**".

ii. INDICATIONS AND USAGE, first bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (1)."

iii. [REDACTED] (b) (4)

iv. [REDACTED] (b) (4)

v. Revise [REDACTED] (b) (4)
[REDACTED] to read "See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide."

vi. [REDACTED] (b) (4)

b. [REDACTED] (b) (4)

c. 1 INDICATIONS AND USAGE:

- Bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus".
- (b) (4)

d. (b) (4)

e. 5.4 Hypoglycemia:

- (b) (4)
- (b) (4)

f. 5.7 Acute Gallbladder Disease: (b) (4)

g. 6.1 Clinical Trials Experience:

▪ Common Adverse Reactions

- (b) (4)
- (b) (4)

▪ Other Adverse Reactions

- Hypoglycemia: (b) (4)
No severe hypoglycemic episodes occurred in the Liraglutide Injection treatment group (severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions).
- Cholelithiasis and cholecystitis: (b) (4)

▪ Laboratory Tests/Lipase and Amylase: (b) (4)

h. 6.2 Immunogenicity:

■ (b) (4) (b) (4)

i. 8.4 Pediatric Use:

■ (b) (4)

■ (b) (4)

j. 8.5 Geriatric Use: (b) (4)

(b) (4)

k. 8.6 Renal Impairment: (b) (4)

(b) (4)

l. 12.3 Pharmacokinetics/ (b) (4)

(b) (4)

m. 14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus, Table 3: Revise (b) (4) to read "-0.3*" and (b) (4) to read "-10*" in the "Liraglutide Injection 1.2 mg" column, (b) (4)

n. (b) (4)

o. 16 HOW SUPPLIED/ STORAGE AND HANDLING: Include the NDC numbers. (b) (4)

(b) (4)

(b) (4) We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.

5. MEDICATION GUIDE

- a. Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).
- b. **What is Liraglutide Injection?**/Liraglutide Injection is an injectable prescription medicine used, bullet: Revise to read "along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes mellitus."
- c. **What are the possible side effects of Liraglutide Injection?**/Liraglutide Injection may cause serious side effects, including, (b) (4)
[Redacted]
[Redacted]
[Redacted]
- d. [Redacted] (b) (4)

6. INSTRUCTIONS FOR USE

- a. [Redacted] (b) (4)
[Redacted]
[Redacted]
[Redacted].
- b. Add the revision date to the end of the Instructions for Use.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

1.3 POST-APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

The screenshot shows a web interface for 'Deficiency Comments'. It features a table with the following columns: 'Creation Cycle', 'Category', 'Deficiency', 'Response/Assessment', and 'Post Approval'. The 'Post Approval' column contains a checkbox. A red arrow points from the 'Deficiency' column to this checkbox, indicating a function to move comments to the Post-Approval section.

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	6 mg/mL – 3 mL Prefilled Pen	9/8/2021	Revise
Blister	N/A	N/A		
Carton	Final	Carton of 2 Prefilled Pens Carton of 3 Prefilled Pens	9/8/2021	Revise

Table 2: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 08/2021	9/8/2021	Revise
Medication Guide	Draft	Revised: August 2021	9/8/2021	Revise
Patient Information	N/A	N/A		
Instructions for Use	Draft	Not provided	9/8/2021	Revise
SPL Data Elements				

4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? Controlled Correspondence: (b) (4) Completed
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? (b) (4)

4.2 MODEL PRESCRIBING INFORMATION

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)	
☒	MOST RECENTLY APPROVED <u>NDA</u> MODEL LABELING <i>(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)</i> NDA#/Supplement# (S-000 if original): NDA022341 / S-036 Supplement Approval Date: 11/20/2020 Proprietary Name: Victoza Established Name: liraglutide injection Description of Supplement: This Prior Approval sNDA provides for the addition of information regarding severe hypoglycemia to Sections 5, 10, and 17, of the Prescribing Information and to the Medication Guide. Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4705241_4293882_090140af805af7f4_NDA022341_3108918
☐	MOST RECENTLY APPROVED <u>ANDA</u> MODEL LABELING
☒	OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out): BPCA template (b) (4) (based on NDA 022341/S-031 approved 6/17/2019).

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 11/05/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA022341) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
18 mg/3 mL (6mg/mL)	6268343*PED	02/22/2023			III	9/8/2021	None
18 mg/3 mL (6mg/mL)	6268343	08/22/2022	U-968	A METHOD FOR IMPROVING GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS	III	9/8/2021	None
18 mg/3 mL (6mg/mL)	7762994*PED	11/23/2024			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	7762994	05/23/2024			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	8114833*PED	02/13/2026			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	8114833	08/13/2025			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	8579869*PED	12/30/2023			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	8579869	06/30/2023			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	8846618*PED	12/27/2022			III	9/8/2021	None
18 mg/3 mL (6mg/mL)	8846618	06/27/2022			III	9/8/2021	None
18 mg/3 mL (6mg/mL)	9265893*PED	03/23/2033			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	9265893	09/23/2032			IV	9/8/2021	None
18 mg/3 mL (6mg/mL)	9968659*PED	07/09/2037			VIII	9/8/2021	Carve-out
18 mg/3 mL (6mg/mL)	9968659	01/09/2037	U-2313	METHOD OF REDUCING THE RISK OF CARDIOVASCULAR DEATH, NON-FATAL MYOCARDIAL INFARCTION, AND/OR NON-FATAL STROKE IN ADULTS WITH TYPE 2 DIABETES	VIII	9/8/2021	Carve-out

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
				MELLITUS AND ESTABLISHED CARDIOVASCULAR DISEASE BY ADMINISTERING LIRAGLUTIDE			
18 mg/3 mL (6mg/mL)	RE41956*PED	07/21/2021			II	9/8/2021	None
18 mg/3 mL (6mg/mL)	RE41956	01/21/2021			II	9/8/2021	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
18 mg/3 mL (6mg/mL)	NPP PED	12/17/2022	NEW PATIENT POPULATION; PEDIATRIC EXCLUSIVITY	Hikma is not seeking approval for its liraglutide recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities	09/08/2021	Carve-out
18 mg/3 mL (6mg/mL)	NPP	06/17/2022	NEW PATIENT POPULATION	Hikma is not seeking approval for its liraglutide	09/08/2021	Carve-out

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
				recombinant 18 mg/3 mL (6 mg/mL) solution product for the listed exclusivities and Hikma's labeling for its drug product does not include the information associated with the listed exclusivities		

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments:		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP)The [USP](#) was searched on 11/05/2021

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		

Deficiency	No Deficiency	
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments:		
Deficiency Comments:		

4.5 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 022341/S-028 approval letter in DARRTS)

Syringe label for 2 Pens/Carton

Expiry/ Batch: Z-50C-1-163656-8

NDC 0159-4060-12 LIST 406012

Rx Only
Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

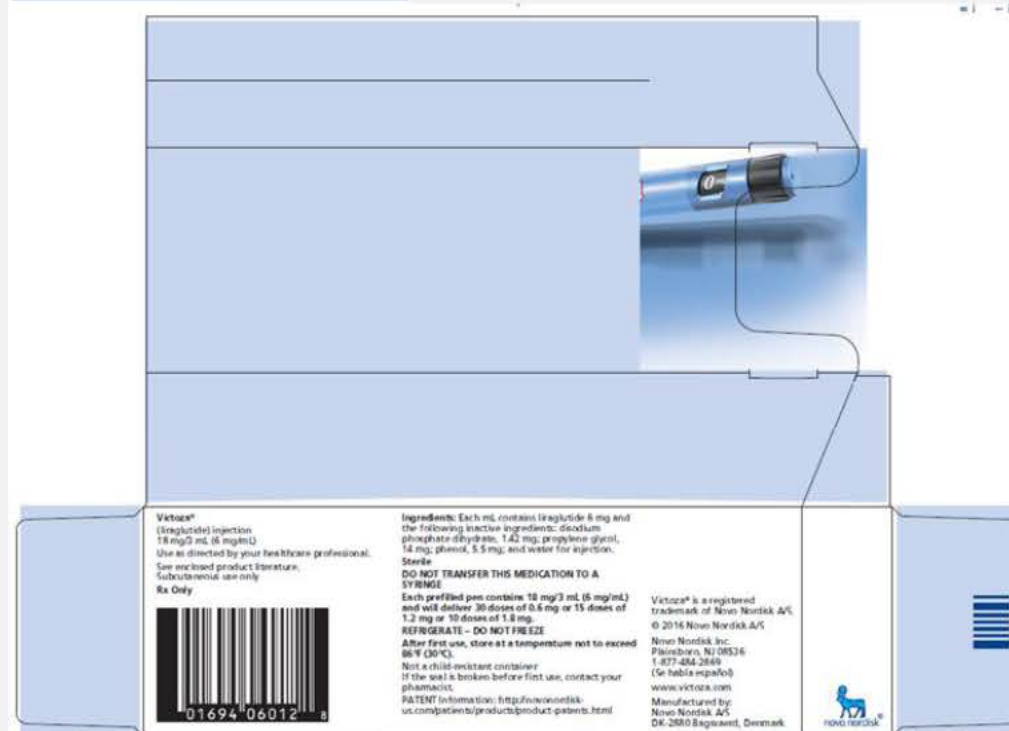
For Single Patient Use Only

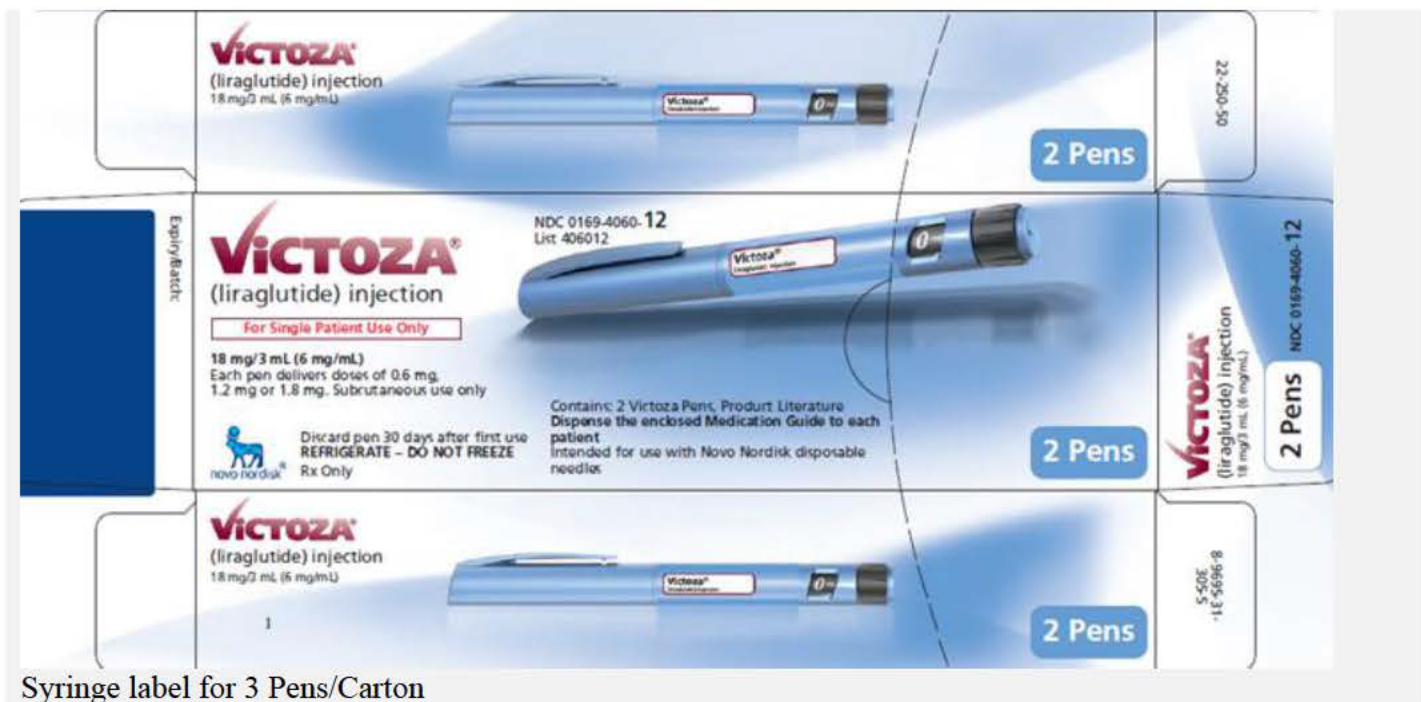
Each prefilled pen contains 18 mg/3 mL (6 mg/mL) and will deliver 30 doses of 0.6 mg or 15 doses of 1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE BEFORE FIRST USE – DO NOT FREEZE

Novo Nordisk Inc.
1-877-484-2869

1





Syringe label for 3 Pens/Carton

Expiry/
Batch:

8-9695-31-
201-6

NDC 0169-4060-13

LIST 406013

Rx Only

Discard pen 30 days after first use.

Victoza®
(liraglutide) injection

For Single Patient Use Only

Each prefilled pen contains
18 mg/3 mL (6 mg/mL) and
will deliver 30 doses of
0.6 mg or 15 doses of 1.2 mg
or 10 doses of 1.8 mg.
REFRIGERATE BEFORE FIRST
USE – DO NOT FREEZE



Novo Nordisk Inc.
1-877-484-2869

1



Victoza®

(liraglutide) injection
18 mg/3 mL (6 mg/mL)
Use as directed by your healthcare professional.
See enclosed product literature.
Subcutaneous use only.
Rx Only



Ingredients: Each mL contains liraglutide 6 mg and
the following inactive ingredients: sodium
phosphate dibutylate, 1.42 mg; polyethylene glycol,
14 mg; phenol, 5.5 mg; and water for injection.
Sterile.

DO NOT TRANSFER THIS MEDICATION TO A SYRINGE
Each prefilled pen contains 18 mg/3 mL (6 mg/mL)
and will deliver 30 doses of 0.6 mg or 15 doses of
1.2 mg or 10 doses of 1.8 mg.

REFRIGERATE – DO NOT FREEZE

After first use, store at a temperature not to exceed
86°F (30°C).

Not a child-resistant container.
If the seal is broken before first use, contact your
pharmacist.

PATENT INFORMATION: [http://www.novonordisk-](http://www.novonordisk-us.com/patents/products/product-patents.html)

[www.novonordisk-](http://www.novonordisk-us.com/patents/products/product-patents.html)
Victoza® is a registered
trademark of Novo Nordisk A/S.

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Novo Nordisk Inc.

Plainsboro, NJ 08536

1-877-484-2869

(See inside for more)

www.victoza.com

Manufactured by:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark





5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

5.1.2 DESCRIPTION

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).
Previous ANDA Labeling	NA
Current ANDA Labeling	Each 1 mL of Liraglutide Injection solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Liraglutide Injection has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous).

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	16.1 How Supplied VICTOZA Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x VICTOZA pen NDC 0169-4060-12 3 x VICTOZA pen NDC 0169-4060-13 16.2 Recommended Storage Prior to first use, VICTOZA should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA and do not use VICTOZA if it has been frozen. After first use of the VICTOZA pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.
Previous ANDA Labeling	NA
Current ANDA Labeling	16.1 How Supplied Liraglutide Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes: 2 x Liraglutide Injection pen NDC 0143-XXXX-02 3 x Liraglutide Injection pen NDC 0143-XXXX-03 16.2 Recommended Storage Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen. After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	NA

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address on ANDA Container/Carton	NA
Name and Address on ANDA Prescribing Information	NA
Current ANDA Labeling	
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	From 3.2.P.3.1 dated 9/8/2021: Drug Product Manufacturer (b) (4) Company: Hybio Pharmaceutical Co., Ltd. (Pingshan factory)*, Hybio Pingshan or Hybio Pingshan site for short. Address: 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China.
Name and Address on ANDA Container/Carton	(b) (4)
Name and Address on ANDA Prescribing Information	Manufactured by: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China. (b) (4) Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	Manufactured for	Distributed by	Distributed for

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		

Deficiency	No Deficiency	
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☒	☐	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)] .
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)] .
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437] .
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6)] or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The container label in in line with the RLD; however, we have comments for the applicant. Please refer to section 5.2.1.1 below.		

(b) (4)

Deficiency Comments:

Deficiency # 1

Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).

Created in C1

Container Label

Response / Assessment:

Deficiency # 2

Created in C1

General Comments

Response / Assessment:

Deficiency # 3

Provide the revised container label and carton labeling in higher resolution.

Created in C1

General Comments

Response / Assessment:

5.2.1 INJECTABLE PRODUCTS**Reviewer Assessment:**

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule overseal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is NA . NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP General Chapter <7> Labeling.
☐	☒	If volume is less than 1 mL, strength per fraction of a milliliter is the only expression of strength.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 1 CFR 201.100(b)(5)(iii) .
☐	☒	Container label includes instructions for reconstitution if applicable.
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information.

Reviewer Comments:
 The RLD does not list the total quantity per total volume followed by the concentration per mL; however, we will request the addition of this to be in line with USP General Chapter <7> labeling.
 Inactive ingredients are not listed on the container label but are listed on the carton labeling. This is in line with the RLD.

Deficiency Comments:
 Deficiency # 1
 Created in C1
 Container Label

Include the strength statement such that the total strength per total volume is the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses, as described in the USP, General Chapter <7> Labeling. For example:

18 mg/3 mL
 (6 mg/mL)

Response / Assessment:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency Comments:
 Deficiency # 1
 Created in C1
 Carton Labeling
 Response / Assessment:

Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).

Deficiency # 2
 Created in C1

We recommend revising the “For Single Patient Use Only” statement on the PDP to use red font to be in accordance with the RLD.

Carton Labeling Response / Assessment:	
Deficiency # 3 Created in C1 Carton Labeling Response / Assessment:	Strength statement: We recommend increasing the prominence of "18 mg/3 mL" on the PDP.

5.4 PRESCRIBING INFORMATION

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at end of HIGHLIGHTS section.
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	Dosage form and route of administration properly listed [21 CFR 201.57(c)(12)(B)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☒	☐	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		
(b) (4)		
Deficiency Comments: Deficiency # 1 Created in C1 Prescribing Information Response / Assessment: (b) (4)		
Deficiency # 2 Created in C1 Prescribing Information Response / Assessment: HIGHLIGHTS/INDICATIONS AND USAGE, first bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (1)."		
Deficiency # 3 Created in C1 Prescribing Information Response / Assessment: HIGHLIGHTS: Revise (b) (4) to read "See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide."		
Deficiency # 4 Created in C1 Prescribing Information Response / Assessment: (b) (4)		

Deficiency # 5 Created in C1 Prescribing Information Response / Assessment:	1 INDICATIONS AND USAGE: - Bullet: Revise to read "as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus". (b) (4)
Deficiency # 6 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 7 Created in C1 Prescribing Information	6.1 Clinical Trials Experience: Common Adverse Reactions - First paragraph, first sentence: Revise to read, "The safety of Liraglutide Injection in subjects with type 2 diabetes was evaluated in 5 glycemic control, placebo-controlled trials in adults [see Clinical Studies (14.1)]. (b) (4) (b) (4)

Response / Assessment:	
Deficiency # 8 Created in C1 Prescribing Information	(b) (4)
Response / Assessment:	
Deficiency # 9 Created in C1 Prescribing Information	(b) (4)
Response / Assessment:	
Deficiency # 10 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 11 Created in C1 Prescribing Information	(b) (4)

Response / Assessment:	(b) (4)
Deficiency # 12 Created in C1 Prescribing Information Response / Assessment:	14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus, Table 3: Revise (b) (4) to read "-0.3*" and (b) (4) to read "-10*" in the "Liraglutide Injection 1.2 mg" column, (b) (4)
Deficiency # 13 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 14 Created in C1 Prescribing Information Response / Assessment:	HIGHLIGHTS/Title: Revise to read " LIRAGLUTIDE injection, for subcutaneous use ".
Deficiency # 15 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 16 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 17 Created in C1 Prescribing Information Response / Assessment:	(b) (4)
Deficiency # 18 Created in C1 Prescribing Information Response / Assessment:	(b) (4)

Deficiency # 19 Created in C1 Prescribing Information Response / Assessment:	5.4 Hypoglycemia: - First paragraph, second sentence: Revise to read "In pediatric patients, the risk of hypoglycemia was higher with Liraglutide Injection regardless of insulin and/or metformin use. [see Adverse Reactions (6.1), Drug Interactions (7.2)]." (b) (4)
Deficiency # 20 Created in C1 Prescribing Information Response / Assessment:	
Deficiency # 21 Created in C1 Prescribing Information Response / Assessment:	16 HOW SUPPLIED/ STORAGE AND HANDLING: Include the NDC numbers. If the NDC numbers are not available at the time of approval, consider stating "NDC numbers pending". We remind you that the NDC numbers must accurately be reflected in your labeling prior to marketing.

5.5 MEDICATION GUIDE

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is up-to-date with model labeling.
☐	☒	Medication Guide meets content, format, and font size .
☒	☐	Phonetic spelling of the established/proprietary name is present and correct.
☐	☒	Description of child-resistant feature (if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	Revision date and approval statement appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a sufficient number of Medication Guides.
☐	☒	Applicant included the 1-800-FDA-1088 phone number.
☒	☐	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		

(b) (4) . Please see below.

Deficiency Comments: Deficiency # 1 Created in C1 Medication Guide Response / Assessment:	Add the phonetic spelling of the established name in the Title in accordance with 21 CFR 208.20(b)(1).
Deficiency # 2 Created in C1 Medication Guide Response / Assessment:	What is Liraglutide Injection? Liraglutide Injection is an injectable prescription medicine used, bullet: Revise to read "along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes mellitus."
Deficiency # 3 Created in C1 General Comments Response / Assessment:	(b) (4)
Deficiency # 4 Created in C1 Medication Guide Response / Assessment:	(b) (4)
Deficiency # 5 Created in C1 Medication Guide Response / Assessment:	(b) (4)

5.6 OTHER PATIENT LABELING

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: The DCR review is pending. Deficiency Comments: Deficiency # 1 Created in C1		

(b) (4)

Instructions for use

Response / Assessment:

Deficiency # 2

Add the revision date to the end of the Instructions for Use.

Created in C1

Instructions for use

Response / Assessment:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other
Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)	
Reviewer Comments:	
Deficiency Comments:	



Esther
Kim

Digitally signed by Esther Kim
Date: 11/23/2021 03:02:21PM
GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo
Date: 11/23/2021 03:42:34PM
GUID: 508da73d0002b687dfbf9b3859d80789

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	215503		
Review Cycle #	3		
Applicant Name	Hikma Pharmaceuticals USA Inc		
Drug Product Name	Liraglutide Injection (synthetic origin)		
Dosage Form. (click (+) for more than one)	Solution		
Proposed Strength(s)	18 mg/3 mL		
Route of Administration (click (+) for more than one)	Subcutaneous		
Maximum Daily Dose	1.8 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.		
Drug Product Description	a sterile, aqueous, clear, colorless (b) (4) solution for subcutaneous use.		
Co-packaged product information	NA		
Device information, if any:	pre-filled, single-patient-use pen		
Storage Temperature/ Conditions	stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Govindaraj Kumaran	Brian Connell

	<i>Drug Product/ Labeling</i>	Stancy Joseph	Hongmei Li
	<i>Manufacturing</i>	Wei Yang	Jean Tang
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Eric Adeeku	Elizabeth Berr
	<i>Other (specify):</i>		
	<i>RBPM</i>	Temitope Oriola	
	<i>ATL</i>	Hongmei Li	
Consults	Discipline Consulted	Recommendation	Date
	CDRH Consult CDRH-ODE	Adequate	12/18/2023
	OBP Immunogenicity	Adequate	12/18/2023
	OPQR-MS and impurity method verification	Adequate	04/22/2024
	OPQR Consult- NMR	Adequate	07/21/2023
	OPQR Consult- Aggregation state	Adequate	11/24/2023

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Submission SD#0019	04/10/2024	OPMA-facility
Submission SD#0018	04/05/2024	OPMA-facility
Submission SD#0016	03/21/2024	DP quality and label
Previous Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0013	09/20/2023	Label

Submission SD#0012	06/30/2023	CR response: DP quality, manufacturing,
Submission SD#0010	04/14/2022	DRL Response-DP quality, manufacturing, microbiology
Submission SD#0009	03/11/2022	Label
Submission SD#0008	03/04/2022	Bioequivalence
Submission SD#0007	02/09/2022	OBP Consult IR Response
Submission SD#0005	01/13/2022	Label IR Response
Submission SD#0004	12/03/2021	DCR Comparative Threshold Analyses IR Response
Submission SD#0002	10/12/2021	DP Quality
Submission SD#0001	09/08/2021	Label, DP Quality, Manufacturing and Facility, Bioequivalence
Non quality: SD#0003, #0006, #0011, #0015, #0017		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	(b) (4) Liraglutide drug substance	R03-Adequate	12/26/2023	Reviewed by Govindaraj Kumaran
	III			Active		
	V			Active		
	III			Active		
	V			Active		
	IV			Active		
	---			---	---	Adequate in CDRH review

			(b) (4)			
--	--	--	---------	--	--	--

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 022341	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge; Approval date: 01/25/2010 Holder: Novo Nordisk [Not for FOIA, (b) (4)]

4. Final Overall recommendation – Approval

Deficiencies (if applicable): None

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

Drug Substance Deficiencies

Drug Product Deficiencies

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

Manufacturing Deficiencies

Microbiology Deficiencies

Other Deficiencies (*Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: Pharm/Tox consult for Drug Product*)

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

ANDA 215503 is for Liraglutide Injection (b) (4) 18 mg/3 mL. This ANDA is recommended for approval per OPQ quality perspective. The identified deficiencies were adequately addressed in this and previous assessment cycles, and DMF (b) (4), DS/DP, Process/facility and Microbiology are all adequate.

NDSRI Impacted Application: No

(b) (5)

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

Drug substance (DS) Liraglutide (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4). DMF (b) (4) is review and adequate.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

The drug product (b) (4)

[Redacted text block]

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

[Redacted text block]

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

Facility Assessment Recommendation: Adequate
Process Assessment Recommendation: Adequate

The latest overall manufacturing inspection recommendation is approval completed on 05/28/2024 on Panorama.

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

[Redacted text block]

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

Remains adequate.

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

6. Life-Cycle Considerations

Established Conditions per ICH Q12: Yes

Comments: None

Comparability Protocols (PACMP): No

Comments: NA

Additional Comments: None



Hongmei
Li

Digitally signed by Hongmei Li

Date: 6/03/2024 11:28:27AM

GUID: 54c94ca000084932f06afe87774bef34



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0005	
Effective Date:	13 Apr 2023	Revision: 05
Page 1 of 83		



Template Revision: 03

ANDA #215503 Assessment #03

(b) (5)

Drug Product Name	Liraglutide Injection (synthetic origin)
Dosage Form	Injectable, solution
Strength	18 mg/3 mL (6 mg/mL)
Route of Administration	For subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA Inc
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0019	04/10/2024	Response to Facility IR
Submission SD#0018	04/05/2024	Response to Facility IR
Submission SD#0016	03/21/2024	DP quality and label
Previous Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0013	09/20/2023	Label
Submission SD#0012	06/30/2023	CR response: DP quality, manufacturing,
Submission SD#0010	04/14/2022	DRL Response-DP quality, manufacturing, microbiology
Submission SD#0009	03/11/2022	Label
Submission SD#0008	03/04/2022	Bioequivalence
Submission SD#0007	02/09/2022	OBP Consult IR Response
Submission SD#0005	01/13/2022	Label IR Response
Submission SD#0004	12/03/2021	DCR Comparative Threshold Analyses IR Response
Submission SD#0002	10/12/2021	DP Quality
Submission SD#0001	09/08/2021	Label, DP Quality, Manufacturing and Facility, Bioequivalence
Non quality: SD#0003, #0006, #0011, #0015, #0017		



Title: Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 2 of 83



1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/Comments
(b) (4)	II	(b) (4)	(b) (4) Liraglutide drug substance	Adequate	12/26/2023	Reviewed by Govindaraj Kumaran
	III		(b) (4)	Active		
	V			Active		
	III			Active		
	V			Active		
	IV			Active		
	---			---	---	Adequate in CDRH review

*Per DARRTSs for same DP

B. Other Documents: IND, RLD, RS, Approved ANDA



Title: Abbreviated New Drug
Application (ANDA) Integrated
Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 3 of 83



Document	Application Number	Description
RLD	NDA 022341	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge Approval date: 01/25/2010 Holder: Novo Nordisk [Not for FOIA, (b) (4)]

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH Consult CDRH-ODE	Complete	Adequate	12/18/2023	Robert Nakielny
Immunogenicity OBP	Completed	Adequate	12/18/2023	Seth Thacker
OPQR-MS	Complete	Adequate	04/22/2024	Daniel Weisz
OPQR Consult- NMR	Completed	Adequate	07/21/2023	Kang Chen
OPQR Consult- Aggregation state	Completed	Adequate	11/24/2023	Haiou Qu
OPQR Consult- Method Verification	Per discussion with OTR method verification is not necessary for this application if the firms address the deficiencies related to the respective analytical methods.			



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 4 of 83			



CHAPTER I: DRUG SUBSTANCE

For more details about the items in this template, please see [Chapter I \(Drug Substance\) of the ANDA IQA Guide](#)

Drug Substance Name	Liraglutide
RANDA Number	215503
Applicant Name	Hikma Pharmaceuticals USA Inc
Assessment Cycle Number	03
DMF Number (if applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Adequate

If Inadequate-Major, select Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary: Liraglutide is a synthetic peptide made by (b) (4). It is a white to off-white powder that is freely soluble in water and has a molecular weight of 3751.26 and molecular formula of C₁₇₂H₂₆₅N₄₃O₅₁. (b) (4). The firm referred to (b) (4) Inc DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Liraglutide. A LOA authorizing the Agency to review this DMF was provided in the application.

Highlight Key Issues from Last Cycle and Their Resolution:

- Method deficiency regarding impurities method is now adequate. The DS impurities method system suitability acceptable
- Clarification for SEC-MALS Test data; applicant reverified a typo and provided updated document.



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 5 of 83			



- The DS impurities method system suitability acceptable pending method verification.

Concise Description of Outstanding Issues (*list bullet points with key information and update as needed*): NA

- **Select Number of Approved Comparability Protocols:** 0



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 6 of 83			



S.1 GENERAL INFORMATION

Summary of the Information: ***Adequate per Review #02***

S.2 MANUFACTURE: ***Adequate per Review #02***



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Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 24 of 83			



U.S. FOOD & DRUG
ADMINISTRATION

(b) (4)

R REGIONAL INFORMATION

Comparability Protocols

Assessment: None

Lifecycle Management Considerations

None provided



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 25 of 83			



DRUG SUBSTANCE LIST OF DEFICIENCIES

None

Primary Drug Substance Assessor Name and Date: Stancy Joseph 04/03/2024

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 05/14/2024*



Title: Abbreviated New Drug
Application (ANDA) Integrated
Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 26 of 83



CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see [Chapter II \(Drug Product\) of the ANDA IQA Guide](#)

ANDA Number	A215503
Assessment Cycle Number	03
Drug Product (DP) Name / Strength	Liraglutide Injection (synthetic origin) 18 mg/3mL (6 mg/mL)
Route of Administration	Subcutaneous
Drug Product Manufacturer	(b) (4)
RLD/RS Information (Brand Name of Product, Applicant)	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge
RLD/RS Number	NDA 022341
Proposed Indication	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Assessment Recommendation: Adequate

If Inadequate-Major, select Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.



Title: Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template
Document ID: OPQ-ALL-TEM-0005
Effective Date: 13 Apr 2023 Revision: 05
Page 27 of 83



Assessment Summary:

(b) (4)
DP Liraglutide Injection solution is supplied in a pre-filled pen with (b) (4) cartridge, rubber plunger stopper (b) (4). Each pre-filled pen contains a 3 mL solution of Liraglutide Injection equivalent to 18 mg liraglutide (free-base, anhydrous). Each mL contains 6.0 mg of Liraglutide, 1.42 mg Sodium phosphate dibasic dihydrate, 5.5 mg phenol, 14.0 mg propylene glycol, hydrochloride acid and sodium hydroxide to adjust to pH 8.15 and q.s. water for injection. The proposed formulation is the same as that of the RLD. Sufficient data is provided to establish API sameness and comparative impurity profile with adequate impurity methods. Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). 6 months accelerated and up to 30 months long-term stability data for three exhibit batches under both horizontal and vertical orientation is provided. (b) (4)

(b) (4). After first use, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). In use stability data of exhibit batches at 0, 12 month and 30 month stability study time points are provided to support the labeling statement for in use storage conditions.

(b) (4)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #02	Comments
Chemical Stability (All CQAs)	High	(b) (4)	Low	(b) (4)



Title: Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 28 of 83



		(b) (4)		(b) (4)
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(b) (4)

(b) (4)

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(b) (4)



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0005	
Effective Date:	13 Apr 2023	Revision: 05
Page 32 of 83		



		(b) (4)		(b) (4)
Meeting USP <1> Requirement	Medium		Low	

Highlight Key Issues from Last Cycle and Their Resolution:

- (b) (4) is not acceptable in stability specification.
- Impurity test method is acceptable.
- Missing reference standards provided.

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): NA

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: **N/A**
- Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal **N/A**
- Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status: **Yes**
- Number of Comparability protocols included: **0**



Title: Abbreviated New Drug
Application (ANDA) Integrated
Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 33 of 83



P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Table 2.3.P.1-1 Composition of Liraglutide Injection 18 mg/3 mL (6 mg/mL)

Ingredients	Function	Quality standard	Amount/3 mL	Concentration	% (w/v)	% (w/w)
Liraglutide	API	In-house	18 mg	6 mg/mL		(b) (4)
Disodium phosphate dihydrate	(b) (4)	USP-NF	(b) (4)	1.42 mg/mL		
Propylene glycol		USP-NF		14 mg/mL		
Phenol		USP-NF		5.5 mg/mL		
Sodium hydroxide	pH modifier	USP-NF	Q.S to adjust pH of 8.15			
Hydrochloric acid						
Water for injection	(b) (4)	USP				(b) (4)

Assessment: Adequate per Review #01

(b) (4)

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immediately following this page



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 79 of 83			



U.S. FOOD & DRUG
ADMINISTRATION

(b) (4)

R REGIONAL INFORMATION

Environmental: Adequate per Review #01

Methods Validation or Verification Package: NA

Comparability Protocols: None



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 80 of 83			



Lifecycle Management Considerations: None

DRUG PRODUCT LIST OF DEFICIENCIES *(All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")*

None

Primary Drug Product Assessor Name and Date: Stancy Joseph 04/08/2024

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 05/14/2024*



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Total Pages:	83		



Template Revision: 03

ANDA 215503 Assessment #03

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the ANDA IQA Guide](#)

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Deficiency #01 (CR dated 02/28/2024): In the Package Insert (PI) label, you stated

(b) (4)

, please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34."

Summary of Applicant's Response (dated 03/21/2024): Hikma has confirmed with the DMF holder that Liraglutide is chemically synthesized. The package insert labeling has been revised in the Description section as requested. The following documents are provided in Module 1.14.



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0005	
Effective Date:	13 Apr 2023	Revision: 05
Page 82 of 83		



Template Revision: 03

Reviewer's Assessment: Adequate

The applicant confirmed with the DMF holder that Liraglutide is chemically synthesized. The package insert labeling Description section was revised accordingly to state Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34." This is acceptable.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 83 of 83			



Template Revision: 03

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES *(All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")*

None

Primary Drug Product Assessor Name and Date: Stancy Joseph 04/08/2024

Secondary Drug Product Assessor Name and Date: Hongmei Li, 05/14/2024



Stancy
Joseph

Digitally signed by Stancy Joseph

Date: 5/21/2024 09:54:51AM

GUID: 590b7a34002919182fed831ba4f29b67



Hongmei
Li

Digitally signed by Hongmei Li

Date: 5/21/2024 09:50:44AM

GUID: 54c94ca000084932f06afe87774bef34

ANDA 215503
Assessment #R04**CHAPTER V: MANUFACTURING**

For more details about the items in this template, please see [Chapter V \(Manufacturing\)](#) of the ANDA IQA Guide

Application ID	ANDA 215503
Drug Product Name	Liraglutide Injection
Strengths	18 mg/3 mL
Dosage Form	Injectable, solution
Administration Route	For subcutaneous injection
Indication	(b) (4)
Applicant Name	Hikma Pharmaceuticals USA Inc
RLD Number	22341
Primary Assessor	Jin Lee, Wei Yang
Secondary Assessor	James Norman, Jean Tang

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

- DP is a multi-dose, disposable pen injector pre-filled with a colorless 3-mL (b) (4) cartridge sealed with a rubber plunger (b) (4) delivers doses of 0.6, 1.2 or 1.8 mg. The formulation consists of the peptide API (Liraglutide) at 6 mg/mL and (b) (4) (propylene glycol) (b) (4) (phenol) (b) (4)

(b) (4)

Update from Amend-12 by YX:

(b) (4)

Facility is adequate in this review cycle.

List Submissions Being Assessed (table):

Document Description (SD #)	Date Received
Original submission (SD 1)	08 September 2021
Response to DRL in R01 (SD 10)	14 April 2022
SD#12 response of CRL	6/30/2023
SD#15 patent Settlement Agreement amendment	12/19/23
CRL Response (SD 16)	03/21/2024
IR Response (SD 18)	04/05/2024
IR Response (SD 19)	04/10/2024

Updates per SD 10 rec'd on 04/14/2022 entered in **Blue Font** in this review.

Update of amend-12 (SD#12) is in red ink.

Highlight Key Issues from Last Cycle and Their Resolution: N/A, first review cycle.**Concise Description of Outstanding Issues** (*list bullet points with key information and update as needed*):**List Number of Comparability Protocols:** None.**1. Lifecycle Management Considerations**

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
---------------------------	-----	--------------------------------------	--------

Hybio Pharmaceutical Co., Ltd. (Pingshan factory)	3011090684	(b) (4)	Deferred-Travel Restrictions-COVID
2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong, China, 518118			Deferred-Travel Restrictions-COVID
Hybio Pharmaceutical Co., Ltd			Approve - Based on Previous History
(b) (4)			
Hybio Pharmaceutical Co., Ltd		(b) (4)	Deferred-Travel Restrictions-COVID
(b) (4)			No Evaluation Necessary

68 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Assessor participated in PAI?	Choose an item.
Issues identified and PAI / 704(a)(4) resolution	
Request for Additional Information (#RAI) and Response	
Outcome	Choose an item.

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jin Lee 01-10-2022 02-17-2022	James Norman	2/18/2022	IR	TBD
2	Jin Lee 05-10-2022 06-02-2022	James Norman	6/6/2022	Deferred-Travel Restrictions-COVID19	Withheld
3 Amend-12	Yan Xu	Tianhong Tim Zhou	1/18/2024	Adequate	Approve
4	Wei Yang	Jean Tang	4/16/2024	Adequate	Approve



Wei
Yang (OPMA)

Digitally signed by Wei Yang (OPMA)

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Jean
Tang

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Date: 5/29/2024 10:14:24AM

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CHAPTER VII: MICROBIOLOGY

Product Information	
ANDA Number	215503
Assessment Cycle Number	01
Drug Product Name / Strength	Liraglutide Injection / 18 mg/3 mL
Route of Administration	Subcutaneous injection
Applicant Name	Hikma Pharmaceuticals USA Inc.
Manufacturing Site	Hybio Pharmaceutical Co., Ltd. 2 nd Luhui Rd, Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China.
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval.

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: (Click link to view [Justification Statements](#))

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if “other” selected as theme.

Dates of Submission(s) Covered by this Review

Submit	Received	eCTD seq./Doc. #	Review Request	Assigned to Reviewer
09/08/2021	09/08/2021	#0000 / 1	N/A	09/21/2021
01/13/2022	01/13/2022	#0005 / 5	N/A	01/13/2022
04/14/2022	04/14/2022	#0010 / 10	N/A	05/09/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: No outstanding issues remain.

Remarks:

This is an electronic submission.
GDUFA goal date is 07/07/2022.
Mid Cycle date is 03/08/2022.

The 04/14/2022 submission is in response to microbiology deficiency conveyed to the applicant in the Agency's Quality Discipline Review Letter (DRL) dated 02/28/2022. The deficiencies are italicized.

Supporting Documents:

(b) (4)

Select Number of Approved Comparability Protocols: 0**P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT**

Description of drug product –

(section 3.2.P.1: Description of dosage form).

Liraglutide Injection is a clear, colorless or almost colorless solution in a pre-filled, disposable and multi-dose pen injector containing 3 mL of drug product at a concentration of 6 mg/mL for subcutaneous injection, and delivering doses of 0.6 mg, 1.2 mg and 1.8 mg of Liraglutide, which is developed and designed in accordance with RLD (VICTOZA®, Novo Nordisk, NDA #022341).

Drug product composition –

(section 3.2.P.1: Description and composition of drug product).

Ingredients	Function	Concn.	Amount / cartridge
Liraglutide (in-house)	Active ingredient	6 mg/mL	18 mg
Disodium phosphate dihydrate, USP-NF	(b) (4)	1.42 mg/mL	(b) (4)
Propylene glycol, USP-NF		14 mg/mL	
Phenol, USP-NF		5.5 mg/mL	
Sodium hydroxide, USP-NF	pH modifier	Q.S to adjust pH of 8.15	

Hydrochloric acid, USP-NF		
Water for injection, USP		(b) (4)

Description of container closure system –
(section 3.2.P.1.4; section 3.2.P.7: Container closure system).

(b) (4)

(b) (4)

Pen-injector delivery system for Generic Liraglutide Injection 18 mg/3 mL
(6 mg/mL) is provided below.

(b) (4)

Container: Single dose

Prior to first use, Liraglutide Injection should be stored in a refrigerator between 36 – 46 °F (2 – 8 °C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Liraglutide Injection and do not use Liraglutide Injection if it has been frozen.

After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature 59 – 86 °F (15 – 30 °C) or in a refrigerator at 36 – 46 °F (2 – 8 °C). Keep the pen cap on when not in use. Protect Liraglutide Injection from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Liraglutide Injection pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, Ph.D., 05/31/2022

Secondary Assessor Name and Date

Elizabeth Bearr, Ph.D., 05/31/2022

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Eric
Adeeku

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Elizabeth
Barr

Digitally signed by Elizabeth Barr
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Hongmei
Li

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Temitope
Oriola

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ANDA Executive Summary

1. Application/Product Information

ANDA Number.	215503		
Review Cycle #	2		
Applicant Name	Hikma Pharmaceuticals USA Inc		
Drug Product Name	Liraglutide Injection		
Dosage Form. (click (+) for more than one)	Injectable		
Proposed Strength(s)	18 mg/3 mL		
Route of Administration (click (+) for more than one)	Subcutaneous		
Maximum Daily Dose	1.8 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.		
Drug Product Description	a sterile, aqueous, clear, colorless (b) (4) solution for subcutaneous use.		
Co-packaged product information			
Device information, if any:	pre-filled, single-patient-use pen		
Storage Temperature/ Conditions	store in a refrigerator between 36°F to 46°F (2°C to 8°C). After first use of the Liraglutide Injection pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use.		
Review Team	Discipline	Primary	Secondary

	<i>Drug Substance</i>	Govindaraj Kumaran	Brian Connell
	<i>Drug Product/ Labeling</i>	Stancy Joseph	Hongmei Li
	<i>Manufacturing</i>	Yan Xu	Tianhong Tim Zhou
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Eric Adeeku	Elizabeth Berr
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Temitope Oriola	
	<i>ATL</i>	Hongmei Li	
Consults	Discipline Consulted	Recommendation	Date
	CDRH Consult CDRH-ODE	Adequate	12/18/2023
	Immunogenicity OBP	Adequate	12/18/2023
	OTR-MS	Inadequate	02/02/2024
	OTR Consult- NMR	Adequate	07/21/2023
	OTR Consult- Aggregation state	Adequate	11/24/2023

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Submission SD#0013	09/20/2023	Label
Submission SD#0012	06/30/2023	CR response: DP quality, manufacturing,
Previous Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0010	04/14/2022	DRL Response-DP quality, manufacturing, microbiology

Submission SD#0009	03/11/2022	Label
Submission SD#0008	03/04/2022	Bioequivalence
Submission SD#0007	02/09/2022	OBP Consult IR Response
Submission SD#0005	01/13/2022	Label IR Response
Submission SD#0004	12/03/2021	DCR Comparative Threshold Analyses IR Response
Submission SD#0002	10/12/2021	DP Quality
Submission SD#0001	09/08/2021	Label, DP Quality, Manufacturing and Facility, Bioequivalence
Non quality: SD#0003, #0006, #0011, #0014		

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	(b) (4) Liraglutide drug substance	Adequate	12/26/2023	Reviewed by Govindaraj Kumaran
	III		(b) (4)	Active		*proposed in A212972- CR
	V			Active		*proposed in A212972- CR
	III			Active		---
	V			Active		*proposed in A212972- CR
	IV			Active		*proposed in A214568- pending
	---			---	---	Adequate in CDRH review

b. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 022341	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge; Approval date: 01/25/2010 Holder: Novo Nordisk [Not for FOIA, (b) (4)] [REDACTED] [REDACTED]

4. Final Overall recommendation – Complete Response-Minor

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.*)

None.

Drug Substance Deficiencies

1. [REDACTED] (b) (4)

Drug Product Deficiencies

1. [REDACTED] (b) (4)
2. [REDACTED]
3. [REDACTED]

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DP and impurity MS method and method validation as listed above. It is determined to be CR minor.

NDSRI Impacted Application: No

(b) (5)

b. Recommendation by Subdiscipline:

Drug Substance: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

--

Drug Product: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

--

Quality Labeling: INADEQUATE-MINOR

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

--

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):

(Click link to view [Justification Statements](#))

Facility Assessment Recommendation: Adequate Process Assessment Recommendation: Adequate

Biopharmaceutics: N/A

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

6. Life-Cycle Considerations

Established Conditions per ICH Q12: Choose an item.

Comments: None

Comparability Protocols (PACMP): Choose an item.

Comments:

Additional Comments: None



Hongmei
Li

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ANDA #215503

Assessment #02

(b) (5)

Drug Product Name	Liraglutide Injection
Dosage Form	Injectable, solution
Strength	18 mg/3 mL (6 mg/mL)
Route of Administration	For subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA Inc
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0013	09/20/2023	Label
Submission SD#0012	06/30/2023	CR response: DP quality, manufacturing,
Previous Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0010	04/14/2022	DRL Response-DP quality, manufacturing, microbiology
Submission SD#0009	03/11/2022	Label
Submission SD#0008	03/04/2022	Bioequivalence
Submission SD#0007	02/09/2022	OBP Consult IR Response
Submission SD#0005	01/13/2022	Label IR Response
Submission SD#0004	12/03/2021	DCR Comparative Threshold Analyses IR Response
Submission SD#0002	10/12/2021	DP Quality
Submission SD#0001	09/08/2021	Label, DP Quality, Manufacturing and Facility, Bioequivalence
Non quality: SD#0003, #0006, #0011, #0014		

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
--------------	-------------	---------------	----------------------------	---------------	--	-------------------------------

(b) (4)	II	Hybio Pharmaceutical Co., Ltd.	(b) (4) Liraglutide drug substance	Adequate	12/26/2023	Reviewed by Govindaraj Kumaran
	III	(b) (4)		Active		*proposed in A212972- CR
	V			Active		(b) (4)
	III			Active		---
	V			Active		(b) (4)
	IV			Active		(b) (4)
	---			---	---	Adequate in CDRH review

*Per DARRTSs for same DP

B. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 022341	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge Approval date: 01/25/2010 Holder: Novo Nordisk [Not for FOIA, (b) (4)]

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH Consult CDRH-ODE	Complete	Adequate	12/18/2023	Robert Nakielny
Immunogenicity OBP	Completed	Adequate	12/18/2023	Seth Thacker
OTR-MS	Complete	Inadequate	02/02/2024	Daniel Weisz
OTR Consult- NMR	Completed	Adequate	07/21/2023	Kang Chen
OTR Consult-Aggregation state	Completed	Adequate	11/24/2023	Haiou Qu
OTR Consult- Method Verification	Per discussion with OTR method verification is not necessary for this application if the firms address the deficiencies related to the respective analytical methods.			

APPEARS THIS WAY ON ORIGINAL

CHAPTER I: DRUG SUBSTANCE

For more details about the items in this template, please see [Chapter I \(Drug Substance\) of the ANDA IQA Guide](#)

Drug Substance Name	Liraglutide
RANDA Number	215503
Applicant Name	Hikma Pharmaceuticals USA Inc

Assessment Cycle Number	02
DMF Number (if applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Inadequate-Minor

If Inadequate-Major, select Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary: Liraglutide is a synthetic peptide made by (b) (4). It is a white to off-white powder that is freely soluble in water and has a molecular weight of 3751.26 and molecular formula of $C_{172}H_{265}N_{43}O_{51}$. (b) (4). The firm referred to (b) (4) DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Liraglutide. A LOA authorizing the Agency to review this DMF was provided in the application.

Highlight Key Issues from Last Cycle and Their Resolution:

- DMF is currently adequate
- Module 3.2.S.1.1 was updated as stated in the applicant's response and is adequate
- Storage condition for sameness study and acknowledge that sameness study was performed at the end of shelf life.
- (b) (4)
- Reference standard provided for (b) (4).

Concise Description of Outstanding Issues (list bullet points with key information and update as needed):

- Method deficiency
- Clarification for SEC-MALS Test data; potential typo
- The DS impurities method system suitability acceptable pending method verification.

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

International Non-Proprietary Name: Liraglutide

Unique Ingredient Identifier (UNII) Name: Liraglutide

US Approved API Name: Liraglutide

Chemical name: Glycine,L-histidyl-L-alanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamylglycyl-L-glutamyl-L-alanyl-L-alanyl-N6-(N-(1-oxohexadecyl)-L-gamma-glutamyl)-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-

Molecular Formula: C₁₇₂H₂₆₅N₄₃O₅₁

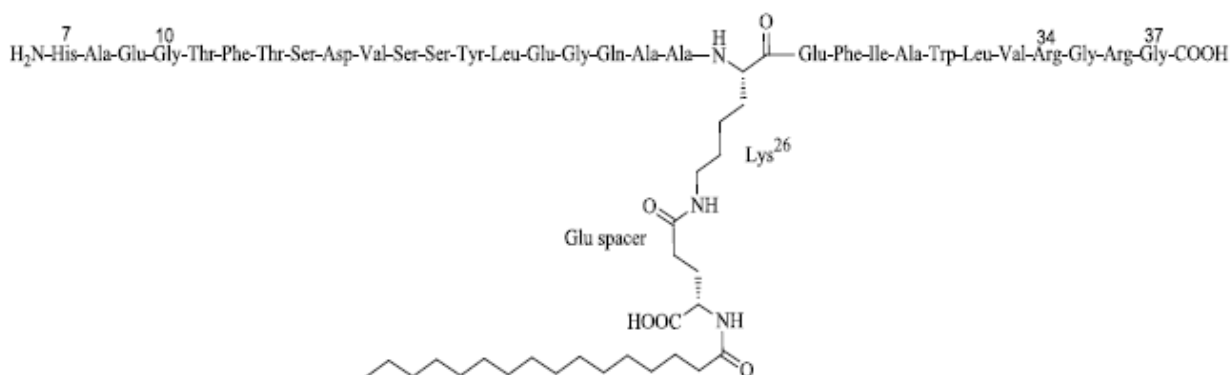
Monoisotopic weight: (b) (4) 3748.9

Average molecular weight: 3751.2

CAS registry number: 204656-20-2

UNII Number: 839I73S42A

Structural formula:



Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26.

Peptide sequence in three letters: H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(Glu-Palm)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH

Sequence shown in one letter as:

H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K(E-Palm)-E-F-I-A-W-L-V-R-G-R-G

Pharmacological class: Indicated for the treatment of Treatment of type 2 diabetes

(b) (4)



Title: Abbreviated New Drug
Application (ANDA) Integrated
Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 50 of
139



U.S. FOOD & DRUG
ADMINISTRATION

(b) (4)

R REGIONAL INFORMATION

Comparability Protocols

Assessment: None

Lifecycle Management Considerations

None provided

DRUG SUBSTANCE LIST OF DEFICIENCIES

1.

(b) (4)



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 51 of 139			



(b) (4)

Primary Drug Substance Assessor Name and Date: Stancy Joseph 11/20/2023

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 01/23/2024*



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0005	
Effective Date:	13 Apr 2023	Revision: 05
Page 52 of	139	



CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see [Chapter II \(Drug Product\) of the ANDA IQA Guide](#)

ANDA Number	A215503
Assessment Cycle Number	02
Drug Product (DP) Name / Strength	Liraglutide Injection 18 mg/3mL (6 mg/mL)
Route of Administration	Subcutaneous
Drug Product Manufacturer	(b) (4)
RLD/RS Information (Brand Name of Product, Applicant)	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge
RLD/RS Number	NDA 022341
Proposed Indication	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Assessment Recommendation: Inadequate-Minor

If Inadequate-Major, select Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))



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Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 53 of 139



Paste appropriate justification statement(s) here or insert "N/A" if not applicable.

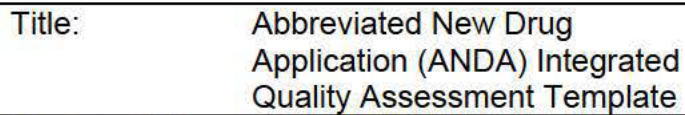
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary: : Liraglutide Injection solution is supplied in a pre-filled pen with a 3 mL (b) (4) cartridge, rubber plunger stopper (b) (4). Each mL contains 6.0 mg of Liraglutide, 1.42 mg Sodium phosphate dibasic dihydrate, 5.5 mg phenol, 14.0 mg propylene glycol, hydrochloride acid and sodium hydroxide to adjust to pH 8.15 and q.s. water for injection. The proposed formulation is the same as that of the RLD. (b) (4)

A (b) (4) expiration period has been requested with a recommended storage condition of refrigerated at 2°C to 8°C (36° to 46°F).

(b) (4)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #02	Comments
Chemical Stability (All CQAs)	High	(b) (4)	High	(b) (4)



Effective Date: 13 Apr 2023 Revision: 05



U.S. FOOD & DRUG
ADMINISTRATION

(b) (4)

(b) (4)



(b) (4)



(b) (4)

(b) (4)



(b) (4)

(b) (4)



Title: Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 58 of 139



U.S. FOOD & DRUG
ADMINISTRATION

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	Medium		Low	

Highlight Key Issues from Last Cycle and Their Resolution:

-
-
-
-
-

Concise Description of Outstanding Issues (*list bullet points with key information and update as needed*):

- Limit for (b) (4) is not acceptable in stability specification
- Impurity test method is not acceptable
- Missing reference standards

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: **N/A**



Title: Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page 59 of 139



- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal N/A*
- *Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status: Yes*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

- Liraglutide injection is (b) (4), colorless or almost colorless solution for subcutaneous use. Each 1 mL of solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. The pH of the solution is approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH.
- Liraglutide injection is refrigerated and is not frozen. After first use, Liraglutide injection is stored at a temperature not exceed 30 °C (86 °F) and is discarded after use for 30 days.

The compositions of Liraglutide Injection 18 mg/3 mL (6mg/mL) are tabulated below.

Table 2.3.P.1-1 Composition of Liraglutide Injection 18 mg/3 mL (6 mg/mL)

Ingredients	Function	Quality standard	Amount/3 mL	Concentration	% (w/v)	% (w/w)
Liraglutide	API	In-house	(b) (4)	6 mg/mL	(b) (4)	(b) (4)
Disodium phosphate dihydrate	(b) (4)	USP-NF	(b) (4)	1.42 mg/mL	(b) (4)	(b) (4)
Propylene glycol	(b) (4)	USP-NF	(b) (4)	14 mg/mL	(b) (4)	(b) (4)
Phenol	(b) (4)	USP-NF	(b) (4)	5.5 mg/mL	(b) (4)	(b) (4)
Sodium hydroxide	pH modifier	USP-NF	Q.S to adjust pH of 8.15	(b) (4)	(b) (4)	(b) (4)
Hydrochloric acid	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Water for injection	(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)

(b) (4)

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Title: Abbreviated New Drug
Application (ANDA) Integrated
Quality Assessment Template

Document ID: OPQ-ALL-TEM-0005

Effective Date: 13 Apr 2023 Revision: 05

Page **137** of
139



U.S. FOOD & DRUG
ADMINISTRATION

(b) (4)

R REGIONAL INFORMATION

Environmental : Adequate per Review #01

Methods Validation or Verification Package: NA



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 138 of 139			



Comparability Protocols: None

Lifecycle Management Considerations: None

DRUG PRODUCT LIST OF DEFICIENCIES *(All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")*

1.

2.

3.

4.

5.

(b) (4)



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 139 of 139			



6.	(b) (4)		

Primary Drug Product Assessor Name and Date: Stancy Joseph 12/01/2023

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 01/23/2024*



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Total Pages:	140		



Template Revision: 03

ANDA 215503 Assessment #02

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the ANDA IQA Guide](#)

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☐ Yes ☒ No

If "No," explain.

This is a synthetic not a recombinant peptide. As such, the description needs to be revised accordingly.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page 141 of 141			



Template Revision: 03

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues:

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES (All information requests and/or deficiencies should follow the four elements described in OPQ MAPP 5016.8 "Communication Guidelines for Quality-Related Information Requests and Deficiencies")

1. In the Package Insert (PI) label, you stated (b) (4)

[REDACTED]

[REDACTED] please revise the above-mentioned section of the PI label description to state "Liraglutide Injection contains liraglutide, an analog of human



Title:	Abbreviated New Drug Application (ANDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0005		
Effective Date:	13 Apr 2023	Revision:	05
Page	142 of 142		



U.S. FOOD & DRUG
ADMINISTRATION

Template Revision: 03

GLP-1 and acts as a GLP-1 receptor agonist. Liraglutide Injection contains chemically synthesized Liraglutide that has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34.

Primary Drug Product Assessor Name and Date: Stancy Joseph 12/01/2023

Secondary Drug Product Assessor Name and Date: Hongmei Li, 01/23/2024



Stancy
Joseph

Digitally signed by Stancy Joseph

Date: 2/06/2024 09:07:10AM

GUID: 590b7a34002919182fed831ba4f29b67



Hongmei
Li

Digitally signed by Hongmei Li

Date: 2/06/2024 08:58:42AM

GUID: 54c94ca000084932f06afe87774bef34

ANDA 215503
Assessment #R03**CHAPTER V: MANUFACTURING**

For more details about the items in this template, please see [Chapter V \(Manufacturing\) of the ANDA IQA Guide](#)

Application ID	ANDA 215503
Drug Product Name	Liraglutide Injection
Strengths	18 mg/3 mL
Dosage Form	Injectable, solution
Administration Route	For subcutaneous injection
Indication	(b) (4)
Applicant Name	Hikma Pharmaceuticals USA Inc
RLD Number	22341
Primary Assessor	Jin Lee
Secondary Assessor	James Norman

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

- DP is a multi-dose, disposable pen injector pre-filled with a colorless 3-mL (b) (4) cartridge sealed with a rubber plunger (b) (4) delivers doses of 0.6, 1.2 or 1.8 mg. The formulation consists of the peptide API (Liraglutide) at 6 mg/mL and (b) (4) (propylene glycol) (b) (4) (phenol) (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

List Number of Comparability Protocols: None.

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Hybio Pharmaceutical Co., Ltd. (Pingshan factory)	3011090684	(b) (4)	Deferred-Travel Restrictions-COVID
2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong, China, 518118			Deferred-Travel Restrictions-COVID
Hybio Pharmaceutical Co., Ltd			Approve - Based on Previous History
Hybio Pharmaceutical (b) (4) Co., Ltd			Deferred-Travel Restrictions-COVID
			No Evaluation Necessary

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VI Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jin Lee 01-10-2022 02-17-2022	James Norman	2/18/2022	IR	TBD
2	Jin Lee 05-10-2022 06-02-2022	James Norman	6/6/2022	Deferred-Travel Restrictions-COVID19	Withheld
3 Amend-12	Yan Xu	Tianhong Tim Zhou	1/18/2024	Adequate	Approve



Yan
Xu

Digitally signed by Yan Xu

Date: 1/24/2024 03:34:07PM

GUID: 5e558a0800641137aea5327d775f7887



Tianhong Tim
Zhou

Digitally signed by Tianhong Tim Zhou

Date: 1/24/2024 08:09:11PM

GUID: 559301040055fd18fd3267e1114a7f62

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☐ Complete Response-Major
☒ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 <i>Choose this option when both of the following apply:</i> • <i>Quality is Adequate except for inspection deferred due to travel restriction</i> <u>AND</u> • <i>OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)</i>

ANDA #215503 Assessment #1

Drug Product Name	Liraglutide (synthetic) injection
Dosage Form	Solution
Strength	18mg/3mL (6 mg/mL) (prefilled pen)
Route of Administration	Subcutaneous Injection
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA Inc
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission (SD1)	9/8/2021	All
Quality / Response to IR (SD7)	2/9/2022	Drug Product (Immunogenicity)
Quality / Response to DRL (SD10)	4/14/2022	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*	Stancy Joseph	Hongmei Li
Drug Product	Stancy Joseph	Hongmei Li
Manufacturing	Jin Lee	James Norman
Microbiology	Eric Adeeku	Elizabeth Bearr
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Temitope Oriola	
Application Technical Lead	Hongmei Li	
Laboratory (OTR)	See Consult Table	
Environmental	N/A	

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the ANDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	(b) (4) Liraglutide drug substance	Inadequate	05/23/2022	Reviewed by Govindaraj Kumaran
	III		(b) (4)	Active		(b) (4)
	V			Active		
	III			Active		
	V			Active		
	IV			Active		

*Per DARRTSs for same DP

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 022341	VICTOZA, Liraglutide Injection, 6 mg/mL, 3 mL cartridge; Approval date: 01/25/2010 Holder: Novo Nordisk

		[Not for FOIA, (b) (4)]

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Complete	Inadequate (Compliance)	6/7/2022	R. Nakielny
Clinical	N/A			
Other – OTR/Aggregation	Complete	Inadequate	5/30/2022	H. Qu
Other – OTR/Mass Spectrometry	Complete	Inadequate	5/31/2022	I. Geerlof-Vidavsky
Other – OTR/NMR	Complete	Inadequate	5/2/2022	K. Chen
Other – Immunogenicity	Complete	Inadequate	6/1/2022	S. Thacker

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the [Abbreviated Executive Summary \(CR Only\) chapter of the ANDA IQA Guide](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response-Major + Travel Comment

This ANDA is not recommended for approval per OPQ quality perspective. It is determined to be CR-major due to insufficient data for API sameness establishment for complex product. The justification for major is listed below.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Inadequate-Major

Drug Substance: Inadequate-Minor

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

DS Liraglutide used in this application is a synthetic peptide made by (b) (4). It is a white to off-white powder that is freely soluble in water and has a molecular weight of 3751.26 and molecular formula of C₁₇₂H₂₆₅N₄₃O₅₁. (b) (4) The firm referred to (b) (4) DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Liraglutide. DMF is found inadequate. There are several minor deficiencies for DS listed below.

Drug Product: Inadequate-Major

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

The drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(I) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Upon Submission, in FDA's judgement, the review of this information will result in substantial expenditure of FDA resources.

2. Insert additional **Major** justification below (if necessary)

Drug product (DP) Liraglutide Injection solution is supplied in a pre-filled pen with a 3 mL (b) (4) cartridge, rubber plunger stopper (b) (4). Each mL contains 6.0 mg of Liraglutide, 1.42 mg Sodium phosphate dibasic dihydrate, 5.5 mg phenol, 14.0 mg propylene glycol, hydrochloride acid and sodium hydroxide to adjust to pH 8.15 and q.s. water for injection. The proposed formulation is the same as that of the RLD. (b) (4)

However, there are insufficient data to establish API sameness (b) (4), comparative impurity methods and profiles as well impurity test/control. There are also deficiencies from OTR and OBP consults. All detailed deficiencies are listed below.

Labeling: Adequate

Insert brief summary of Labeling assessment and deficiencies.

B. Manufacturing:

a. Process: Inadequate-Minor

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:

- *Process status: Inadequate Minor*
- *DP is a multi-dose, disposable pen injector pre-filled with a colorless 3-mL (b) (4) cartridge sealed with a rubber plunger (b) (4) that delivers doses of 0.6, 1.2 or 1.8 mg. The formulation consists of the peptide API (Liraglutide) at 6 mg/mL (b) (4) (propylene glycol) (b) (4) (phenol) (b) (4)*

(b) (4)

b. Facilities: Deferred-Travel Restriction-COVID19

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:

Both drug product (DP) and drug substance (DS) manufacturing facilities need pre-approval inspection as there is no prior FDA inspection history before the sites can be considered acceptable. (b) (4)

[REDACTED]

Relevant facility language was conveyed to the applicant as a comment in this review cycle.

C. Biopharmaceutics: N/A

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Biopharmaceutics assessment and deficiencies.

D. Microbiology: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Microbiology assessment and deficiencies.

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines*) - None

Drug Substance Deficiencies

1.

(b) (4)

2.

3.

4.

5.

6.

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Application Technical Lead Name and Date: Hongmei Li, 6/15/2022



Hongmei
Li

Digitally signed by Hongmei Li

Date: 6/16/2022 12:42:38PM

GUID: 54c94ca000084932f06afe87774bef34

ANDA #215503

Assessment #01a

Drug Product Name	Liraglutide Injection
Dosage Form	Injectable, solution
Strength	18 mg/3 mL (6 mg/mL)
Route of Administration	For subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Hikma Pharmaceuticals USA Inc
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Submission SD#0010	04/14/2022	DRL Response-DP quality, manufacturing, microbiology
Submission SD#0009	03/11/2022	Label
Submission SD#0008	03/04/2022	Bioequivalence
Submission SD#0007	02/09/2022	OBP Consult IR Response
Submission SD#0006	01/21/2022	Administrative
Submission SD#0005	01/13/2022	Label IR Response
Submission SD#0004	12/03/2021	DCR Comparative Threshold Analyses IR Response
Submission SD#0003	11/22/2021	Administration
Quality Submission SD#0002	10/12/2021	DP Quality
Quality Submission SD#0001	09/08/2021	Label, DP Quality, Manufacturing and Facility, Bioequivalence

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	(b) (4) Liraglutide drug substance	Inadequate	05/23/2022	Reviewed by Govindaraj Kumaran
	III		(b) (4)	Active		(b) (4)

(b) (4)	V	(b) (4)	Active		(b) (4)
	III		Active		
	V		Active		
	IV		Active		
	---		---	---	

*Per DARRTSs for same DP

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	NDA 022341	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge Approval date: 01/25/2010 Holder: Novo Nordisk [Not for FOIA, (b) (4)]

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH Consult CDRH-ODE	Complete	Inadequate	06/07/2022	Robert Nakielny
Immunogenicity OBP	Complete	Inadequate	06/01/2022	Seth Thacker
OTR-MS	Complete	Inadequate	05/31/2022	Ilan Geerlof- Vidavsky
OTR Consult- NMR	Complete	Inadequate	05/02/2022	Kang Chen
OTR Consult-Aggregation state	Complete	Inadequate	05/31/2022	Haiou Qu
OTR Consult- Method Verification Program	Pending based on defciencie s issued in CR letter	(b) (4)		

CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Liraglutide
ANDA Number	215503
Applicant Name	Hikma Pharmaceuticals USA Inc
Assessment Cycle Number	01a
DMF Number (if applicable)	(b) (4)
DMF Status	Inadequate-Minor
DMF Holder	(b) (4)

Assessment Recommendation: Inadequate-Minor

If Inadequate-Major, select Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

Assessment Summary: Liraglutide is a synthetic peptide made by (b) (4). It is a white to off-white powder that is freely soluble in water and has a molecular weight of 3751.26 and molecular formula of $C_{172}H_{265}N_{43}O_{51}$. (b) (4). The firm referred to (b) (4) DMF (b) (4) for information regarding the chemistry, manufacturing and controls used in the production of Liraglutide. A LOA authorizing the Agency to review this DMF was provided in the application.

Highlight Key Issues from Last Cycle and Their Resolution: First Cycle (NA)

Concise Description of Outstanding Issues (list bullet points with key information and update as needed):

- DMF is inadequate
- Module 3.2.S.1.1 was not updated as stated in the applicant's response
- Storage condition for sameness study and acknowledge that sameness study will be performed at the end of shelf life.
- Resolution of (b) (4) not acceptable for (b) (4)

- The DS impurities method is not acceptable.

- (b) (4)

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

Summary of the Information

International Non-Proprietary Name: Liraglutide

Unique Ingredient Identifier (UNII) Name: Liraglutide

US Approved API Name: Liraglutide

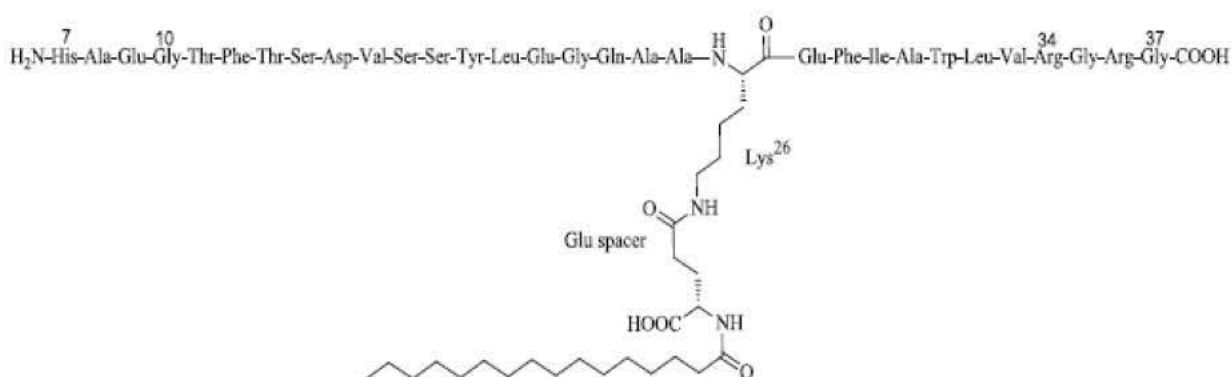
Chemical name: Glycine,L-histidyl-L-alanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamylglycyl-L-glutaminy-L-alanyl-L-alanyl-N6-(N-(1-oxohexadecyl)-L-gamma-glutamyl)-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginyl-

Molecular Formula: C₁₇₂H₂₆₅N₄₃O₅₁

Monoisotopic weight: (b) (4)

CAS registry number: 204656-20-2

Structural formula:



Liraglutide is a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26.

R REGIONAL INFORMATION

Comparability Protocols

Assessment: *None*

Lifecycle Management Considerations

None provided

DRUG SUBSTANCE LIST OF DEFICIENCIES

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

(b) (4)

Comment:

9.

(b) (4)

Primary Drug Substance Assessor Name and Date:
Stancy Joseph Ph.D. 10/25/2021, 05/04/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 2/8/2022, 5/20/2022

CHAPTER II: DRUG PRODUCT

For more details about the items in this template, please see [Chapter II \(Drug Product\) of the ANDA IQA Guide](#)

ANDA Number	A215503
Assessment Cycle Number	01a
Drug Product (DP) Name / Strength	Liraglutide Injection 18 mg/3mL (6 mg/mL)
Route of Administration	Subcutaneous
Drug Product Manufacturer	Hybio Pharmaceutical (Pingshan factory) Co., Ltd
RLD/RS Information (Brand Name of Product, Applicant)	Victoza®, Liraglutide Injection, 6 mg/mL, 3 mL cartridge
RLD/RS Number	NDA 022341
Proposed Indication	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Assessment Recommendation: Inadequate-Major

If Inadequate-Major, select Theme:

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☒ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

If Inadequate-Major, enter Justification: (Click link to view [Justification Statements](#))

Insufficient data to demonstrate drug substance sameness (especially for complex drug products) The drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(I) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July
--

2018). Upon Submission, in FDA's judgement, the review of this information will result in substantial expenditure of FDA resources

Other (Requires Division Director Approval) – Assessor writes justification here if “other” selected as theme.

Assessment Summary: Liraglutide Injection solution is supplied in a pre-filled pen with a 3 mL (b) (4) cartridge, rubber plunger stopper (b) (4). Each mL contains 6.0 mg of Liraglutide, 1.42 mg Sodium phosphate dibasic dihydrate, 5.5 mg phenol, 14.0 mg propylene glycol, hydrochloride acid and sodium hydroxide to adjust to pH 8.15 and q.s. water for injection. The proposed formulation is the same as that of the RLD. (b) (4)

(b) (4) a recommended storage condition of refrigerated at 2°C to 8°C (36° to 46°F).

(b) (4)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments
Chemical Stability (All CQAs)	High	(b) (4)	High	(b) (4)

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	Medium		Low	

Highlight Key Issues from Last Cycle and Their Resolution: First Cycle (NA)

Concise Description of Outstanding Issues (list bullet points with key information and update as needed):

-
-
-
-
-
-
-

(b) (4)

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: **N/A***
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data meets revised specifications (if applicable) to confirm shelf life proposal **N/A***
- *Elemental impurity controlled per USP<232> and <233> requirements or ICH Q3D recommendations – status: **Yes***
- *Number of Comparability protocols included: **0***

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Liraglutide injection is (b) (4) clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. The pH of the solution is approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH.

Liraglutide injection contains synthesized Liraglutide, a fragment of the naturally occurring human GLP-1 (Glucagon-like peptide-1) sequence position 7-37 having two modifications: 1) substitution of the naturally occurring lysine amino acid residue in position 34 by arginine, and 2) addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysine in position 26. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C₁₇₂H₂₆₅N₄₃O₅₁ and the molecular weight is 3751.2 Daltons. The structural formula of Liraglutide (Figure 2.3.P.1-1) is shown below:

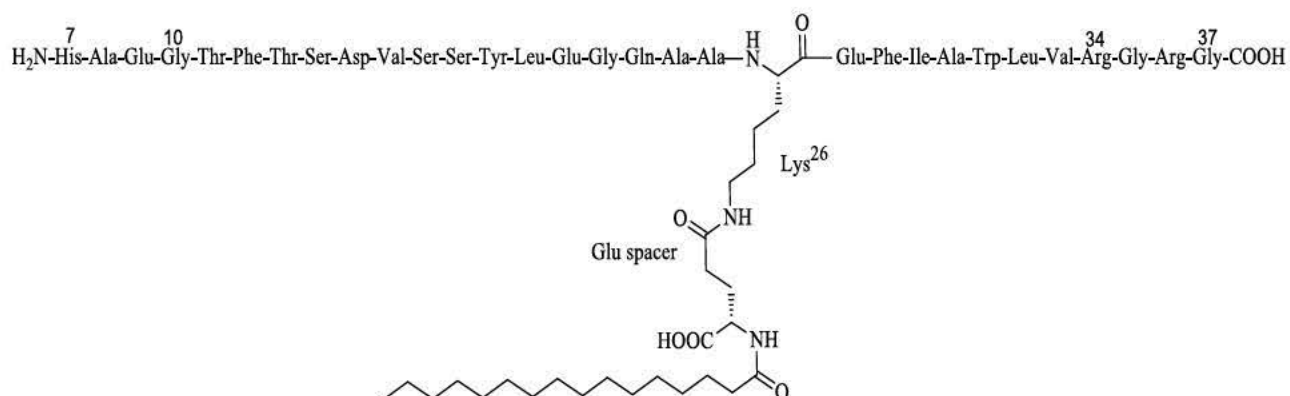


Figure 2.3.P.1-1 Structural formula of Liraglutide

Liraglutide injection is refrigerated and is not frozen. After first use, Liraglutide injection is stored at a temperature not exceed 30 °C (86 °F) and is discarded after use for 30 days.

The compositions of Liraglutide Injection 18 mg/3 mL (6mg/mL) are tabulated below.

Table 2.3.P.1-1 Composition of Liraglutide Injection 18 mg/3 mL (6 mg/mL)

Ingredients	Function	Quality standard	Amount/3 mL	Concentration	% (w/v)	% (w/w)	
Liraglutide	Active ingredient	In-house	18 mg	6 mg/mL	(b) (4)		
Disodium phosphate dihydrate	(b) (4)	USP-NF	(b) (4)	1.42 mg/mL	(b) (4)		
Propylene glycol		USP-NF		14 mg/mL			
Phenol		USP-NF		5.5 mg/mL			
Sodium hydroxide	pH modifier	USP-NF	Q.S to adjust pH of 8.15				
Hydrochloric acid							
Water for injection	(b) (4)	USP		(b) (4)			

The excipients used in Liraglutide Injection 18 mg/3 mL (6 mg/mL) include disodium phosphate dihydrate, propylene glycol, phenol, sodium hydroxide and diluted hydrochloric acid and water for injection, and they comply to current USP-NF compendial standard. As shown in the following table, the level of each excipient is well within the IID limit for this route of administration, therefore no special safety concerns regarding excipient concentrations exist in the drug product.

Table 2.3.P.1-2 IID limits of Each Excipient in Liraglutide Injection

Ingredients	Amount per 3 mL of Liraglutide injection 18 mg/3 mL (6 mg/mL)	% (w/v)	IID levels (Subcutaneous injection)*	Quality Standard	Justification
Disodium phosphate dihydrate	(b) (4)	(b) (4)	Not applicable	USP-NF	In accordance with RLD
Propylene glycol			1.4% w/v	USP-NF	In accordance with RLD and conform to IID level
Phenol			0.55% w/v	USP-NF	
Sodium hydroxide			1% w/v	USP-NF	
Hydrochloric acid			0.61% w/v	USP-NF	
Water for injection			Not applicable	USP	In accordance with RLD
Conclusion	The ingredient levels of drug product conform to IID levels or in accordance with the RLD.				

* Information is from FDA IID database updated on April 28, 2021.

Generic Liraglutide injection 18 mg/3 mL (6 mg/mL) is Q1/Q2 the same as the RLD, VICTOZA[®]. No differences between them exist. The table below gives the Q1/Q2 comparison details.

Table 2.3.P.1-3 Comparison of Drug Formulation between Generic Liraglutide Injection 18 mg/3 mL (6 mg/mL) and RLD

RLD* (VICTOZA [®])				Hybio			
Ingredient	Function	Amount	Conc.	Ingredient	Function	Amount	Conc.
Liraglutide	Active ingredient	18 mg	6 mg/mL	Liraglutide	Active ingredient	18 mg	6 mg/mL

RLD* (VICTOZA®)				Hybio			
Ingredient	Function	Amount	Conc.	Ingredient	Function	Amount	Conc.
Disodium phosphate dihydrate		(b) (4)	1.42 mg/mL	Disodium phosphate dihydrate		(b) (4)	1.42 mg/mL
Propylene glycol			14 mg/mL	Propylene glycol			14 mg/mL
Phenol			5.5 mg/mL	Phenol			5.5 mg /mL
Sodium hydroxide/ Hydrochloric acid	pH modifier	Q.S. to adjust pH to 8.15		Sodium Diluted hydrochloric acid	pH modifier	Q.S. to adjust pH to 8.15	
Water for injection	(b) (4)			Water for injection	(b) (4)		
Conclusion	The generic Liraglutide Injection 18 mg/3 mL (6 mg/mL) is qualitatively and quantitatively (Q1/Q2) the same as RLD.						

* Information from the labeling of VICTOZA®.

Liraglutide sameness is essential to the therapeutic equivalence between the generic product and RLD following the FDA Guidance-*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (October 2017) and details refer to Section 3.2.S.3.1.

There is no difference between the formulation of generic Liraglutide injection 18 mg/3 mL (6 mg/mL) and RLD. In light of above, the generic product is demonstrated therapeutic equivalence to the RLD

Assessment: **Inadequate pre Review #01**



Not for FOIA- (b) (4)

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R REGIONAL INFORMATION

Environmental

Assessment: Adequate

The applicant requested a categorical [exclusion](#) from the requirement to prepare and submit an environmental assessment, in accordance with 21 CFR 25.15(a), for DP application for Liraglutide Injection. It was noted that there was no extraordinary circumstances exist (21 CFR 25.15(d)), which may significantly affect the quality of the human environment, since approval of the application will not increase the use of the active moiety, Liraglutide. This is acceptable.

Methods Validation or Verification Package

Assessment: NA

Comparability Protocols

Assessment: None

Lifecycle Management Considerations

None

DRUG PRODUCT LIST OF DEFICIENCIES

1.

2.

(b) (4)

3 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

17

(b) (4)

Primary Drug Product Assessor Name and Date: 11/22/2021, 5/17/2022

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Hongmei Li, 2/17/2022, 5/23/2022*

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the ANDA IQA Guide](#)

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If "No", what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g., diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A

(b) (4)

(b) (4)

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☐ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): NA

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling Assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: NA

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date:
Stancy Joseph Ph.D. 11/22/2021

Secondary Drug Product Assessor Name and Date: Hongmei Li, 2/17/2022



Stancy
Joseph

Digitally signed by Stancy Joseph

Date: 6/08/2022 07:05:17AM

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Hongmei
Li

Digitally signed by Hongmei Li

Date: 6/08/2022 08:11:09AM

GUID: 54c94ca000084932f06afe87774bef34

ANDA 215503

Assessment #R01

CHAPTER V: MANUFACTURING

For more details about the items in this template, please see [Chapter V \(Manufacturing\) of the ANDA IQA Guide](#)

Application ID	ANDA 215503
Drug Product Name	Liraglutide Injection
Strengths	18 mg/3 mL
Dosage Form	Injectable, solution
Administration Route	For subcutaneous injection
Indication	(b) (4)
Applicant Name	Hikma Pharmaceuticals USA Inc
RLD Number	22341
Primary Assessor	Jin Lee
Secondary Assessor	James Norman

I. Manufacturing Summary

Facility Assessment Recommendation: *Deferred-Travel Restrictions-COVID19*

Process Assessment Recommendation: *Inadequate - Minor*

Assessment Summary:

- DP is a multi-dose, disposable pen injector pre-filled with a colorless 3-mL (b) (4) cartridge sealed with a rubber plunger (b) (4) delivers doses of 0.6, 1.2 or 1.8 mg. The formulation consists of the peptide API (Liraglutide) at 6 mg/mL and (b) (4) (propylene glycol) (b) (4) (phenol) (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

•

List Submissions Being Assessed (table):

Document Description (SD #)	Date Received
Original submission (SD 1)	08 September 2021
Response to DRL in R01 (SD 10)	14 April 2022

Updates per SD 10 rec'd on 04/14/2022 entered in **Blue Font** in this review.

Highlight Key Issues from Last Cycle and Their Resolution: N/A, first review cycle.

Concise Description of Outstanding Issues (*list bullet points with key information and update as needed*):

•

•

•

(b) (4)

- Both drug product and drug substance manufacturing facilities need pre-approval inspection as there is no prior FDA inspection history before the sites can be considered acceptable.

List Number of Comparability Protocols: None.

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose an item.	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Hybio Pharmaceutical Co., Ltd. (Pingshan factory)	3011090684	(b) (4)	Deferred-Travel Restrictions-COVID
2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong, China, 518118			Deferred-Travel Restrictions-COVID
Hybio Pharmaceutical Co., Ltd		(b) (4)	Approve - Based on Previous History
Hybio Pharmaceutical Co., Ltd		(b) (4)	Deferred-Travel Restrictions-COVID
			No Evaluation Necessary

63 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

1. In your response to Question 1 of the CDRH deficiencies on page 83 of the Discipline Review Letter you submitted your CAPA Management Procedure, document #1-SOP (b) (4) to support your meeting the requirements of 21 CFR 820.100 for Corrective and Preventative Action. However, your Standard Operating Procedure does not include steps for addressing all the required elements of a complete CAPA plan. Please revise your procedure to include the following deficient elements of CAPA as identified in 21 CFR 820.100:
 - a. Procedures for review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.
 - b. Procedures for appropriate statistical analysis of these quality data to detect recurring quality problems.
 - c. Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications.
 - d. Procedures to ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Jin Lee 01-10-2022 02-17-2022	James Norman	2/18/2022	IR	TBD
2	Jin Lee 05-10-2022 06-02-2022	James Norman	6/6/2022	Deferred-Travel Restrictions-COVID19	Withheld
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.



James
Norman

Digitally signed by James Norman

Date: 6/06/2022 03:20:06PM

GUID: 54d1401f0008405d17dd845b922ef0b9



Jin
Lee

Digitally signed by Jin Lee

Date: 6/06/2022 02:08:37PM

GUID: 5e29af84001305aa1126fc98d5370bf6

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 215503

Drug Product: Liraglutide Injection

DMF#: (b) (4)

DMF Subject (API name): liraglutide, non-sterile bulk drug substance

DMF Holder: (b) (4)

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

1. Are there any **secondary DMFs** referenced by this DMF? ☐ Yes ☒ No

If yes, fill in the following table.

Secondary DMF #	Subject of the DMF	Intermediate/Starting material?

Note: If the secondary DMF is for a regulatory starting material, a review of the secondary DMF may not be needed.

2. **For original DMFs only: Is the regulatory starting material appropriately designated as per ICH Q11 guidelines?** ☒ Yes ☐ No ☐ N/A

If No, has the firm provided complete facility information?

☐ Yes. Fill in the following table and send a directed update to the RBPM under the most recent DMF project in Panorama. Use IR comment #1 in TCIR-IR Comments template ([SharePoint: DLAPI/TCIR/TCIR-IR Comments](#)).

☐ No. Fill in what has been provided and send a directed update to the RBPM under the most recent DMF project in Panorama for missing information. Use IR comment in #2 in TCIR-IR Comments template ([SharePoint: DLAPI/TCIR/TCIR-IR Comments](#)).

Facility Name and Address [#]	FEI/DUNS	Intermediate critical (Y/N)**	Justification*
* Re-designation of the KSM may result in a starting material facility becoming an intermediate manufacturing facility, therefore please select a justification(s) from the following:			

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
4. Intermediate is not deemed critical because the criteria above do not apply.
5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre-existing facility and was not evaluated for other applications.

****Note: Add "Pending Evaluation" as the initial assessment. Update this once the response to IR is received.**

Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.

3. Are there any intermediate facilities listed in the 356h? ☐Yes ☒No

If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
4. Intermediate is not deemed critical because the criteria above do not apply.
5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre-existing facility and was not evaluated for other applications.

4. Does the Type II API DMF list any manufacturing facilities, intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐Yes ☒No

If yes, include the information identifying each facility and its function below:

Facility Name and Address [#]	Function [§]	Justification if Intermediate facility*	FEI/DUNS [#]
* If an intermediate facility is identified, please select justification(s) from the following: 1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation. 2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification. 3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification. 4. Intermediate is not deemed critical because the criteria above do not apply. 5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre-existing facility and was not evaluated for other applications. Note: If intermediate facility is not deemed critical, the facility IR comment is NOT issued to the ANDA applicant.			

[§] Facility function codes for hidden and critical intermediate facilities:

CSN: Non-Sterile API by Chemical Synthesis

CSS: Sterile API by Chemical Synthesis

CSP: Chemical Sterilization

LCP: Laboratory, Chemical/Physical Testing

LBi: Laboratory, Biological Testing

LMS: Laboratory, Microbiological – Sterility Testing

LMN: Laboratory, Microbiological – Non-Sterility Testing

CXA: Plant/Animal Extraction Purified API

CFN: Non –Sterile API by Fermentation

CFS: Sterile API by Fermentation

CRU: API Non-Sterile/Intermediate (**Note: The only code to be used for the intermediate facilities**)

#Note: *Not for FOI boxes (refer to SOP for format) need to be used if the facility information is submitted in a secondary DMF.*

Note to Reviewer: *Do not alter this language beyond providing the specifics for the yellow and blue text.*

DMF hidden facility language to be issued to ANDA applicant if the site is in primary or secondary DMF:

*There **is a facility/are facilities** (e.g. DS manufacturing, intermediate, or release/stability testing sites) that **is/are** included in **DMF [primary DMF#]** **OR** a DMF that is referenced by DMF [primary DMF#] for [API name] that **was/were** not listed in your application (i.e. Form FDA 356h and/or in Section 3.2.S.2.1). Please note that the Agency cannot provide to you the status of facilities not listed in your application. Please contact your DMF holder to identify and resolve any discrepancies and clarify which DMF related facilities support your application. We recommend that the DMF related facilities supporting your application be added to your Form FDA 356h and in Section 3.2.S.2.1. If only a subset of the facilities in the DMF will be referenced by your application to support commercial manufacturing and/or testing, your LOA should specify those facilities. Absent this specificity, the Agency intends to assume that all facilities listed in a DMF support your application. Note, there may be an extension of the performance goal date if any facilities have been added to the DMF since the last application assessment cycle.*

5. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult? ☐Yes ☒No

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

6. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☐No ☒N/A

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☒No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:



Brian
Connell

Digitally signed by Brian Connell

Date: 9/30/2021 10:42:48AM

GUID: 516c077a000104b263ffe9850300abc1

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: August 14, 2024

Reviewer: Ian Dunne, PharmD, BCPS
Safety Evaluator, Division of Pharmacovigilance I (DPV-I)

Team Leader: Daniel Woronow, MD, FACC
DPV-I

(Deputy) Division Director: Lisa Wolf, PharmD, BCCCP
Deputy Director, DPV-I

Product Names, Application Types/Numbers, Applicants:

Product Name	Active Ingredient(s)	NDA/BLA	Applicant
Byetta	Exenatide synthetic	021773	AstraZeneca AB
Byetta	Exenatide synthetic	021919	Amylin
Bydureon	Exenatide synthetic, extended release	022200	AstraZeneca AB
Bydureon BCise	Exenatide synthetic, extended release	209210	AstraZeneca AB
Victoza	Liraglutide recombinant	022341	Novo Nordisk Inc.
Saxenda	Liraglutide recombinant	206321	Novo Nordisk Inc.
Xultophy 100/3.6	Insulin degludec, liraglutide	208583	Novo Nordisk Inc.
Tanzeum	Albiglutide	125431	GlaxoSmithKline
Trulicity	Dulaglutide	125469	Eli Lilly and Co.
Adlyxin	Lixisenatide	208471	Sanofi-Aventis US
Soliqua 100/33	Insulin glargine, lixisenatide	208673	Sanofi-Aventis US
Ozempic	Semaglutide	209637	Novo Nordisk Inc.
Rybelsus	Semaglutide	213051	Novo Nordisk Inc.
Rybelsus	Semaglutide	213182	Novo Nordisk Inc.
Wegovy	Semaglutide	215256	Novo Nordisk Inc.
Mounjaro	Tirzepatide	215866	Eli Lilly and Co.
Zepbound	Tirzepatide	217806	Eli Lilly and Co.

Subject: Altered Skin Sensations

TTT Record ID:

SS ID #:



TABLE OF CONTENTS

Executive Summary	3
1 Introduction.....	4
1.1 Background	4
1.2 Regulatory History	6
1.3 Relevant Product Labeling.....	8
2 Methods and Materials.....	9
2.1 Case Definition.....	9
2.2 Causality Criteria.....	9
2.3 FAERS Search Strategy	10
2.4 Data Mining Search Strategy	11
2.5 Literature Search Strategy	11
2.6 Information Requests	12
3 Results.....	13
3.1 FAERS and IR Responses Case Selection	13
3.2 Data Mining.....	22
3.3 Literature Results	23
3.4 Information Request Responses	23
4 Discussion	31
5 Conclusion and Recommendations.....	33
6 References.....	35
7 Appendices.....	40
7.1 Appendix A. FDA Adverse Event Reporting System.....	40
7.2 Appendix B. Line Listing of GLP-1 RAs and Altered Skin Sensations Case Series....	41
7.3 Appendix C. Additional FAERS Search for Non-Serious Cases of GLP-1 RAs and Altered Skin Sensations	44

EXECUTIVE SUMMARY

The purpose of this pharmacovigilance review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of altered skin sensations associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS), the medical literature, and information provided by the Applicants. Information and recommendations from this review will aid DDLO in their evaluation of the current labeling for GLP-1 RA products and determination of whether any regulatory action is warranted regarding altered skin sensations.

We identified 62 cases sourced from FAERS (n=56) or the Applicants' Information Request (IR) Responses (n=6) with serious outcomes or direct reports of altered skin sensations with use of semaglutide (n=50), tirzepatide (n=10), or dulaglutide (n=2). DPV-I assessed these cases as probable (n=14) and possible (n=48) causality. Of the 62 cases, 24 cases reported altered skin sensations, which were coded with a serious regulatory outcome, having manifestations of the event that included difficulty wearing clothes (n=17), difficulty sleeping (n=4), difficulty grooming (n=1), difficulty showering (n=1), and reduced ability to work (n=1), noting a case may report more than one of these.

For completeness, we also searched the FAERS database for non-serious reports with the four products (i.e., albiglutide, exenatide, liraglutide, lixisenatide) that were not otherwise captured in our case series to further inform this safety issue. This search strategy identified eight non-serious cases of altered skin sensations with exenatide (n=4), liraglutide (n=3, including 1 case with a probable causal association), and albiglutide (n=1) use.

The evidence supporting a causal association between altered skin sensations and GLP-1 RAs includes a temporal relationship, recovery following discontinuation, and recurrence after therapy interruption and repeat exposure. DPV-I did not identify literature or other data sources to substantiate a potential underlying mechanism for the altered skin sensations.

In conclusion, we find an association between the class of GLP-1 RAs and altered skin sensations. DPV-I recommends the following:

-  (b) (4)

1 INTRODUCTION

The purpose of this pharmacovigilance review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of altered skin sensations associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS), the medical literature, and information provided by the Applicants. Information and recommendations from this review will aid DDLO in their evaluation of the current labeling for GLP-1 RA products and determination of whether any regulatory action is warranted regarding altered skin sensations.

1.1 BACKGROUND

Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.^{1,2,3} **Hyperpathia** is a painful syndrome characterized by an abnormally painful reaction to a stimulus as well as an increased threshold.¹ **Dysesthesia** (dysaesthesia) and **paresthesia** (paraesthesia) are both abnormal sensations, but dysesthesia describes an unpleasant abnormal sensation.¹ **Hyperesthesia** (hyperaesthesia) describes increased sensitivity to stimulation and is used to indicate both an increased response to stimuli that are normally recognized and a diminished threshold to any stimulus.¹ **Hyperalgesia** describes increased pain from a stimulus that normally provokes pain.¹ **Allodynia** describes pain due to a stimulus that does not normally provoke pain.¹ Although each of these pain terms are distinct in definition regarding the individual pain experience, some terms may be broader overarching terms (e.g., hyperpathia may occur with dysesthesia, hyperesthesia, hyperalgesia, or allodynia) and some terms may be overlapping terms (e.g., hyperalgesia and allodynia may overlap in certain circumstances, such as with pressure or temperature).¹ For the purposes of this pharmacovigilance review, the consolidated term 'altered skin sensation' will capture the associated pain terms hyperpathia, dysesthesia, hyperesthesia, hyperalgesia, and allodynia.

Neuropathies

Neuropathy is a disturbance of function or pathological change in a nerve.¹ Peripheral neuropathic pain can result from mononeuropathy, mononeuropathy multiplex, or polyneuropathy (PN).^{1,4} Assessment involves evaluation of system involvement, distribution of weakness, nature of sensory involvement, evidence of upper motor neuron involvement, and temporal evolution.^{4,5} Causes of PN include hereditary, injury, tumors, autoimmune disorders, infections, vascular disorders, systemic disorders, medications, toxins, nutritional deficiencies, and metabolic disorders.^{4,5} Management includes treatment of the underlying process and symptom alleviation.

Drug-induced PN results from peripheral nerve damage through different drug-mediated mechanisms.⁶ Drugs or drug classes most implicated include antimicrobials (e.g., dapsone, isoniazid, metronidazole, nitrofurantoin, penicillamine),^{7,8,9,10,11} anti-cancer therapeutics (e.g., cisplatin, oxaliplatin, docetaxel, paclitaxel, bortezomib, vincristine, thalidomide),^{12,13,14,15,16,17,18} tumor necrosis factor inhibitors (e.g., infliximab, certolizumab),^{19,20} colchicine,²¹ disulfiram,²² and phenytoin.^{6,23,24} Drug-induced PN can appear within weeks to months after initiation of a medication. Management includes drug discontinuation, dosage minimization, and neuropathic

pain pharmacotherapy (e.g., tricyclic antidepressants, gabapentinoids, serotonin-norepinephrine reuptake inhibitors).⁶

Diabetic PNs (DPNs) are distinguished by onset, fiber type affected, pathology, physiology, and clinical features.^{25,26} DPNs associated with clinical features of painful sensations include distal symmetric sensorimotor PN, diabetic distal small fiber neuropathy, diabetic lumbosacral radiculoplexus neuropathy, and treatment-induced neuropathy of diabetes.²⁶ Management includes optimizing metabolic factors and treating neuropathic pain with pharmacotherapy, although the neuropathic pain with treatment-induced neuropathy of diabetes is reported to be poorly responsive to pharmacotherapy.

Obesity is a risk factor for musculoskeletal system disorders likely related to the mechanical load of excessive body weight, yet there is limited evidence describing the relationship between obesity and PN.^{27,28,29} Limited information exists for neuropathy associated with rapid weight loss except for peroneal neuropathy with weight reduction.³⁰

Nutritional deficiencies of thiamine (Vitamin B1), cobalamin (Vitamin B12), and pyridoxine (Vitamin B6) can result in PN with sensory, motor, or sensorimotor involvement. Major causes of thiamine deficiency include chronic and excessive alcohol intake, recurrent vomiting, and severe malabsorption.^{31,32,33} Major causes of cobalamin deficiency include pernicious anemia, severe malabsorption, and mild malabsorption.^{32,33,34} Major causes of pyridoxine deficiency include end-stage kidney disease on hemodialysis, pregnancy and lactation, advanced age, chronic and excessive alcohol use, and medications (e.g., isoniazid, penicillamine).^{8,11,32,34}

Glucagon-like peptide-1 (GLP-1) Receptors in the Nervous System

Both the central nervous system (CNS) and the peripheral nervous system express GLP-1 receptors.^{35,36} Due to the short half-life of endogenous GLP-1, there is limited understanding of the function of GLP-1 receptors in the human CNS. Certain GLP-1 RAs (e.g., exenatide, liraglutide, lixisenatide) can penetrate the CNS following peripheral administration, although the degree of blood-brain barrier penetration varies.^{35,37,38,39} Within the peripheral nervous system, limited evidence with certain GLP-1 RAs (e.g., exenatide, dulaglutide, semaglutide) demonstrates a potential improvement of nerve excitability and morphological abnormalities in DPN.^{40,41} Ongoing clinical research seeks to investigate neurological effects (including the potential neuroprotective effect) of GLP-1 RAs in humans.⁴²

Summary of Events Leading to this Review

On August 4, 2023, the Applicant for semaglutide products submitted the Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report (PSUR/PBRER) for the reporting period of June 1, 2022, through May 31, 2023.⁴³ The Applicant reported ongoing signal evaluation for 'altered skin sensation' detected on April 17, 2020. The Applicant reported that the following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) were included in the signal evaluation: *Burning sensation, Dysaesthesia, Hyperaesthesia, Neuralgia, Pain of skin, Paraesthesia, and Skin burning sensation*. As part of the signal evaluation, the Applicant evaluated recent clinical trial data from OASIS 1 and PIONEER PLUS. In OASIS 1, events related to altered skin sensation were reported in a higher proportion of participants receiving oral semaglutide 50 mg [62 events in 12.6% (42/334) of participants] versus placebo [4 events in

1.2% (4/333) of participants].⁴⁴ In PIONEER PLUS, events related to altered skin sensation were reported for oral semaglutide at dosages of 14 mg [8 events in 1.1% (6/534) of participants], 25 mg [11 events in 2.1% (11/534) of participants], and 50 mg [38 events in 5.2% (28/534) of participants].⁴⁵



On September 15, 2023, DDLO sent a General Advice Letter to the Applicant for semaglutide products and referenced the PSUR/PBRER for the reporting period of June 1, 2022, through May 31, 2023.⁴⁶ DDLO conveyed the following comments and recommendations:



On November 14, 2023, DPV-I opened a newly identified safety signal (NISS) 1005228 for the GLP-1 RA class and PT *Dysaesthesia* (noting reports coded for related PTs may also represent the event of altered skin sensations). On November 30, 2023, DDLO and DPV-I met to discuss the NISS. There was consensus to move the NISS to the evaluation phase and to send Information Requests (IRs) to the Applicants for their respective GLP-1 RA products.



1.2 REGULATORY HISTORY

Currently, there are six GLP-1 RAs approved by FDA and currently marketed under one or more tradenames (see Table 1 below). The first GLP-1 RA product, Byetta (exenatide synthetic, NDA 021773), was approved on April 28, 2005, in the United States (U.S.).

Tanzeum (albiglutide, BLA 125431) was previously marketed in the U.S. until July 2018, but currently has a voluntary “revoked” status due to a business decision (low usage of the product) and not related to safety or efficacy.^{49,50,51} Bydureon (exenatide extended release, NDA 022200) was previously marketed in the U.S., but the Applicant submitted a permanent withdrawal from

sale for business reasons effective March 2021.^{52,53} Adlyxin (lixisenatide, BLA 208471) was previously marketed in the U.S., but the Applicant submitted a notification of permanent discontinuation for business reasons on February 22, 2023, and a General Correspondence on July 31, 2024, notifying the Agency of plans to formally withdraw the BLA.^{54,55,56}

All GLP-1 RA products except for weight management formulations are indicated as adjunct therapy to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus (T2DM).^{57,58,59,60,61,62,63,64,65,66,67} This indication is extended to pediatric patients aged 10 years and older for Bydureon BCise (exenatide synthetic, extended release), Victoza (liraglutide), and Trulicity (dulaglutide).^{59,60,62} Victoza (liraglutide), Trulicity (dulaglutide), and Ozempic (semaglutide) are also indicated to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease.^{60,62,65} Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) are indicated for chronic weight management (CWM) in adults (Saxenda and Wegovy at higher daily doses compared to the subcutaneous products of the same ingredients indicated for glycemic control and also pediatric patients aged 12 years and older).^{68,69,70} Wegovy (semaglutide) is also indicated to reduce the risk of major adverse cardiovascular events in adults with established cardiovascular disease and either obesity or overweight.⁶⁹

Table 1 lists currently marketed FDA-approved GLP-1 RA products, including single-ingredient products and fixed ratio drug-drug combinations, in the U.S.

Table 1. Currently Marketed GLP-1 RAs in the United States				
Product Name NDA/BLA Applicant	Active Ingredient(s), Formulation	Indication(s)	Dosage Ranges	Approval Date
Byetta 021773 AstraZeneca AB	Exenatide synthetic, SC Inj	T2DM in adults	5 mcg to 10 mcg twice daily	4/28/2005
Bydureon BCise 209210 AstraZeneca AB	Exenatide synthetic, extended release, SC Inj	T2DM in adults, pediatrics ≥ 10 years	2 mg every 7 days	10/20/2017
Victoza 022341 Novo Nordisk Inc.	Liraglutide recombinant, SC Inj	T2DM in adults, pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM and established CVD	0.6 mg titrated to 1.8 mg daily	1/25/2010
Saxenda 206321 Novo Nordisk Inc.	Liraglutide recombinant, SC Inj	Weight management in adults*, pediatrics ≥ 12 years†	0.6 mg titrated to 3 mg daily	12/23/2014
Xultophy 100/3.6 208583 Novo Nordisk Inc.	Insulin degludec + liraglutide, SC Inj	T2DM in adults	10 units titrated to 50 units daily	11/21/2016
Trulicity 125469 Eli Lilly and Co.	Dulaglutide, SC Inj	T2DM in adults, pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM	0.75 mg titrated to 4.5 mg weekly‡	9/18/2014

Table 1. Currently Marketed GLP-1 RAs in the United States				
		and established CVD or multiple CV risk factors		
Soliqua 100/33 208673 Sanofi-Aventis US	Insulin glargine + lixisenatide, SC Inj	T2DM in adults	15 units titrated to 60 units daily	11/21/2016
Ozempic 209637 Novo Nordisk Inc.	Semaglutide, SC Inj	T2DM in adults; reduce the risk of MACE in adults with T2DM and established CVD	0.25 mg titrated to 2 mg weekly	12/5/2017
Rybelsus 213051 Novo Nordisk Inc.	Semaglutide, oral tablet	T2DM in adults	3 mg titrated to 14 mg daily	9/20/2019
Wegovy 215256 Novo Nordisk Inc.	Semaglutide, SC Inj	Weight management in adults [§] , pediatrics ≥ 12 years ; reduce the risk of MACE in adults with established CVD and either obesity or overweight	0.25 mg titrated to 2.4 mg weekly	6/4/2021
Mounjaro 215866 Eli Lilly and Co.	Tirzepatide, SC Inj [¶]	T2DM in adults	2.5 mg titrated to 15 mg weekly	5/13/2022
Zepbound 217806 Eli Lilly and Co.	Tirzepatide, SC Inj [¶]	Weight management in adults ^{**}	2.5 mg titrated to 15 mg weekly	11/8/2023
Source: Drugs@FDA * Adults with an initial BMI of 30 kg/m ² or greater (obese), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia) † Pediatrics with body weight > 60 kg and an initial BMI corresponding to 30 kg/m ² for adults (obese) ‡ In pediatrics, the maximum recommended dosage is 1.5 mg once weekly § Adults with an initial BMI of 30 kg/m ² or greater (obesity), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia) Pediatrics with an initial BMI at the 95th percentile or greater for age and sex (obesity) ¶ Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist ** Adults with an initial BMI of 30 kg/m ² or greater (obesity), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, T2DM, obstructive sleep apnea, or CVD) Abbreviations: BLA=Biologics License Application, BMI=body mass index, CV=cardiovascular, CVD=cardiovascular disease, GLP-1 RA=glucagon-like peptide-1 receptor agonist, Inj=injection, MACE=major adverse cardiovascular events, NDA=New Drug Application, SC=subcutaneous, T2DM=type 2 diabetes mellitus				

1.3 RELEVANT PRODUCT LABELING

DPV-I reviewed the USPIs for currently available single-ingredient GLP-1 RA products and fixed ratio drug-drug combination GLP-1 RA products.

For single-ingredient GLP-1 RA products, the USPI for Wegovy (semaglutide) mentions the term "Dysesthesia" footnoted with "Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin" in the ADVERSE REACTIONS *Clinical Trials Experience* section.⁶⁹ The term "Dysaesthesia" was added to the USPI for Wegovy following approval of a PAS (Supplement-11).⁷¹ The USPIs for the remaining

currently available single-ingredient GLP-1 RA products do not contain language regarding altered skin sensations or related terms.

For fixed ratio drug-drug combination GLP-1 RA products, the USPIs for Xultophy 100/3.6 and Soliqua 100/33 include labeling language regarding "acute painful peripheral neuropathy" in relation to initiation of insulin-containing products and intensification of glucose control.^{61,64} Table 2 provides a summary table of USPI labeling for fixed ratio drug-drug combination GLP-1 RA products with language relevant to acute painful peripheral neuropathy.

Table 2. Summary Table of USPI Labeling for Currently Marketed Multi-Ingredient GLP-1 RAs with Language Relevant to "Acute Painful Peripheral Neuropathy"		
BLA	Active Ingredients (Product Name)	USPI Labeling for Section 6 ADVERSE REACTIONS
208583	insulin degludec, liraglutide (Xultophy 100/3.6)	Section 6.1 Clinical Trials Experience <i>Initiation of insulin containing products and intensification of glucose control</i> Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
208673	insulin glargine, lixisenatide (Soliqua 100/33)	Section 6.1 Clinical Trials Experience <i>Insulin Initiation and Intensification of Glucose Control</i> Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
Abbreviations: BLA=biologics license application, GLP-1 RA=glucagon-like peptide-1 receptor agonist, USPI=United States Prescribing Information		

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

DPV-I used the following case definition to develop the case series of GLP-1 RAs and altered skin sensations:

- Cases reporting diffuse and painful skin sensations.

2.2 CAUSALITY CRITERIA

Causality was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment (Table 3).⁷² A conservative approach to

assessing causality was used in this review. Criteria for unlikely causal association are modified to address concerns specific to altered skin sensations. Cases were excluded if causality was determined to be unlikely or unassessable.

Table 3. Causality Categories and Criteria Adapted from the WHO-UMC System⁷²	
Category	Criteria
Probable	• Event or laboratory test abnormality with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable
Possible	• Event or laboratory test abnormality with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (however, not impossible) • Disease or other drugs provide more plausible explanations (e.g., pre-existing neurological disorder, pre-existing chronic cutaneous disorder, other suspect medication with a more likely association with altered skin sensations) • Alternative etiology (e.g., cutaneous hypersensitivity reactions, cutaneous events reporting erythema or physical signs of skin irritation, injection site reactions) • Case more consistent with diabetic neuropathies, especially isolated distal polyneuropathies (see Section 1.1)
Unassessable	• Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified • Reports describing altered skin sensations without enough information to exclude the possibility of a cutaneous hypersensitivity reaction or an injection site reaction • Reports indicating a compounded product containing a GLP-1 RA (e.g., cyanocobalamin/semaglutide)
Abbreviations: GLP-1 RA= glucagon-like peptide-1 receptor agonists, WHO-UMC=World Health Organization-Uppsala Monitoring Centre	

2.3 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategies described in Table 4. Please note that our initial scoping search strategy that did not restrict to serious outcome or direct reports retrieved 913 reports. DPV-I and DDLO met to discuss the review search strategy on November 30, 2023, and determined that for the purpose of this review, we would restrict our search strategy to reports with a serious regulatory outcome and direct reports (Table 4).

Table 4. FAERS Search Strategy*	
Date of search	March 27, 2024
Time period of search	All reports through March 26, 2024

Table 4. FAERS Search Strategy*	
Search type	RxLogix Quick Query
Product terms	Therapeutic drug class: “GLP-1 Receptor Agonist [EPC]” [†]
MedDRA search terms (Version 26.1)	PTs <i>Allodynia, Burning sensation, Dysaesthesia, Hyperaesthesia, Hyperpathia, Pain of skin, Sensitive skin, Skin burning sensation, Skin discomfort, Skin sensitisation</i>
Other criteria	Search #1: Serious outcome [‡] Search #2: Direct reports
* See Appendix A for a description of the FAERS database. [†] Although Tanzeum (albiglutide) has a voluntary “revoked” status, Bydureon (exenatide extended release) is permanently withdrawn from sale, and Adlyxin (lixisenatide) is permanently discontinued, these products were included in the search to assess FAERS reports within the GLP-1 RA drug class. [‡] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. Abbreviations: EPC=established pharmacologic class, FAERS=FDA Adverse Event Reporting System, GLP-1=glucagon-like peptide-1, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.4 DATA MINING SEARCH STRATEGY

DPV-I used the Empirica Signal software with the strategy described in Table 5 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”). If a drug-event combination has an EB05 ≥ 2 , this indicates with 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining results do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Table 5. Data Mining Search Strategy*	
Data refresh date	March 24, 2024
Product terms	albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide
Empirica Signal run name	PAM(S)
MedDRA search strategy	PTs <i>Allodynia, Burning sensation, Dysaesthesia, Hyperaesthesia, Hyperpathia, Pain of skin, Sensitive skin, Skin burning sensation, Skin discomfort, Skin sensitisation</i>
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAM=product active moiety, PT=Preferred Term	

2.5 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategies described in Table 6 and Table 7.

Table 6. Literature Search Strategy	
Date of search	March 27, 2024

Table 6. Literature Search Strategy	
Years included in search	All
Database	Embase
Search terms	('glucagon like peptide 1 receptor agonist'/exp OR 'glucagon like peptide 1'/exp OR 'glucagon like peptide 1 receptor'/exp OR 'incretin'/exp OR 'semaglutide'/exp OR 'tirzepatide'/exp OR 'liraglutide'/exp OR 'lixisenatide'/exp OR 'dulaglutide'/exp OR 'albiglutide'/exp OR 'exendin 4'/exp) AND ('allodynia'/exp OR 'dysesthesia'/exp OR 'hyperesthesia'/exp OR 'tactile hypersensitivity'/exp OR 'hyperalgesia'/exp OR 'insulin neuritis'/exp OR 'altered skin sensation') AND 'human'/de

Table 7. Literature Search Strategy	
Date of search	March 27, 2024
Years included in search	All
Database	PubMed@FDA
Search terms	(incretins [mh] OR incretins [pharmacological action] OR incretins [tw] OR incretin [tw] OR "incretin based" [tw] OR exenatide [tw] OR "exendin 4" [tw] OR "exendin-4" [tw] OR liraglutide [tw] OR lixisenatide [tw] OR dulaglutide [tw] OR semaglutide [tw] OR tirzepatide [tw] OR "GLP-1RA" [tw] OR "GLP-1RAS" [tw] OR "GLP1-RA" [tw] OR "GLP1-RAS" [tw] OR "GLP-1R agonist" [tw] OR "GLP-1R agonists" [tw] OR glucagon-like peptide 1 receptor agonist* [tw] OR glucagon-like peptide 1 agonist* [tw] OR "glucagon-like peptide 1 analog*" [tw] OR GLP-1 receptor agonist* [tw] OR glp1 receptor agonist* [tw] OR GLP-1 agonist* [tw] OR glp1 agonist* [tw] OR GLP-1 analog* [tw] OR "GLP1 analog*" [tw] OR "Glucagon-Like Peptide-1 Receptor/agonists"[Mesh] OR "Glucagon-Like Peptide 1/agonists"[Mesh] OR "Glucagon-Like Peptide 1/analogs and derivatives"[Mesh] OR "glucagon-like peptide 1" [mh] OR "glucagon-like peptide 1" [tw] OR "GLP-1" [tw] OR GLP1 [tw]) AND (allodynia OR dysesthesia OR hyperesthesia OR tactile hypersensitivity OR hyperpathia OR insulin neuritis OR skin sensitization OR skin sensitivity OR skin sensitisation OR skin sensitive OR skin burning)
Limits	Human

2.6 INFORMATION REQUESTS^{73,74,75,76,77,78,79,80,81,82}

On January 9, 2024, DDLO sent IRs to the Applicants for their respective GLP-1 RA products. In the IRs, the Agency requested the following:

1. "We request that you perform a cumulative review of all cases of 'altered skin sensations' (e.g., hyperesthesia, dysesthesia, allodynia, skin burning sensation) for [TRADENAME]. The analysis should include clinical trial data, spontaneous reports, and a review of the literature. Also, include a discussion on biological plausibility and potential mechanism of this adverse reaction. At a minimum, include in your search the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): allodynia,

burning sensation, dysaesthesia, hyperaesthesia, hyperpathia, pain of skin, sensitive skin, skin burning sensation, skin discomfort, skin sensitization."

2. "Provide tabular listings and brief narrative summaries that include the following: demographics/clinical characteristics, medical history, dose, duration of treatment, concomitant medications, and the adverse reaction details (e.g., MedDRA PT/Reported Term, time to onset, severity/seriousness, relatedness to product, action taken, dechallenge and rechallenge information, and event outcome). Provide (if applicable) an analysis of clinical trial data comparing adverse event incidence by dose of study GLP-1 RA treatment compared to placebo or other non-GLP-1 RA comparators. Where applicable, data should be stratified according to indication for use."

3 RESULTS

3.1 FAERS AND IR RESPONSES CASE SELECTION

The FAERS searches retrieved 337 reports. After applying the case definition in Section 2.1, the causality criteria in Section 2.2, and accounting for duplicate reports, 56 cases from FAERS were included in the case series of altered skin sensations reported with GLP-1 RA use. Six additional cases were identified from the IR Responses for inclusion in the case series, for a total of 62 cases in the case series (see Figure 1 and Table 8). We did not retrieve any additional case reports from our medical literature search (see Section 3.3 for additional details).

Figure 1. FAERS Case Selection

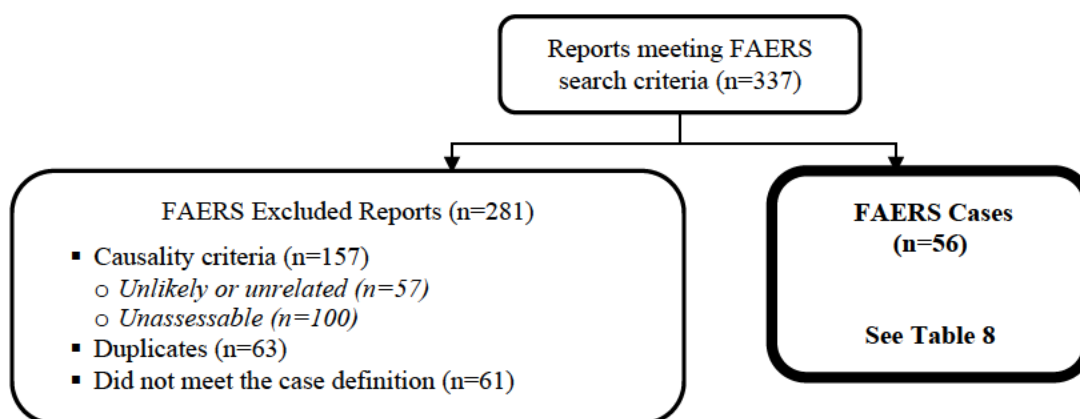


Table 8 summarizes the 62 cases from FAERS (n=56) and the IR Responses (n=6) of altered skin sensations reported with GLP-1 RA use for this case series.

Appendix B contains a line listing of the 62 cases in this case series.

Table 8. Descriptive Characteristics of Altered Skin Sensations With GLP-1 RAs in This Case Series from FAERS through March 26, 2024, and IR Responses Received by FDA (N=62)

Characteristic	Categories	Dulaglutide (n=2)	Semaglutide (n=50)*	Tirzepatide (n=10) [†]	Total (n=62)
Case source [‡]	FAERS IR Responses	1 1	46 4	9 1	56 6
Age, years (n=59)	Mean Median Range	57.5 57.5 57-58	49.9 51 25-75	47.7 47.5 38-57	49.8 51 25-75
Sex	Male Female NR	1 1 0	12 36 2	2 8 0	15 45 2
Initial year of report	2019 2021 2022 2023 2024 NR [§]	0 0 1 0 0 1	2 1 4 28 11 4	0 0 1 8 0 1	2 1 6 36 11 6
Country	U.S. Foreign NR**	1 0 1	44 6 0	8 1 [¶] 1	53 7 2
FAERS case type (n=56)	Expedited Direct	0 1	5 41	1 8	6 50
Serious outcome ^{††} (n=24)	Other Disability Required Intervention	1 0 0	14 3 2	4 1 0	19 4 2
Causality	Probable Possible	2 0	10 40	2 8	14 48
Reporter	Healthcare professional Consumer NR	1 1 0	12 35 3	1 9 0	14 45 3
Reported PTs ^{‡‡}	<i>Allodynia</i> <i>Burning sensation</i> <i>Dysaesthesia</i> <i>Hyperaesthesia</i> <i>Hyperpathia</i> <i>Pain of skin</i> <i>Sensitive skin</i> <i>Skin burning sensation</i> <i>Skin discomfort</i> <i>Skin sensitisation</i>	0 0 0 0 0 2 0 1 0 0	15 4 4 14 0 13 5 11 0 2	2 1 0 1 0 5 1 2 0 0	17 5 4 15 0 20 6 14 0 2
Reason for use	Glycemic control related Weight management related Other ^{§§} NR	2 0 0 0	9 32 4 5	7 3 0 0	18 35 4 5
GLP-1 RA dose at time of event	Starting dose (per USPI) Middle dose ^{¶¶} Maximum dose ^{***} NR	1 1 0 0	1 29 12 8	2 5 2 1	4 35 14 9
Event occurrence in dose series	First dose Second dose Dose titration NR	1 0 0 1	8 1 6 35	3 1 0 6	12 2 6 42

Table 8. Descriptive Characteristics of Altered Skin Sensations With GLP-1 RAs in This Case Series from FAERS through March 26, 2024, and IR Responses Received by FDA (N=62)

Characteristic	Categories	Dulaglutide (n=2)	Semaglutide (n=50)*	Tirzepatide (n=10) [†]	Total (n=62)
TTO from initiation (days)^{†††}	≤ 24 hours	0	4	1	5
	> 1 to 2 days	1	3	2	6
	> 2 to 7 days	0	1	0	1
	> 7 to 30 days	0	4	3	7
	> 30 to 60 days	0	3	0	3
	> 60 to 90 days	0	9	0	9
	> 90 to 182 days	0	12	2	14
	> 182 days to 365 days	0	1	1	2
	NR	1	13	1	15
Additional management (e.g., procedures, tests, treatments) (n=28)	GLP-1 RA discontinuation only	1	17	2	20
	Pharmacologic treatment ^{†††}	1	2	1	4
	Nerve conduction study	0	0	1 ^{§§§}	1
	Laboratory tests	0	3 ^{¶¶¶}	3 ^{****}	6
Manifestation(s) of events^{††††} (n=19)	Difficulty grooming	0	0	1	1
	Difficulty showering	0	1	0	1
	Difficulty sleeping	0	2	2	4
	Difficulty wearing clothes	0	13	4	17
	Reduced ability to work	0	1	0	1
GLP-1 RA disposition	Discontinued	1	19	3	23
	Therapy interrupted ^{††††}	1	11	3	15
	Dose decreased	0	4	2	6
	Continued	0	14	2	16
	NR	0	2	0	2
Event outcome	Recovered	2	23	3	28
	Partially recovered	0	2	2	4
	Not recovered	0	22	5	27
	NR	0	3	0	3

Table 8. Descriptive Characteristics of Altered Skin Sensations With GLP-1 RAs in This Case Series from FAERS through March 26, 2024, and IR Responses Received by FDA (N=62)

Characteristic	Categories	Dulaglutide (n=2)	Semaglutide (n=50)*	Tirzepatide (n=10) [†]	Total (n=62)
* Cases include reports for Wegovy (n=32), Ozempic (n=13), Rybelsus (n=3), and "semaglutide" (n=2). [†] Cases include reports for Mounjaro (n=10). [‡] FAERS: includes any case identified in either FAERS alone or in both FAERS and the IR Responses; IR Responses: includes cases only identified in the Applicants' IR Responses. [§] These six cases were identified in the Applicants' IR Responses and did not include the initial year of the report. Denmark (n=2), Colombia (n=1), Japan (n=1), Norway (n=1), and United Kingdom (n=1) [¶] Japan (n=1) ** These two cases were identified in the Applicants' IR Responses and reported "unknown origin". ^{††} For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. ^{‡‡} A case may be coded for more than one PT. A case may be coded for the same PT more than once. ^{§§} Other indications included "Obesity" and "Hyperlipidemia" (n=1), "Weight loss and prediabetes" (n=1), "PCOS insulin issues" (n=1), and "Various" (n=1). Cases reporting use of FDA approved initial dose. ^{¶¶} Cases reporting use of a dose between the FDA approved initial dose and maximum dose for glycemic control (e.g., dulaglutide 4.5 mg, oral semaglutide 14 mg, semaglutide 2 mg, tirzepatide 15 mg) or weight management (e.g., semaglutide 2.4 mg, tirzepatide 15 mg). *** Cases reporting use of FDA approved maximum dose for glycemic control (e.g., oral semaglutide 14 mg, semaglutide 2 mg, tirzepatide 15 mg) or weight management (e.g., semaglutide 2.4 mg, tirzepatide 15 mg). ^{†††} Two cases reported background therapy with other medications associated with altered skin sensations; however, no preceding altered skin sensations were reported with these medications prior to the initiation of the GLP-1 RA. Background therapy medications included citalopram (n=1) and lisinopril/hydrochlorothiazide (n=1). ^{‡‡‡} Pharmacologic treatments included "antihistamines" (n=1), ibuprofen (n=1), "pain reliever" (n=1), "paracetamol" (n=1), topical depilatory cream (n=1), topical diclofenac gel (n=1), and topical lidocaine cream (n=1). A case may report more than one treatment. ^{§§§} This case reported "a nerve conduction study ... was normal", but additional information was not reported. A case may report more than one laboratory test. ^{¶¶¶} One case reported the following laboratory testing and results: "Vitamin B12" result value 218 pg/mL (normal range 200-1100 pg/mL), "Folate, serum" result value 7.9 ng/mL (normal range > 5.4 ng/mL), "Vitamin D, 25-OH, Total, IA" result value 22 ng/mL (normal range ≥ 30 ng/mL), and Covid-19 testing (unspecified testing type) resulting negative "twice". One case reported unspecified laboratory testing ("13 different lab tests") and "normal" results. One case reported unspecified laboratory testing and "negative" results. **** One case reported unspecified "blood and urine tests...came back normal". One case reported laboratory testing for "deficiencies" and "normal" results. One case reported unspecified "bloodwork" and "unremarkable" results. ^{††††} A case may report more than one manifestation of events. ^{‡‡‡‡} Two cases reported therapy interruption followed by dose decreased, although these two cases were not counted as "dose decreased". Abbreviations: FAERS=FDA Adverse Event Reporting System, GLP-1 RA=glucagon-like peptide-1 receptor agonist, IR=information request, mL=milliliter, ng=nanogram, NR=not reported, pg=picogram, PT=preferred term, TTO=time to onset, USPI=U.S. Prescribing Information					

Of the 15 cases reporting GLP-1 RA disposition as therapy interrupted, 12 cases reported the altered skin sensations recovered following therapy interruption. These 12 cases were noteworthy due to recurrence of altered skin sensations upon restarting the GLP-1 RA.^a

From the Applicants' IR Responses, DPV-I included 11 cases in our case series that were identified only in the Applicants' IR Responses (n=6) or were crossmatched with FAERS cases previously included in our case series (n=5). Table 9 summarizes the cases and compares the Applicants' case assessments with DPV-I's case assessments.

^a FAERS Cases #s: 23043319, 23067472, 23515518, 22130649, 22798120, 22850419, 22930714, 16168258, 21440326, 21968957; MCNs US202302004365 and GB202305002810

Table 9. Comparison of Applicants' Comments from IR Responses with DPV-I Assessment of Cases within our Case Series of Altered Skin Sensations Reported with GLP-1 RA Use

(N=11)*

MCN	FAERS Case #	Active Ingredient (Product Name)	Brief Narrative or Summary	Applicant's Assessment	DPV-I Assessment of Case and Applicant's Comments	DPV-I Causality Assessment (WHO-UMC)
GB202305002810	NA	Dulaglutide (Trulicity)	57-year-old male experienced "skin pain ... since starting dulaglutide" 1.5 mg weekly for T2DM. After 6 weeks, the patient stopped dulaglutide and the pain "gradually subsided over the next 10 weeks". Dulaglutide was restarted and the pain returned. Dulaglutide was discontinued again, and the pain subsided.	The Applicant categorized this "key case" as a case of "positive rechallenge". The Applicant noted the improvement with the use of topical diclofenac gel. The Applicant did not report a causality assessment.	DPV-I notes the altered skin sensations recovered after therapy interruption. DPV-I notes the recurrence of altered skin sensations after restarting dulaglutide. Although the Applicant categorizes this as a "key case" it is unclear if the Applicant considers this a causally related case.	Probable
NO-NOVOPROD-1124447	23067472	Semaglutide (Wegovy)	56-year-old female experienced "skin pain and Touch sensitivity increased" with semaglutide 1.7 mg for "Obesity" and "Hyperlipidemia". Concomitant medication included atorvastatin. Semaglutide was tapered followed by "a drug break in the summer" and the patient recovered from the altered skin sensations. The physician reporter stated, "After restarting and dose titration in the autumn, the problems have returned. No other known cause was found for the symptoms, which coincide in time with the use of Wegovy." The reporter stated that the altered skin sensations reduced the patient's ability to work. Semaglutide was discontinued.	The Applicant assessed this case as unlikely causality, stating that "The causal association between the event and the drug has been assessed as unlikely based on the alternative explanation for the event including coadministered atorvastatin"	DPV-I notes the altered skin sensations temporally correlated with changes in exposure to semaglutide, but did not correlate with continued exposure to atorvastatin, supporting semaglutide as the causally related drug. DPV-I disagrees with the Applicant's assessment of unlikely causality.	Probable
US-NOVOPROD-1123905	23043319	Semaglutide (Ozempic)	61-year-old female experienced "skin was painful to touch" with semaglutide for "diabetes mellitus". Past medical history included "diabetes". The patient noted the altered skin sensations occurred prior to the therapy	The Applicant assessed this case as unassessable causality, stating that "The causal association between the event and the drug is unassessable"	DPV-I notes the altered skin sensations recovered after therapy interruption. DPV-I notes the recurrence of altered skin	Probable

Table 9. Comparison of Applicants' Comments from IR Responses with DPV-I Assessment of Cases within our Case Series of Altered Skin Sensations Reported with GLP-1 RA Use

(N=11)*

			interruption. The patient reported a therapy interruption for a hysterectomy. The altered skin sensations recovered during the therapy interruption. One week after resuming semaglutide, the "skin being painful to touch came back". After restarting semaglutide with recurrence of altered skin sensations, the action taken with semaglutide and the outcome of altered skin sensations were not reported.	[sic] due to the missing information pertaining to the concomitant medication, therapy..." [remainder of comment not included in IR Response]	sensations 1 week after restarting semaglutide. DPV-I disagrees with the Applicant's assessment of unassessable causality.	
1085023	22675649	Semaglutide (Ozempic)	44-year-old female experienced "Sensation of severe sunburn when skin was brushed" with semaglutide 1 mg for "weight loss". There was "No actual rash, redness or sunburn anywhere on affected area". Semaglutide was discontinued. The patient recovered from the altered skin sensations.	"Possible- The causal association between the event and the drug has been assessed as possible based on the plausible temporal relationship, positive dechallenge and no alternative explanation from the available medical history and concomitant medications."	DPV-I notes the altered skin sensations recovered after discontinuation of semaglutide. DPV-I agrees with the Applicant's assessment of possible causality.	Possible
881512	NA	Semaglutide (Ozempic)	45-year-old female experienced "increased skin sensitivity in feet and knee" within 1 day of starting semaglutide for T2DM. Semaglutide was discontinued. The patient recovered from the altered skin sensations.	"Possible- The causal association between the event and the drug has been assessed as possible based on the plausible temporal relationship, positive dechallenge and no alternative explanation from the available medical history and concomitant medications."	DPV-I notes the temporal relationship of 1 day and the altered skin sensations recovered after discontinuation of semaglutide. DPV-I agrees with the Applicant's assessment of possible causality.	Possible
1103853	NA	Semaglutide (Rybelsus)	A patient of unreported age and gender experienced "Burning sensation and tingling sensation in the full body" while receiving oral semaglutide 7 mg for T2DM. Semaglutide was discontinued. The patient recovered from the altered skin sensations.	"Possible- The causal association between the event and the drug has been assessed as possible based on the plausible temporal relationship, positive dechallenge and no alternative	DPV-I notes the altered skin sensations recovered after discontinuation of oral semaglutide. DPV-I agrees with the Applicant's assessment of possible causality.	Possible

Table 9. Comparison of Applicants' Comments from IR Responses with DPV-I Assessment of Cases within our Case Series of Altered Skin Sensations Reported with GLP-1 RA Use

(N=11)*

				explanation from the available medical history and concomitant medications."		
US-NOVOPROD-1085858	22833284	Semaglutide (Wegovy)	59-year-old male experienced "burning sensation on back, forearms and outer thighs" with semaglutide 1.7 mg for "weight loss and prediabetes". On an unspecified date, the patient also reported experiencing "pins and needles feeling, cold sensation to various parts of body, and felt he had possible permanent nerve damage". Semaglutide was discontinued due to the altered skin sensations. The patient recovered from "burning sensation on back, forearms and outer thighs". The remaining events were reported as not recovered at the time of the report.	The Applicant assessed this case as unlikely causality, stating that "The causal association between the event and the drug has been assessed as unlikely based on the negative..." [remainder of comment not included in IR Response]	DPV-I notes the altered skin sensations partially recovered after discontinuation of semaglutide, although the initial FDA received date was only 1 month after semaglutide discontinuation. DPV-I disagrees with the Applicant's assessment of unlikely causality.	Possible
1069235	NA	Semaglutide (Wegovy)	53-year-old male experienced "dysaesthesia" with semaglutide 0.5 mg for "obesity". The altered skin sensations "worsened after dose escalation to 1 mg". Semaglutide was discontinued. The patient recovered from the altered skin sensations.	"Possible- The causal association between the event and the drug has been assessed as possible based on the plausible temporal relationship, positive dechallenge and no alternative explanation from the available medical history and concomitant medications."	DPV-I notes the worsening of dysaesthesia upon dose titration. DPV-I notes the altered skin sensations recovered after discontinuation of semaglutide. DPV-I agrees with the Applicant's assessment of possible causality.	Possible
1105254	NA	Semaglutide (Wegovy)	67-year-old female experienced "allodynia" with semaglutide 1 mg for "overweight". Semaglutide was discontinued. The patient recovered.	"Possible- The causal association between the event and the drug has been assessed as possible based on the plausible temporal relationship, positive dechallenge and no alternative explanation from the available medical history and concomitant medications."	DPV-I notes the altered skin sensations recovered after discontinuation of semaglutide. DPV-I agrees with the Applicant's assessment of possible causality.	Possible

Table 9. Comparison of Applicants' Comments from IR Responses with DPV-I Assessment of Cases within our Case Series of Altered Skin Sensations Reported with GLP-1 RA Use

(N=11)*

JP202307017345	22782749	Tirzepatide (Mounjaro)	51-year-old female experienced "pain of skin" after starting tirzepatide 2.5 mg for T2DM. Six days after increasing the dose to tirzepatide 5 mg, she visited a hospital for generalized skin pain. Tirzepatide was discontinued and semaglutide was started. After 4 weeks, the patient reported improvement in the generalized symptoms, although the patient was still experiencing a sensation reported as "sunburn".	The Applicant categorized this "key case" as a case with "serious adverse event" and noted a positive dechallenge. The Applicant did not report a causality assessment.	DPV-I notes the worsening of the altered skin sensations following dose titration. DPV-I notes the altered skin sensations partially recovered after discontinuation of tirzepatide and initiation of semaglutide. Although the Applicant categorizes this as a "key case" it is unclear if the Applicant considers this a causally related case.	Possible
US202302004365	NA	Tirzepatide (Mounjaro)	46-year-old female experienced "skin sensitivity from head to her toes" within 1 day of tirzepatide 10 mg for T2DM. Her primary care physician recommended to discontinue tirzepatide. Following discontinuation, "It took about 10 days to subside and 2 weeks for it to fully go away". She restarted the historical medication of dulaglutide, but then switched back to tirzepatide. After restarting tirzepatide, "She was experiencing it all over again, no one can touch her because it hurts".	The Applicant categorized this "key case" as a case of "positive de-challenge and re-challenge". The Applicant noted "Corrective treatment not reported, and the outcome of event was unknown". The Applicant did not report a causality assessment.	DPV-I notes the altered skin sensations recovered after therapy interruption. DPV-I notes the recurrence of altered skin sensations after restarting tirzepatide. Although the Applicant categorizes this as a "key case" it is unclear if the Applicant considers this a causally related case.	Possible

* Includes cases identified only in the Applicants' IR Responses (n=6) and cases identified in both our FAERS search and the Applicant's IR Responses (n=5)

Abbreviations: AE=adverse event, IR=Information Request, FAERS= FDA Adverse Event Reporting System, GLP-1 RA=glucagon-like peptide-1 receptor agonist, MCN=Manufacturer Control Number, mg=milligram, NA=not applicable, PT=preferred term, T2DM=type 2 diabetes mellitus, WHO-UMC= World Health Organization-Uppsala Monitoring Centre

Three cases assessed as probable causality are discussed below. Also, these are all direct reports, with serious regulatory outcomes that are related to altered skin sensations.

3.1.1 Best Representative Cases

FAERS Case #22359601; 2023; USA; Direct; Serious Outcome: Other

A 50-year-old female self-reported her case of altered skin sensations with the use of semaglutide (Ozempic) for "various" indications. Past medical history included "high blood pressure", "high cholesterol", and essential thrombocythemia. The report contained no information about diabetes or weight. Concomitant medications included metoprolol succinate, modafinil, and ondansetron. She started semaglutide 0.25 mg with "no side effects" and approximately 2 months later the dose was titrated to semaglutide 0.5 mg with "no side effects". Approximately 4 months after semaglutide initiation, the dose was titrated to semaglutide 1 mg and she "began experiencing a Sunburn feeling on back, torso, and scalp with no visible marks". She reported that "The lightest touch became painful and clothing rubbing on my skin became intolerable". She continued experiencing painful sensations while receiving semaglutide. She reported that "Four days after I stopped the injections the sunburned feeling went away".

Reviewer's Comments: The patient experienced diffuse and painful skin sensations following a dose titration of semaglutide and the patient continued to experience the altered skin sensations until discontinuation of semaglutide. There is a reasonable temporal relationship between the dose titration of semaglutide and the onset of altered skin sensations in addition to the resolution of altered skin sensations four days after discontinuation of semaglutide. None of the chronic medications contain labeling language related to altered skin sensations. DPV-I assessed this case as probable causality based on the reasonable temporal relationship, resolution of symptoms following discontinuation of semaglutide, and the relative lack of other more plausible explanations that would completely account for the altered skin sensations.

FAERS Case #21572772; 2022; USA; Direct; Serious Outcome: Other

A pharmacist reported a case of a 58-year-old female who experienced altered skin sensations after the first dose (0.75 mg) of dulaglutide for T2DM. Past medication history included T2DM, atrial fibrillation, hypertension, hyperlipidemia, obesity, "PCOS", asthma, "OSA", diverticulosis, and proteinuria. Concomitant medications included metformin extended release and atorvastatin. Within 1 hour of the first dose of dulaglutide, the patient experienced "dispersed nerve pain...in legs and arms" and within 1 day the patient experienced "sharp pain under skin...along with burning and itching." The patient fully recovered from the altered skin sensations at the time of the report (report submitted 7 days after the initial administration of dulaglutide). Dulaglutide was discontinued.

Reviewer's Comments: The patient experienced diffuse and painful skin sensations following initiation of dulaglutide. There is a close temporal relationship between the first and only dose of dulaglutide and the onset of altered skin sensations within 1 hour to 1 day in addition to the resolution of altered skin sensations within 7 days after the initial dose of dulaglutide. None of the chronic concomitant medications contain labeling language for painful altered skin sensations. DPV-I assessed this case as probable causality based on the reasonable temporal

relationship, resolution of symptoms following discontinuation of dulaglutide, and the relative lack of other more plausible explanations that would completely account for the altered skin sensations.

FAERS Case #23409284; 2024; USA; Direct; Serious Outcome: Other

A 51-year-old female self-reported her case of altered skin sensations with the use of semaglutide (Wegovy) for "weight loss". Past medical history included Graves' disease and hypertension. Concomitant medications included levothyroxine, spironolactone, metoprolol succinate, potassium chloride, omeprazole, gabapentin, "topamax", and "Wellbutrin". The patient reported a therapy change from liraglutide (Saxenda) to semaglutide (Wegovy) due to manufacturer back order. Within 10 days after starting semaglutide, the patient experienced "skin pain ... all over 100% of my body the entire time I was on the medication". The patient reported that "It hurt to the touch, it hurt to wear clothes". The patient discontinued semaglutide and restarted liraglutide (no doses reported). The patient reported recovery of the altered skin sensations, stating that "after about 10-14 days, it progressively went away & is now 100% gone".

Reviewer's Comments: The patient experienced diffuse and painful skin sensations after starting semaglutide and the patient continued to experience the altered skin sensations until discontinuation of semaglutide. There is a reasonable temporal relationship between the initiation of semaglutide and the onset of altered skin sensations within 10 days in addition to the resolution of altered skin sensations 10-14 days after discontinuation of semaglutide. None of the chronic concomitant medications contain labeling language for painful altered skin sensations. It is noteworthy that altered skin sensations occurred with use of once weekly Wegovy, but not with once daily Saxenda. DPV-I assessed this case as probable causality based on the reasonable temporal relationship, resolution of symptoms following discontinuation of semaglutide, and the relative lack of other more plausible explanations that would completely account for the altered skin sensations.

3.2 DATA MINING

Table 10 summarizes the results of the data mining search using Empirica Signal for altered skin sensations with GLP-1 RA use that had an EB05 $\geq$ 2.

Table 10. Data Mining Results Using Empirica Signal for Altered Skin Sensations Reported with GLP-1 RA Use, Sorted by Decreasing EB05*						
	Product Active Moieties	MedDRA Preferred Terms	N	EB05	EBGM	EB95
1	SEMAGLUTIDE	<i>Allodynia</i>	124	47.636	55.357	64.035
2	SEMAGLUTIDE	<i>Hyperaesthesia</i>	90	7.247	8.647	10.255
3	SEMAGLUTIDE	<i>Skin sensitisation</i>	16	5.121	7.883	11.815
4	SEMAGLUTIDE	<i>Sensitive skin</i>	99	5.107	6.041	7.106
5	SEMAGLUTIDE	<i>Pain of skin</i>	91	2.124	2.531	2.997
* An EB05 $\geq$ 2 indicates with 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected." Events with EB05 < 2 are not included in this table. Abbreviations: GLP-1 RA=glucagon-like peptide-1 receptor agonist, MedDRA= Medical Dictionary for Regulatory Activities						

3.3 LITERATURE RESULTS

Using the search strategy listed in Table 6, the Embase search retrieved 229 citations. Using the search strategy listed in Table 7, the PubMed@FDA search retrieved 28 citations. After deduplication (n=3), there were 254 unique citations from the published medical literature. The titles and abstracts of the articles were reviewed to identify articles specific to GLP-1 RAs and altered skin sensations.

Of the 254 unique citations, DPV-I did not identify case reports or case series related to altered skin sensations with GLP-1 RAs. DPV-I did not identify any new safety findings related to altered skin sensations with GLP-1 RAs from published medical literature. Table 11 lists the reasons for exclusion for the 254 citations.

Table 11. Literature Articles Excluded (n=254)*		
Exclusion Reason	Embase (n=229)	PubMed@FDA (n=25)*
Unrelated to the topic of GLP-1 RAs and altered skin sensations	60	10
Review article	152	3
General article	11	12
Professional Guidelines	6	0
* The PubMed@FDA search retrieved three duplicate excluded articles from the Embase search. These articles are included in the Embase column and not the PubMed@FDA column.		

3.4 INFORMATION REQUEST RESPONSES

The Applicants' IR Responses are summarized below.

3.4.1 Tirzepatide^{83,84}

The Applicant assessed the safety data cumulatively through December 31, 2023. The Applicant searched both its Clinical Trial database, Lilly Safety System (LSS) global database, and the EudraVigilance database with the PTs *Allodynia*, *Burning sensation*, *Dysaesthesia*, *Hyperaesthesia*, *Hyperpathia*, *Pain of skin*, *Sensitive skin*, *Skin burning sensation*, *Skin discomfort*, and *Skin sensitisation*. The Applicant also searched the scientific literature.

Clinical Trials

For the Clinical Trials database search, the Applicant performed separate analyses of the clinical trial data for T2DM and CWM indications.

From pooled trials for T2DM, the Applicant reported 14 (0.21%) participants in the tirzepatide group (n=6,819) experienced altered skin sensations compared with 5 (0.15%) participants in the comparator group (n=3,282), representing a minor numerical imbalance with tirzepatide. In the tirzepatide group, the 16 treatment-emergent adverse events (TEAEs) (14 participants) were reported with tirzepatide 5 mg (n=4), tirzepatide 10 mg (n=4), and tirzepatide 15 mg (n=8). The 16 TEAEs were reported as non-serious. Of these 16 TEAEs, the Investigator considered 4 TEAEs (2 participants) as related to tirzepatide. These four TEAEs for tirzepatide 15 mg were

coded for PTs *Burning sensation* (n=3) and *Sensitive skin* (n=1). The Applicant did not provide case narrative information for case level analysis.

From pooled trials for CWM, the Applicant reported 20 (0.51%) participants in the tirzepatide group (n=3,907) experienced altered skin sensations compared with 1 (0.06%) participant in the comparator group (n=1,743), representing a numerical imbalance with tirzepatide. In the tirzepatide group, the 23 TEAEs (20 participants) were reported with tirzepatide 5 mg (n=1), tirzepatide 10 mg (n=3), tirzepatide 15 mg (n=5), and tirzepatide "maximum tolerated dose (aimed at a maximum dose of 15 mg, unless not tolerated)" (n=14). The 23 TEAEs were reported as non-serious. Of these 23 TEAEs, the Investigator considered 16 TEAEs (14 participants) as related to tirzepatide 5 mg (n=1), tirzepatide 10 mg (n=2), tirzepatide 15 mg (n=3), or tirzepatide "maximum tolerated dose" (n=10). These 16 TEAEs were coded for PTs *Skin burning sensation* (n=4), *Burning sensation* (n=3), *Sensitive skin* (n=3), *Allodynia* (n=2), *Dysaesthesia* (n=2), *Hyperaesthesia* (n=1), and *Pain of skin* (n=1). The Applicant provided a case summary for one case of positive dechallenge and positive rechallenge that the Investigator considered related to tirzepatide. DPV-I reviewed the case summary and assessed the case as unassessable due to confounding factors (i.e., history of intervertebral disc disorder) and limited information (e.g., concomitant medications, location(s) of events in relation to the injection site).

For the LSS global database search of clinical trials, the Applicant retrieved zero serious reports.

Postmarketing

DPV-I reviewed the Applicant's postmarketing information in the IR Response. All relevant reports are included in our case series and discussed in Table 9, and the remaining reports did not meet our case selection criteria.

Scientific Literature

The Applicant searched Embase cumulatively to December 31, 2023. The Applicant's literature search "did not identify any association studies between GLP-1 RAs or tirzepatide and dysaesthesia or altered skin sensations".

Biological Plausibility

The Applicant stated that "a review of the literature did not identify a likely mechanism for a GLP-1 RA to result in abnormal skin sensation".

Applicant's Conclusion

The Applicant concluded that "after a comprehensive analysis of overall data, there was an increased incidence of dysaesthesia in CWM clinical trials and numerical imbalance in T2DM clinical trials with the use of tirzepatide, especially at higher doses". The Applicant also stated that "A similar presentation for dysaesthesia event was noted in the description of cases reported in PM [Postmarketing] setting". The Applicant proposed to update the core data sheet for tirzepatide with "dysaesthesia as an ADR [Adverse Drug Reaction]" and to continue monitoring events of dysaesthesia by standard pharmacovigilance activities.

Following the IR Response, the Applicant submitted a PAS for both Mounjaro and Zepbound to update the USPIs with new safety language for dysaesthesia (see Sections 1.1 and 4).^{47,48}

3.4.2 Dulaglutide⁸⁵

The Applicant assessed the safety data cumulatively through December 31, 2023. The Applicant searched both its Clinical Trial database, LSS global database, and the EudraVigilance database with the PTs *Allodynia*, *Burning sensation*, *Dysaesthesia*, *Hyperaesthesia*, *Hyperpathia*, *Pain of skin*, *Sensitive skin*, *Skin burning sensation*, *Skin discomfort*, and *Skin sensitisation*. The Applicant also searched the scientific literature.

Clinical Trials

For the Clinical Trials database search, the Applicant reported 33 (0.26%) participants in the dulaglutide group (n=12,530) experienced altered skin sensations compared to 2 (0.28%) participants in the GLP-1 RA comparator group (n=713) and 30 (0.36%) participants in the non-GLP-1 RA comparator group (n=8,407), representing no apparent numerical imbalance. In the dulaglutide group, the 35 TEAEs (33 participants) were reported with dulaglutide 0.75 mg (n=7) or dulaglutide 1.5 mg (n=28). The 35 TEAEs were reported as non-serious. Of the 35 TEAEs, the Investigator considered 2 TEAEs (2 participants) as related to dulaglutide. These two TEAEs for dulaglutide 1.5 mg were coded for PT *Burning sensation* (n=2). The Applicant did not provide case narrative information for case level analysis.

For the LSS global database search of clinical trials, the Applicant retrieved zero serious reports.

Postmarketing

DPV-I reviewed the Applicant's postmarketing information in the IR Response. All relevant reports are included in our case series and discussed in Table 9, and the remaining reports did not meet our case selection criteria.

Scientific Literature

The Applicant searched Embase cumulatively to December 31, 2023. The Applicant's literature search "did not identify any association studies between GLP-1 RAs or dulaglutide and Dysaesthesia or Altered skin sensations".

Biological Plausibility

The Applicant stated that "a review of the literature did not identify a likely mechanism for a GLP-1 RA to result in abnormal skin sensation".

Applicant's Conclusion

The Applicant concluded that "data do not support a causal association between dulaglutide and events of Dysaesthesia" and that "No changes to the CDS are warranted".

3.4.3 Liraglutide and Semaglutide^{86,87}

The Applicant submitted a combined IR Response for liraglutide and semaglutide products. The Applicant assessed the safety data cumulatively until the data lock point date of January 31, 2024. The Applicant searched both its Clinical Trials database and its postmarketing safety database with the PTs *Allodynia*, *Burning sensation*, *Dysaesthesia*, *Hyperaesthesia*, *Hyperpathia*, *Pain of skin*, *Paraesthesia*, *Sensitive skin*, *Skin burning sensation*, *Skin discomfort*, and *Skin sensitisation*. The Applicant also searched the scientific literature.

Clinical Trials

For each product, the Applicant provided line listing tabulations, but the Applicant did not provide case narratives for case level analysis. The Applicant assessed the safety data separately for each GLP-1 RA product and the indication [i.e., for pooled trials for T2DM, for pooled trials for CWM, and for the cardiovascular outcomes trials (CVOTs)].

For **liraglutide**, the Applicant identified 43 events (39 participants) from pooled trials for T2DM, 57 events (48 participants) from pooled trials for CWM, and 1 event (1 participant) from the CVOT. **For pooled trials for T2DM**, the Applicant reported 39 (0.8%) participants in the liraglutide group (n=4,842) experienced altered skin sensations compared with 8 (0.5%) participants in the non-GLP-1 RA comparator group (n=1,672) and 6 (0.5%) participants in the placebo group (n=1,288), and the Applicant noted a "minor numerical imbalance" with liraglutide. In the liraglutide group, the 43 events were reported with liraglutide 0.6 mg (n=6), liraglutide 1.2 mg (n=17), and liraglutide 1.8 mg (n=20). The 43 events were reported as non-serious. The Investigator considered these 43 events as "unlikely" (n=32), "possibly" (n=10), and "probably" (n=1) related to liraglutide. The 11 events (11 participants) considered "possibly" or "probably" related were coded for PTs *Paraesthesia* (n=9), *Burning sensation* (n=1), and *Hyperaesthesia* (n=1). **For pooled trials for CWM**, the Applicant reported 48 (1.2%) participants in the liraglutide group (n=4,000) experienced altered skin sensations compared with 17 (0.7%) participants in the placebo group (n=2,325), and the Applicant noted a "numerical imbalance" with liraglutide. In the liraglutide group, the 57 events were reported with liraglutide 3 mg. The 57 events were reported as non-serious. The Investigator considered these 57 events as "unlikely" (n=43), "possible" (n=10), and "probable" (n=4) relatedness to liraglutide. The 14 events (10 participants) considered "probable" or "possible" relatedness were coded for PTs *Paraesthesia* (n=10), *Dysaesthesia* (n=3), and *Hyperaesthesia* (n=1). **For the CVOT**, the Applicant reported one (<0.1%) participant in the liraglutide group (n=4,657) experienced altered skin sensations compared to zero participants in the placebo group (n=4,664), and the Applicant noted "reporting rates are low due to the selective AE [Adverse Event] collection methodology applied in this clinical study". In the liraglutide group, the one event was reported with liraglutide 1.8 mg. The one event was reported as serious. The Investigator considered the one event as "unlikely" related.

For **insulin degludec/liraglutide**, the Applicant reported 30 (0.7%) participants in the insulin degludec/liraglutide group (n=4,437) experienced altered skin sensations compared to 18 (0.7%) participants in the non-GLP-1 RA comparator group (n=2,559) and 0 participants in the placebo group (n=146), representing no apparent numerical imbalance. In the insulin degludec/liraglutide group, the Applicant did not report the dose at which the 32 events (30 participants) were reported because the product "is administered as a fixed combination product with dose steps". The 32 events were reported as non-serious. The Investigator considered these 32 events as "unlikely" (n=28) and "possible" (n=4) relatedness to insulin degludec/liraglutide. The four events (four participants) considered "possible" relatedness were coded for PTs *Paraesthesia* (n=3) and *Dysaesthesia* (n=1).

For **subcutaneous semaglutide**, the Applicant identified 40 events (36 participants) from pooled trials for T2DM, 109 events (83 participants) from the pooled trials for CWM, 21 events (20 participants) from the CVOT for Ozempic, and 126 events (106 participants) from the CVOT for

Wegovy. **For pooled trials for T2DM**, the Applicant reported 36 (0.5%) participants in the semaglutide group (n=7,392) experienced altered skin sensations compared with 17 (0.7%) participants in the non-GLP-1 RA comparator group (n=2,538) and 3 (0.7%) participants in the placebo group (n=413), representing no apparent numerical imbalance. In the semaglutide group, the 40 events were reported with semaglutide 0.5 mg (n=13), semaglutide 1 mg (n=26), and semaglutide 2 mg (n=1). The 40 events were reported as non-serious. The Investigator considered these 40 events as "unlikely" (n=25), "multiple" (n=7), "possible" (n=5), and "probable" (n=3) relatedness to semaglutide. The eight events (eight participants) considered "possible" or "probable" were coded for PTs *Paraesthesia* (n=6) and *Burning sensation* (n=2). **For pooled trials for CWM**, the Applicant reported 83 (1.8%) participants in the semaglutide group (n=4,558) experienced altered skin sensations compared with 24 (0.9%) participants in the placebo group (n=2,617), representing a numerical imbalance with semaglutide. In the semaglutide group, the 109 events were reported with semaglutide 1 mg (n=4), semaglutide 1.7 mg (n=1), and semaglutide 2.4 mg (n=104). The events were reported as serious (n=1) and non-serious (n=108). The Investigator considered these 109 events as "unlikely" (n=67), "possible" (n=31), and "probable" (n=11) relatedness to semaglutide. The 42 events (30 participants) considered "possible" or "probable" relatedness were coded for PTs *Pain of skin* (n=9), *Skin burning sensation* (n=9), *Paraesthesia* (n=8), *Hyperaesthesia* (n=5), *Sensitive skin* (n=5), *Allodynia* (n=3), *Burning sensation* (n=2), and *Dysaesthesia* (n=1). **For the CVOT for Ozempic**, the Applicant reported 20 (1.2%) participants in the semaglutide group (n=1,642) experienced altered skin sensations compared with 15 (0.9%) participants in the placebo group (n=1,644), representing a minor numerical imbalance with semaglutide. In the semaglutide group, the 21 events were reported with semaglutide 0.5 mg (n=15) and semaglutide 1 mg (n=6). The 21 events were reported as non-serious. The Investigator considered these 21 events as "unlikely" (n=20) and "possible/probably" (n=1) relatedness. The Applicant did not provide a line listing tabulation for the CVOT for Ozempic. **For the CVOT for Wegovy**, the Applicant reported zero participants in the semaglutide group (n=8,803) experienced altered skin sensations compared with three (<0.1%) participants in the placebo group (n=8,801) in Table 3-2 from the IR Response (Study EX9536-4388); however, in Table 6 of Appendix 1K in the IR Response (Study EX9536-4388), the Applicant reported 106 (3.3%) participants in the semaglutide group (n=3,169) experienced 126 events of altered skin sensations compared with 51 (1.6%) participants in the placebo group (n=3,199) experienced 57 events, representing a numerical imbalance with semaglutide. In the semaglutide group, the 126 events were reported with semaglutide 2.4 mg. The 126 events were reported non-serious. The Investigator considered these 126 events as "unlikely" (n=84), "possible" (n=33), and "probable" (n=9) relatedness to semaglutide. The 42 events (34 participants) considered "possible" or "probable" were coded for PTs *Paraesthesia* (n=10), *Hyperaesthesia* (n=9), *Sensitive skin* (n=7), *Allodynia* (n=6), *Skin burning sensation* (n=5), *Dysaesthesia* (n=3), and *Pain of skin* (n=2).

For oral semaglutide, the Applicant identified 89 events (73 participants) from pooled trials for T2DM and 80 events (55 participants) from pooled trials for CWM. **For pooled trials for T2DM**, the Applicant reported 32 (0.52%) participants in oral semaglutide 3 mg, 7 mg, 14 mg, or "oral semaglutide flexible dose (3, 7 or 14 mg)" groups (n=6,119) experienced altered skin sensations compared with 8 (0.5%) participants in the non-GLP-1 RA comparator group (n=1,483) and 2 (0.2%) participants in the placebo group (n=845), representing no apparent numerical imbalance. In the oral semaglutide group, the 89 events occurred with oral

semaglutide strengths that are not FDA approved (i.e., 25 mg and 50 mg) (n=51), with FDA approved oral semaglutide strengths (i.e., 3 mg, 7 mg, and 14 mg) (n=35), and with "oral semaglutide flexible dose (3, 7 or 14 mg)" (n=3). The 35 events with FDA approved oral semaglutide strengths occurred with oral semaglutide 3 mg (n=8), oral semaglutide 7 mg (n=5), and oral semaglutide 14 mg (n=22). The 35 events were reported as serious (n=1) and non-serious (n=34). The Investigator considered these 35 events as "unlikely" (n=31), "possible" (n=3), and "probable" (n=1) relatedness. The four events (four participants) considered "probable" and "possible" relatedness were coded for PTs *Paraesthesia* (n=2), *Hyperaesthesia* (n=1), and *Sensitive skin* (n=1). **For pooled trials for CWM**, DPV-I did not assess the data because this indication is not currently FDA approved for oral semaglutide.

Postmarketing

The Applicant retrieved 2,023 reports from the postmarketing database search. Of these 2,023 reports, the Applicant identified 18 cases for detailed assessment. The 18 cases included reports for Ozempic (n=11), Victoza (n=2), Wegovy (n=2), Rybelsus (n=1), Saxenda (n=1), and Xultophy 100/3.6 (n=1). Of these 18 cases, 2 cases reported a serious outcome. The Applicant assessed these 18 cases as possible causality "based on the plausible temporal relationship, positive dechallenge and no alternative explanation from the available medical history and concomitant medications".

DPV-I crossmatched two cases^b with FAERS reports previously identified from the FAERS search. One report^c was previously excluded from our case series based on an assessment of unlikely causality due to a history of traumatic brain injury without additional information. One report^d was previously included as a FAERS case^e in our case series, and both the Applicant and DPV-I assessed this case as possible causality (see Table 9).

All relevant cases from the Applicant's IR Response are included in our case series and discussed in Table 9, and the remaining reports did not meet our case selection criteria.

Scientific Literature

The Applicant searched Embase, Medline, Current Contents Search, and BIOSIS Previews cumulatively to February 9, 2024. The Applicant identified three publications for assessment.^{88,89,90} DPV-I previously identified all three of these publications with our literature search strategy (see Section 2.5).^{88,89,90} None of these three publications were case reports or case series related to the safety topic of altered skin sensations. DPV-I previously excluded all three publications as "Unrelated to the topic of GLP-1 RAs and altered skin sensations" because the publications reported terms related to paraesthesia (i.e., "injection site paresthesia", "numbness", and "paraesthesia"), and this term was not captured in the consolidated term 'altered skin sensations' for the purposes of this review.

Biological Plausibility

^b MCNs 1085023 and 1038004

^c FAERS #22213715

^d MCN 1085023

^e FAERS Case #22675649

The Applicant discussed theoretical mechanisms but determined that there is not a "substantiated explanation for the underlying mechanism for adverse events of dysaesthesia".

Applicant's Conclusion

The Applicant concluded that "the totality of data included in this report does not support an increased risk of dysaesthesia with GLP-1 RA use at currently marketed doses for T2D [Type 2 diabetes mellitus] and Saxenda". The Applicant stated that "Dysaesthesia is already considered a non-important identified risk for semaglutide s.c. [subcutaneous] for weight management (Wegovy, USPI Section 6.1 ADVERSE REACTIONS *Clinical Trials Experience*), as well as for the development programme of oral semaglutide for weight management." The Applicant determined that "no updates to the product labels for currently marketed doses, nor risk management plans are warranted". The Applicant proposed to "continue to monitor reports of adverse drug reactions, including dysaesthesia, through routine pharmacovigilance".

3.4.4 Exenatide^{91,92,93}

The Applicant assessed the safety data cumulatively through January 10, 2024. The Applicant searched both its Clinical Trials database and its Global Patient Safety Database with the PTs *Allodynia, Burning sensation, Dysaesthesia, Hyperaesthesia, Hyperpathia, Pain of skin, Sensitive skin, Skin burning sensation, Skin discomfort, and Skin sensitisation*. The Applicant also searched the scientific literature.

Clinical Trials

For pooled studies of exenatide twice daily, the Applicant reported crude incidence rates of 0.05% in the exenatide twice daily group, 0.07% in the placebo group, and 0% in the comparator group, representing no apparent numerical imbalance. In the exenatide twice daily group, the Applicant identified three events, which were reported as non-serious (n=3). The Investigator reported causality as not related for all three events.⁹⁴

For pooled studies of exenatide once weekly, the Applicant reported crude incidence rates of 0.22% in the exenatide once weekly group, 0.13% in the comparator group, 0% in the exenatide twice daily group, and 0% in the placebo group, representing a minor numerical imbalance with exenatide once weekly. In the exenatide once weekly group, the Applicant identified nine events, which were reported as non-serious (n=9). Of these nine events, the Investigator considered six events as not related to exenatide. The remaining three events were considered related to exenatide and were coded for PTs *Burning sensation* (n=1), *Dysaesthesia* (n=1), and *Pain of skin* (n=1).^{95,96} The Applicant did not provide case narrative information for case level analysis.

For the dose specific evaluation of clinical data from pooled studies, the Applicant identified four events for exenatide once weekly. The Applicant reported that these four events were non-serious and did not lead to product discontinuation.^{97,98} The Applicant did not provide case narrative information for case level analysis.

Postmarketing

DPV-I reviewed the Applicant's postmarketing information in the IR Response. There were no relevant reports from the Applicant's IR Response that met our case selection criteria.

Scientific Literature

The Applicant searched Embase and “Insight Meme” cumulatively up to January 10, 2024. The Applicant determined that none of the results retrieved from the literature search were relevant to the safety topic of altered skin sensations and exenatide or GLP-1 RA products.

Biological Plausibility

The Applicant did not mention a potential mechanism for altered skin sensations and exenatide.

Applicant's Conclusion

The Applicant concluded that "there is insufficient evidence to suggest a causal association between dysaesthesia and related terms and exenatide use". The Applicant determined that "no potential amendment to the product information and/or the risk management plan is warranted at this time".

3.4.5 Lixisenatide^{99,100}

The Applicant submitted separate IR Responses for Adlyxin and Soliqua 100/33. The Applicant applied the same search strategy for both IR Responses. The Applicant assessed the safety data cumulatively through January 15, 2024. The Applicant searched both its Clinical Trials database and its Global Pharmacovigilance Database with the PTs *Allodynia*, *Burning sensation*, *Dysaesthesia*, *Hyperaesthesia*, *Hyperpathia*, *Pain of skin*, *Sensitive skin*, *Skin burning sensation*, *Skin discomfort*, and *Skin sensitization*. The Applicant also searched the scientific literature.

Clinical Trials

For pooled studies of lixisenatide, the Applicant reported crude incidence rates of 0.38% in the lixisenatide group and 0.5% in the placebo group, representing no apparent numerical imbalance. In the lixisenatide group, the Applicant identified 21 events (18 participants) in lixisenatide arms. The 21 events were reported as non-serious. Of these 21 events, the Investigator considered the events as "not causally related" (n=18) or "causally related" (n=3) to lixisenatide. The three events (three participants) considered "causally related" were coded for PT *Burning sensation* (n=3). The Applicant did not provide case narrative information for case level analysis.

For pooled studies of insulin glargine/lixisenatide, the Applicant reported crude incidence rates of 0.24% in the insulin glargine/lixisenatide group, 0.43% in the lixisenatide group, and 0.12% in the comparator group, representing minor numerical imbalances with insulin glargine/lixisenatide and lixisenatide. In the insulin glargine/lixisenatide group, the Applicant identified two events (two participants) in insulin glargine/lixisenatide arms and one event (one participant) in lixisenatide arms. The three events were reported as non-serious. The Investigator considered all three events as not causally related to study treatment. The Applicant did not provide case narrative information for case level analysis.

Postmarketing

DPV-I reviewed the Applicant's postmarketing information in the IR Response. There were no relevant reports from the Applicant's IR Response that met our case selection criteria.

Scientific Literature

The Applicant searched Medline and Embase cumulatively through January 15, 2024. The Applicant's literature search did not retrieve any literature results "discussing or suggesting an association between dysaesthesia" and lixisenatide or insulin glargine/lixisenatide.

Biological Plausibility

The Applicant stated that "no mechanism has been identified for dysaesthesia" with lixisenatide, insulin glargine/lixisenatide, or other GLP-1 RAs.

Applicant's Conclusion

The Applicant concluded that "The cumulative weight of evidence is insufficient to support a causal association between dysaesthesia" and lixisenatide or insulin glargine/lixisenatide.

4 DISCUSSION

We identified 62 cases sourced from FAERS^f (n=56) or the Applicants' IR Responses (n=6) of altered skin sensations with use of semaglutide (n=50), tirzepatide (n=10), or dulaglutide (n=2); we did not identify any cases involving albiglutide, exenatide, liraglutide, or lixisenatide. DPV-I assessed these cases as probable (n=14) and possible (n=48) causality. Of the 62 cases, 24 cases reported altered skin sensations which were coded with a serious regulatory outcome, having manifestations of the event that included difficulty wearing clothes (n=17), difficulty sleeping (n=4), difficulty grooming (n=1), difficulty showering (n=1), and reduced ability to work (n=1), noting a case may report more than one of these.

The evidence supporting a causal association between altered skin sensations and GLP-1 RAs includes a temporal relationship, recovery following discontinuation, and recurrence after therapy interruption and repeat exposure. Thirty-one cases reported time to onset within 90 days of GLP-1 RA initiation. Twelve cases reported altered skin sensations after the first dose with a time to onset within 24 hours (n=5), 24 to 48 hours (n=6), or 4 days (n=1). DPV-I identified 28 cases reporting the altered skin sensations recovered following GLP-1 RA discontinuation or therapy interruption. Table 9 includes additional details regarding some cases of therapy interruption, all of which suggested therapy interruption was for more than one week. Twelve of the cases reporting therapy interruption reported event recurrence upon restarting the GLP-1 RA, further strengthening the causal association between altered skin sensations and GLP-1 RAs.^f DPV-I did not identify literature or other data sources to substantiate a potential underlying mechanism for the altered skin sensations.

For completeness, we also searched the FAERS database for non-serious reports with the four products (i.e., albiglutide, exenatide, liraglutide, lixisenatide) that were not otherwise captured in our case series to further inform this safety issue, as noted in Appendix C. This search strategy identified eight non-serious cases of altered skin sensations with exenatide (n=4), liraglutide (n=3, including 1 case with a probable causal association), and albiglutide (n=1) use. Similar to the aforementioned case series, these cases described a temporal relationship, recovery following discontinuation, and recurrence after therapy interruption and repeat exposure. Five cases reported time to onset within 90 days of GLP-1 RA initiation. Five cases reported the altered skin sensations recovered following GLP-1 RA discontinuation or therapy interruption. Two of

^f The search strategy only included reports with a serious outcome or those received directly by FDA.

these cases reporting therapy interruption reported event recurrence upon restarting the GLP-1 RA, further strengthening the causal association between altered skin sensations and GLP-1 RAs. The case details and DPV-I comments for these eight cases are summarized in Appendix C.

Assessment of Applicants' IR Responses

From the Applicants' **pooled clinical trial data for CWM**, we assessed a consistent trend for a numerical imbalance across products with CWM indications, which includes tirzepatide (Zepbound), liraglutide (Saxenda), and semaglutide (Wegovy). We cannot exclude the possibility that the trend for a numerical imbalance with products that have CWM indications may be related to the generally higher doses for these products, as compared with GLP-1 RA products with glycemic control indications. From the Applicants' **pooled clinical trial data for CVOTs**, we assessed variability across the individual products. We assessed a numerical imbalance for semaglutide (Wegovy), a minor numerical imbalance for semaglutide (Ozempic), and no apparent imbalance for liraglutide (Victoza). From the Applicants' **pooled clinical trial data for T2DM**, we assessed variability across the individual products. We assessed a minor numerical imbalance for tirzepatide (Mounjaro), liraglutide (Victoza), exenatide once weekly (Bydureon and Bydureon BCise), lixisenatide, and insulin glargine/lixisenatide. We assessed no apparent imbalance for dulaglutide, semaglutide (Ozempic), oral semaglutide (Rybelsus), insulin degludec/liraglutide, and exenatide twice daily (Byetta).

The Applicants for dulaglutide, exenatide, and lixisenatide products determined that there is insufficient evidence to support a causal association between dysesthesia and their respective GLP-1 RA products. The Applicant for tirzepatide proposed to update the core data sheet for tirzepatide with "dysaesthesia as an ADR [Adverse Drug Reaction]" after assessing both "an increased incidence of dysaesthesia in CWM clinical trials and numerical imbalance in T2DM clinical trials with the use of tirzepatide, especially at higher doses" and "A similar presentation for dysaesthesia event ... in the description of cases reported in PM [Postmarketing] setting". The Applicant for liraglutide and semaglutide stated that "Dysaesthesia is already considered a non-important identified risk for semaglutide s.c. [subcutaneous] for weight management (Wegovy, USPI Section 6.1 ADVERSE REACTIONS *Clinical Trials Experience*), as well as for the development programme of oral semaglutide for weight management", but determined that "the totality of data included in this report does not support an increased risk of dysaesthesia with GLP-1 RA use at currently marketed doses for T2D [Type 2 diabetes mellitus] and Saxenda".

DPV-I performed a case level analysis of postmarketing cases included in the Applicants' IR Responses. DPV-I included 11 cases in our case series that were identified only in the Applicants' IR Responses (n=6) or were crossmatched with FAERS cases previously included in our case series (n=5). DPV-I assessed these 11 cases as probable (n=3) and possible (n=8) causal association. For the cases of dulaglutide (n=1) and tirzepatide (n=2) in Table 9, it is unclear if the Applicants considered the "key cases" as causally related. For the cases of semaglutide (n=8) in Table 9, both the Applicant and DPV-I assessed five cases as possible causal association, and DPV-I did not agree with the Applicants' assessments for the remaining three semaglutide cases.

Considerations for Labeling

The Guidance for Industry Adverse Reactions Section of Labeling states that the ADVERSE REACTIONS section "must list adverse reactions identified from domestic and foreign

spontaneous reports...Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug."¹⁰¹ The case series included 24 cases coded with a serious regulatory outcome. DPV-I assessed the cases in the case series (n=62) as probable (n=14) and possible (n=48) causal association. Although there were no lixisenatide cases meeting the case definition and causality criteria, we note that lixisenatide has accounted for less than 0.1% of U.S. outpatient GLP-1 RA prescriptions.¹⁰²

Altered skin sensations can result in functional impairment with activities of daily living including sleep disturbances or deprivation. Language describing altered skin sensations with GLP-1 RA use may assist healthcare professionals and patients in identifying the GLP-1 RA as a potential cause and minimizing the risk of repeat exposure.

The findings from this review of altered skin sensations support the addition of the term "dysesthesia" in the ADVERSE REACTIONS *Postmarketing Experience* section of the USPIs for the class of GLP-1 RAs. Dysesthesia describes an unpleasant abnormal sensation and effectively captures the associated pain terms included in the consolidated term 'altered skin sensations' used for this review. We note that the USPI for Wegovy (semaglutide) mentions the term "Dysesthesia" footnoted with "Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin" in the ADVERSE REACTIONS *Clinical Trials Experience* section.⁶⁹ Additionally, we note that the Applicant for tirzepatide products submitted a PAS for both Mounjaro and Zepbound to update the ADVERSE REACTIONS *Postmarketing Experience* section of the USPIs to include "dysesthesia".^{47,48}

Limitations of this Review

We recognize the high background rate of PN as a potential confounding factor, particularly for DPN and idiopathic PN. The case series included cases reporting GLP-1 RA use for both glycemic control (n=18) and weight management (n=35) indications. We attempted to control for confounding from T2DM by assessing cases reporting events more consistent with DPN, especially isolated distal polyneuropathies, as unlikely causality. From the Applicants' pooled clinical trial data for CWM, we assessed a consistent trend for a numerical imbalance across products with CWM indications. Although there may be a high background rate for PN among people who are prescribed GLP-1 RAs, this does not negate the potential causal association between GLP-1 RAs and altered skin sensations that we have detailed within our case series and mentioned above in this discussion, including temporal relationships, the influence of exposure to patients' symptoms, and the outcome following GLP-1 RA discontinuation.

We note the lack of detailed reporting, especially regarding objective information (e.g., nerve conduction study, skin biopsy for intraepidermal nerve fiber density, radiologic imaging, magnitude of change for glycemic parameters, magnitude of change for weight loss). Additionally, there were FAERS reports describing painful altered skin sensations, but these reports lacked the necessary information to exclude the possibility of injection site reactions.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, we find an association between the class of GLP-1 RAs and altered skin sensations. DPV-I recommends the following:

- [REDACTED] (b) (4)

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81. FDA. BLA 125469. Sponsor Notification of Safety Signal and Information Request. January 9, 2024. DARRTS Reference ID: 5306956.
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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that the Office of Surveillance and Epidemiology (OSE) uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. LINE LISTING OF GLP-1 RAS AND ALTERED SKIN SENSATIONS CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Dulaglutide (n=2)									
1	08-NOV-2022	21572772	1	Direct report	Direct	58	Female	USA	OT
2	NA	NA	NA	GB202305002810	NA	57	Male	NR	
Semaglutide (n=50)									
3	09-OCT-2023	23043319	1	US-NOVOPROD-1123905	Expedited	61	Female	USA	OT
4	16-OCT-2023	23067472	1	NO-NOVOPROD-1124447	Expedited	56	Female	NOR	DS
5	13-FEB-2024	23515518	1	US-NOVOPROD-1173656	Expedited	64	Female	USA	OT
6	06-JUL-2023	22675649	2	GB-NOVOPROD-1085023	Expedited	44	Female	GBR	OT
7	17-AUG-2023	22833284	2	US-NOVOPROD-1085858	Expedited	59	Male	USA	OT
8	05-APR-2019	16168258	1	Direct report	Direct	52	Male	USA	
9	05-APR-2019	16168264	1	Direct report	Direct	64	Female	USA	
10	01-OCT-2021	19906764	1	Direct report	Direct	75	Male	USA	
11	08-JUN-2022	20938108	1	Direct report	Direct	41	Female	USA	
12	27-AUG-2022	21265583	1	Direct report	Direct	68	Female	USA	
13	04-OCT-2022	21410893	1	Direct report	Direct	51	Male	USA	
14	09-OCT-2022	21440326	1	Direct report	Direct	43	Female	USA	
15	22-MAR-2023	22130649	1	Direct report	Direct	45	Male	USA	
16	20-APR-2023	22239357	1	Direct report	Direct	65	Male	USA	OT
17	14-MAY-2023	22325054	1	Direct report	Direct	43	Female	USA	
18	23-MAY-2023	22359601	1	Direct report	Direct	50	Female	USA	OT
19	02-JUN-2023	22520207	1	Direct report	Direct	73	Female	USA	
20	29-JUN-2023	22655639	1	Direct report	Direct	62	Male	USA	
21	20-JUL-2023	22736123	1	Direct report	Direct	35	Female	USA	
22	21-JUL-2023	22743115	1	Direct report	Direct	48	Male	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
23	07-AUG-2023	22798120	1	Direct report	Direct	55	Female	USA	
24	07-AUG-2023	22799747	1	Direct report	Direct	56	Female	USA	
25	11-AUG-2023	22820237	1	Direct report	Direct	51	Female	USA	OT
26	24-AUG-2023	22866097	1	Direct report	Direct	64	Male	USA	DS, RI
27	30-AUG-2023	22889240	1	Direct report	Direct	56	Female	USA	OT
28	07-SEP-2023	22925288	1	Direct report	Direct	NR	Female	USA	RI
29	08-SEP-2023	22930714	1	Direct report	Direct	47	NR	USA	
30	20-SEP-2023	22967619	1	Direct report	Direct	31	Female	USA	
31	26-SEP-2023	22991971	1	Direct report	Direct	55	Female	USA	DS
32	04-OCT-2023	23028182	1	Direct report	Direct	53	Female	USA	
33	11-OCT-2023	23058482	1	Direct report	Direct	45	Female	USA	
34	11-OCT-2023	23058562	1	Direct report	Direct	34	Female	USA	
35	23-OCT-2023	23100020	1	Direct report	Direct	34	Female	USA	OT
36	31-OCT-2023	23134013	1	Direct report	Direct	NR	Female	USA	OT
37	01-NOV-2023	23138699	1	Direct report	Direct	56	Female	USA	
38	30-DEC-2023	23357273	1	Direct report	Direct	46	Female	USA	
39	04-JAN-2024	23366649	1	Direct report	Direct	NR	NR	USA	
40	15-JAN-2024	23409284	1	Direct report	Direct	51	Female	USA	OT
41	17-JAN-2024	23416397	1	Direct report	Direct	47	Male	USA	
42	14-FEB-2024	23526540	1	Direct report	Direct	25	Female	USA	
43	15-FEB-2024	23531731	1	Direct report	Direct	43	Female	USA	
44	15-FEB-2024	23531749	1	Direct report	Direct	31	Female	USA	
45	01-MAR-2024	23586241	1	Direct report	Direct	32	Female	USA	
46	12-MAR-2024	23622758	1	Direct report	Direct	53	Female	USA	OT
47	15-MAR-2024	23637143	1	Direct report	Direct	37	Female	USA	
48	20-MAR-2024	23658187	1	Direct report	Direct	32	Female	USA	OT
49	NA	NA	NA	1069235	NA	53	Male	DNK	
50	NA	NA	NA	1103853	NA	46	Male	JPN	
51	NA	NA	NA	1105254	NA	67	Female	DNK	
52	NA	NA	NA	881512	NA	45	Female	COL	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Tirzepatide (n=10)									
53	03-AUG-2023	22782749	1	JP- ELI_LILLY_AND_C OMPANY- JP202307017345	Expedited	51	Female	JPN	DS
54	04-DEC-2022	21683929	1	Direct report	Direct	49	Female	USA	OT
55	24-JAN-2023	21909126	1	Direct report	Direct	38	Female	USA	OT
56	07-FEB-2023	21968957	1	Direct report	Direct	46	Female	USA	
57	06-AUG-2023	22795053	1	Direct report	Direct	57	Male	USA	
58	21-AUG-2023	22850419	1	Direct report	Direct	43	Female	USA	
59	21-AUG-2023	22853089	1	Direct report	Direct	55	Female	USA	OT
60	26-OCT-2023	23115281	1	Direct report	Direct	38	Male	USA	OT
61	16-DEC-2023	23308958	1	Direct report	Direct	54	Female	USA	
62	NA	NA	NA	US202302004365	NA	46	Female	NR	
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome. Abbreviations: COL=Colombia, DNK=Denmark, DS=disability, GBR=United Kingdom, JPN=Japan, NA=not available, NOR=Norway, NR=not reported, OT=other medically significant, RI=required intervention									

7.3 APPENDIX C. ADDITIONAL FAERS SEARCH FOR NON-SERIOUS CASES OF GLP-1 RAS AND ALTERED SKIN SENSATIONS

DPV-I searched the FAERS database with the strategies described in Table 12 for non-serious reports with the four products that were not otherwise captured in our case series (Section 3.1) to further inform this safety issue.

Table 12. FAERS Search Strategy*	
Date of search	July 26, 2024
Time period of search	All reports through July 25, 2024
Search type	RxLogix Quick Query
Product terms	Product active moiety: albiglutide, exenatide, liraglutide, lixisenatide [†]
MedDRA search terms (Version 27.0)	PTs <i>Allodynia, Burning sensation, Dysaesthesia, Hyperaesthesia, Hyperpathia, Pain of skin, Sensitive skin, Skin burning sensation, Skin discomfort, Skin sensitisation</i>
Case Seriousness	Non-serious
* See Appendix A for a description of the FAERS database. † Although Tanzeum (albiglutide) has a voluntary “revoked” status, Bydureon (exenatide extended release) is permanently withdrawn from sale, and Adlyxin (lixisenatide) is permanently discontinued, these products were included in the search to assess FAERS reports within the GLP-1 RA drug class. Abbreviations: FAERS=FDA Adverse Event Reporting System, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

The FAERS search retrieved 281 reports. After applying the case definition in Section 2.1, the causality criteria in Section 2.2, and accounting for duplicate reports, we identified 8 additional FAERS cases of altered skin sensations reported with exenatide (n=4), liraglutide (n=3), and albiglutide (n=1); there were no cases identified with lixisenatide. These eight cases are not included in the aforementioned case series (n=62). DPV-I assessed these cases as probable (n=1) and possible (n=7) causal association. These eight cases are further described in Table 13.

Table 13. Additional Non-Serious FAERS Cases of Altered Skin Sensations Reported with GLP-1 RA Use Retrieved From the Search Strategy in Table 12

(N=8)

	FAERS Case # / MCN	Brief Narrative or Summary	DPV-I Causality Assessment (WHO-UMC) and Reviewer Comments
Exenatide (n=4)			
1	6720117 / US200803006819	51-year-old female experienced "burning feet" with exenatide (Byetta) 5 mcg twice daily for T2DM. Concomitant medication included metformin. After 2 weeks, the patient experienced "burning in her feet". Exenatide therapy was interrupted and the altered skin sensations resolved. Exenatide was restarted and the events returned with exenatide 10 mcg twice daily. After restarting exenatide with recurrence of altered skin sensations, the action taken with exenatide was reported as continued and the outcome of altered skin sensations was reported as "continuing".	Possible: DPV-I notes the altered skin sensations recovered after therapy interruption. DPV-I notes the recurrence of altered skin sensations after restarting exenatide. Also, the history of T2DM cannot completely account for the events, noting the initial event recovered following exenatide interruption and the events recurred after restarting exenatide.
2	6745817 / US200805002778	40-year-old male experienced "painful area of skin" with exenatide (Byetta) 10 mcg twice daily for T2DM. Concomitant medication included metformin. After an unreported time on exenatide 5 mcg twice daily, the dose was increased to exenatide 10 mcg twice daily. "With the start of a new 10 mcg pen, the patient experienced painful area of skin ... on the lower back up to the underarms and around to the front of the body". The report stated that "No changes in the appearance of the skin in the affect area were reported". Exenatide was continued. The events were reported as "ongoing".	Possible: DPV-I notes a reasonable temporal relationship is suggested (but not specified) between the dose titration of exenatide and the onset of altered skin sensations. Concomitant medication metformin does not contain labeling language for painful altered skin sensations.
3	6260737 / 2006PV017583	71-year-old female experienced "lower part of her body was burning" with exenatide (Byetta) 5 mcg twice daily for T2DM. Past medical history included T2DM. After receiving exenatide for 14 days, the patient experienced "lower part of her body was burning 'like her skin was on fire'" and "outside of her skin hurt". The action taken with exenatide and the outcome of the events were not reported.	Possible: DPV-I notes a reasonable temporal relationship between exenatide initiation and the onset of events.
4	6152540 / 2006PV014981	66-year-old male experienced "fingertips and palms burning" with exenatide (Byetta) 10 mcg twice daily for T2DM. Concomitant medications included metformin, glimepiride, "Avandia", quinapril, "Crestor", fish oil, and "Tricor". After receiving exenatide for approximately 6 months, the patient experienced burning sensation reported as "fingertips and palms burning". Exenatide was discontinued. The patient recovered from the altered skin sensations.	Possible: DPV-I notes the altered skin sensations recovered after discontinuation of exenatide. None of the chronic concomitant medications contain labeling language for painful altered skin sensations. Also, the history of T2DM cannot completely account for the events, noting the events recovered following discontinuation of exenatide.
Liraglutide (n=3)			
5	13433031 / US-NOVOPROD-534300	A male of unreported age experienced "burning sensation" with liraglutide (Saxenda) for "weight loss". The patient experienced "burning sensation in his feet at night" and reported "could not sleep while using Saxenda". Liraglutide therapy was interrupted "for a couple of days" and the altered skin sensations resolved. Liraglutide was restarted and "the burning sensation came back". After restarting liraglutide with recurrence of altered skin sensations, the action taken with liraglutide and the outcome of altered skin sensations were not reported.	Probable: DPV-1 notes the altered skin sensations recovered after therapy interruption. DPV-I notes the recurrence of altered skin sensations after restarting liraglutide. The report did not mention a history of diabetes mellitus, noting the indication of "weight loss" for liraglutide use.

6	14590841 / US-NOVOPROD-575245	79-year-old male experienced "burning in feet" with liraglutide (Victoza) for T2DM. Past medical history included T2DM. "Historical drug" included metformin. The patient received liraglutide for 59 days. On an unreported date, the patient experienced "burning in feet". Liraglutide was discontinued. The patient recovered from the altered skin sensations.	Possible: DPV-I notes the altered skin sensations recovered after discontinuation of liraglutide. DPV-I notes a reasonable temporal relationship based on the reported dates of liraglutide treatment. Also, the history of T2DM cannot completely account for the events, noting the events recovered following liraglutide discontinuation.
7	9504115 / US-NOVOPROD-363860	68-year-old female experienced "burning sensation throughout body" with liraglutide (Victoza) for T2DM. Past medical history included T2DM. The patient received liraglutide for approximately 2-3 months. The events occurred during the first month of liraglutide treatment. Liraglutide was discontinued. The patient recovered from the altered skin sensations.	Possible: DPV-I notes the altered skin sensations recovered after discontinuation of liraglutide. DPV-I notes a reasonable temporal relationship based on the reported dates of liraglutide treatment and reported onset of events. Also, the history of T2DM cannot completely account for the events, noting the events recovered following liraglutide discontinuation.
Albiglutide (n=1)			
8	12285897 / US-GLAXOSMITHKLINE-US2016047584	50-year-old female experienced "burning skin" with albiglutide (Tanzeum) 50 mg weekly for "diabetes". Concomitant medications included metformin, glimepiride, valsartan, atorvastatin, and fenofibrate. After receiving albiglutide 30 mg weekly for 35 days, the dose was increased to albiglutide 50 mg weekly. On the same day as the dose increase, the patient experienced "skin burns around her left abdomen near the waist line". The injection location was the thigh. Albiglutide was continued and the event outcome was reported as "unchanged".	Possible: DPV-I notes a reasonable temporal relationship between the dose titration of albiglutide and the onset of altered skin sensations. None of the chronic concomitant medications contain labeling language for painful altered skin sensations.
Abbreviations: FAERS= FDA Adverse Event Reporting System, GLP-1 RA=glucagon-like peptide-1 receptor agonist, MCN=Manufacturer Control Number, T2DM=type 2 diabetes mellitus, WHO-UMC= World Health Organization-Uppsala Monitoring Centre			

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: July 24, 2024

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Subject: Alopecia

Application Type/Number:

Drug name	Active ingredient	Application	Applicant
Byetta	Exenatide	NDA 021773	AstraZeneca AB
Byetta	Exenatide synthetic	NDA 021919	Amylin
Bydureon	Exenatide synthetic, extended release	NDA 022200	AstraZeneca AB
Bydureon BCISE	Exenatide	NDA 209210	AstraZeneca AB
Victoza	Liraglutide	NDA 022341	Novo Nordisk Inc
Saxenda	Liraglutide	NDA 206321	Novo Nordisk Inc

Xultophy 100/3.6	Insulin degludec, liraglutide	BLA 208583	Novo Nordisk Inc.
Tanzeum	Albiglutide	BLA 125431	GlaxoSmithKline
Trulicity	Dulaglutide	BLA 125469	Eli Lilly
Adlyxin	Lixisenatide	BLA 208471	Sanofi-Aventis US
Soliqua 100/33	Insulin glargine, lixisenatide	BLA 208673	Sanofi-Aventis US
Ozempic	Semaglutide	NDA 209637	Novo Nordisk Inc
Rybelsus	Semaglutide	NDA 213051	Novo Nordisk Inc
Rybelsus	Semaglutide	NDA 213182	Novo Nordisk Inc.
Wegovy	Semaglutide	NDA 215256	Novo Nordisk Inc
Mounjaro	Tirzepatide	NDA 215866	Eli Lilly
Zepbound	Tirzepatide	NDA 217806	Eli Lilly

SS ID #: 5117

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TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	2
1.1 Background	2
1.2 Regulatory History	4
1.3 Relevant Product Labeling.....	6
2 Methods and Materials.....	6
2.1 Case Definition.....	7
2.2 Causality Criteria	7
2.3 FAERS Search Strategy	7
2.4 Literature Search Strategy.....	8
2.5 Information Request.....	10
2.6 Drug Utilization	11
3 Results.....	11
3.1 FAERS Case Selection.....	11
3.2 Literature Cases.....	19
3.3 Information Request	20
3.4 Drug Utilization.....	23
4 Discussion	28
5 Conclusion and Recommendations.....	30
6 References.....	30
7 Appendices.....	34
7.1 Appendix A. FDA Adverse Event Reporting System (FAERS).....	34
7.2 Appendix B. Drug Utilization Database Descriptions	35
7.3 Appendix C. FAERS Line Listing of GLP-1 RA Alopecia Case Series.....	37
7.4 Appendix D. Estimated Number of Prescriptions Dispensed for GLP-1 RAs.....	41
7.5 Appendix E. Diagnosis Associated with the Use of GLP-1 RAs.....	42

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance and Drug Utilization Review is for the Division of Pharmacovigilance (DPV-I) and the Division of Epidemiology II (DEPI-II) to provide the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of alopecia associated with the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS) and medical literature. This signal was identified as part of routine pharmacovigilance surveillance based on a news article featured on NBCNews.com reporting the risk of hair loss with the use of weight loss drugs (i.e., Ozempic, Wegovy, Mounjaro). The information and recommendations in this review will assist DDLO to determine if alopecia should be added to labeling for the GLP-1 RA drug class.

This review identified 82 postmarketing cases of alopecia associated with exenatide (n=19) including Byetta (n=16), Bydureon (n=2), and Bydureon BCISE (n=1); liraglutide (n=13) including Victoza (n=9) and Saxenda (n=4); dulaglutide (n=16); semaglutide (n=28) including Ozempic (n=23) and Wegovy (n=5); tirzepatide (n=4); and albiglutide (n=2). The median patient age was 45 years with a predominance in females (70/78, 90%). The median time to onset in our series was 3 months (range same day to 35 months, see Discussion for details). Most cases reported glycemic control as the indication or reason for use of the GLP-1 RA product. Sixteen cases were assessed as probable causality, and this included all GLP-1 RAs in our case series except for liraglutide and tirzepatide. Five cases reported exacerbation of symptoms with dose increases of the GLP-1 RA including semaglutide (Ozempic) (n=3), dulaglutide (n=1) and albiglutide (1). In all cases alopecia resolved upon discontinuation of the suspect drug. Alopecia associated with concomitant weight loss was reported in 20 of our cases. Our series, however, also described cases of hair loss with no reported concomitant weight loss, where the event resolved upon discontinuation of the suspect drug.

The Drug Utilization analyses from United States outpatient retail and mail-order/specialty pharmacies showed that the estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022, with semaglutide accounting for the highest number of prescriptions dispensed in 2022.

In conclusion, we find an association between GLP-1 RA use and hair loss. We acknowledge our case series did not identify cases of hair loss in association with lixisenatide. Wegovy and Zepbound contain the term hair loss in ADVERSE REACTIONS Clinical Trials Experience, and all exenatide products contain the term alopecia in ADVERSE REACTIONS Postmarketing Experience. Based on this review, we recommend the following:

- Update ADVERSE REACTIONS *Postmarketing Experience* to reflect the potential risk of hair loss with all GLP-1 RAs, except exenatide, which includes the term alopecia within this section of labeling.*

* *Postmarketing Experience* alopecia labeling for Wegovy and Zepbound may not be required, as this information exists in *Clinical Trials Experience*, as noted above.

1 INTRODUCTION

The purpose of this Pharmacovigilance and Drug Utilization Review is for the Division of Pharmacovigilance (DPV-I) and the Division of Epidemiology II (DEPI-II) to provide the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of alopecia associated with the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS) and medical literature. This signal was identified as part of routine pharmacovigilance surveillance based on a news article featured on NBCNews.com reporting the risk of hair loss with the use of weight loss drugs (i.e., Ozempic, Wegovy, Mounjaro).¹ The information and recommendations in this review will assist DDLO to determine if alopecia should be added to labeling for the GLP-1 RA drug class.

On May 8, 2023, DPV-I presented the safety signal at the DDLO-OSE Joint Safety Meeting to determine if a newly identified safety signal (NISS) should be opened for alopecia and the GLP-1 RA drug class. On May 9, 2023, DPV-I opened NISS ID #5117, and moved the NISS to the evaluation phase after conferring with DDLO, which is the basis for this review.

1.1 BACKGROUND

1.1.1 *Gastrointestinal Peptides*

Glucose homeostasis is dependent upon a complex interaction of several hormones, insulin and amylin, produced by pancreatic beta cells; glucagon, produced by pancreatic alpha cells; and gastrointestinal peptides, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP; formerly called gastric inhibitory polypeptide).² GLP-1 and GIP are incretin hormones that link the absorption of nutrients from the gastrointestinal tract with pancreatic hormone secretion. They are released in the setting of a meal and provide one of the physiologic connections between eating and insulin release.³

GLP-1 binds to a specific GLP-1 receptor, which is expressed in various tissues, including pancreatic beta cells, pancreatic ducts, gastric mucosa, kidney, and lungs.³ GLP-1 exerts its effect by stimulating glucose-dependent insulin release from the pancreatic islets. It has also been shown to slow gastric emptying,⁴ inhibit inappropriate post-meal glucagon release,⁵ and reduce food intake.⁵ GLP-1 exhibits a short half-life of 1 to 2 minutes due to N-terminal degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). Synthetic GLP-1 receptor agonists are resistant to degradation by DPP-4 and therefore have a longer half-life, facilitating clinical use. Longer-acting GLP-1 RAs can be administered once daily or once weekly.

GIP binds to a specific GIP receptor, which is expressed in various tissues, including pancreatic beta cells, pancreatic alpha cells, subcutaneous and visceral adipose tissue, bone, and heart. In the postprandial state, GIP is secreted with GLP-1 and interacts in an additive fashion to potentiate glucose-induced insulin secretion.⁶ GIP, however, exhibits different effects than GLP-1 on glucagon secretion. In the euglycemic or hypoglycemic states, GIP enhances glucagon activity.⁷ A synthetic dual-acting GIP and GLP-1 RA (tirzepatide) is available for the treatment of hyperglycemia in patients with type 2 diabetes (T2DM). Tirzepatide has a half-life of 5 days, allowing for once-weekly administration.

GLP-1 RAs were initially approved for the treatment of T2DM. One of the mechanisms by which GLP-1 RAs improve glycemia in diabetes is due to their ability to induce weight loss. Weight loss is common with GLP-1 RA-based therapies.^{8,9,10} Weight loss may be due, in part, to the effects of GLP-1 on slowed gastric emptying. GLP-1 RAs are also associated with nausea and vomiting. However, slowed gastric emptying is attenuated over time, in longer-acting GLP-1 RAs, and these agents are known to increase satiety through effects on the appetite centers in the brain.^{11,12} Three GLP-1 Ras, which are all administered by subcutaneous injection, have been approved in the United States for weight management or to reduce weight: liraglutide, semaglutide, and tirzepatide.

1.1.2 Alopecia

Alopecia is defined as “the absence or loss of hair in an area where it is expected to be present.”¹³ Hair follicles generate the hair shaft (i.e., strand of hair), specifically in the hair matrix. Hair follicles undergo cycling defined by periods of hair growth (anagen, 2-6 years), follicle transition and hair growth cessation (catagen, 2-3 weeks) and follicle rest (telogen, 2-3 months).¹⁴ Telogen involves the shedding of hair shaft allowing for the growth of a new hair shaft. Prolongation of the telogen phase, as may occur in telogen effluvium, results in hair thinning due to longer periods of hair follicle rest and delay of anagen. Telogen effluvium occurs 3 months after a triggering event, such as psychological stress, chronic illness, pregnancy or postpartum, malnutrition, severe infection, endocrine disorders, metabolic disturbances, surgery, and medications, such as anticonvulsants, antidepressants, anticoagulants, oral contraceptive pills, and retinoids.¹³ Telogen effluvium typically lasts for about 6 months.¹³

Hair loss disorders are divided into scarring (i.e., cicatricial alopecia), non-scarring alopecia, and structural hair disorders.¹⁵ Cicatricial alopecia includes inflammatory conditions that destroy hair follicles causing permanent hair loss and may be triggered by infections, chemical exposure, or autoimmune disorders. In nonscarring alopecia, the hair follicles remain intact, hence, hair loss is reversible because the hair matrix can resume the production of the hair strand. Nonscarring alopecia includes androgenetic alopecia, alopecia areata, and telogen effluvium. The diagnosis of a specific alopecia is made by history and clinical examination. When the diagnosis is in doubt, additional laboratory investigations or a scalp biopsy may be performed to aid in the diagnosis.¹⁵

1.1.3 Metabolic and Bariatric Surgery and Alopecia

According to the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel on the *Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, overweight is defined as a body mass index (BMI) of 25 to 29.9 kg/m², and obesity is defined as a BMI $\geq$ 30 kg/m².¹⁶ As an initial goal for weight loss, the panel recommends the loss of 10 percent of baseline weight at a rate of 1 to 2 pounds per week.¹⁶ As hair follicles are among the most metabolically active in the body, hair growth may be impacted by calorie and protein malnutrition as well as micronutrient deficiency.¹⁷ Rapid weight loss (>1 to 1.5 kg per week) can lead to hair loss.^{18,19} For example, hair loss is a recognized complication of metabolic and bariatric surgery (MBS). A review of 18 mostly observational studies reported that 57% of patients had hair loss after MBS.²⁰ Another study reported that 15.4% of patients experienced hair loss within 3 months after Roux-en-Y gastric bypass (RYGB).²¹ A previous study by these authors found that the incidences were 55% and 40% after laparoscopic sleeve gastrectomy

(LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB), respectively within 6 months. This is similar to Ruiz-Tovar et al reporting 41% after LSG in 2014.²² Others have found the incidence to be as high as 80% after laparoscopic gastric plication (LGP) or LSG.²³ Ledoux et al. found that, in subjects with hair loss, blood parameters of protein were significantly lower than in subjects without hair loss.²⁴ Postoperative excess weight loss was found to be a significant factor in the study by Guo et al., which was hypothesized to play a role in the etiopathogenesis of hair loss after MBS.²⁵

1.2 REGULATORY HISTORY²⁶

Currently, there are six GLP-1 RAs approved by the FDA. Table 1 lists all GLP-1 RA products, including fixed ratio drug-drug combinations, currently marketed in the United States. The first GLP-1 RA product, Byetta (exenatide synthetic, NDA 021773), was approved on April 28, 2005.

Tanzeum (albiglutide, BLA 125431) was previously marketed in the U.S. until July 2018, but currently has a voluntary revoked status due to a business decision (low usage of the product) and not related to safety or efficacy.^{27,28,29} The Applicant for Bydureon (exenatide extended release, NDA 022200) submitted a permanent withdrawal from sale effective March 2021 for business reasons.^{30,31} Adlyxin (lixisenatide, BLA 208471) was previously marketed in the U.S., but the Applicant submitted a notification of permanent discontinuation for business reasons on February 22, 2023.^{32,33}

All GLP-1 RA products except Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) are indicated as adjunct therapy to diet and exercise to improve glycemic control in patients with T2DM.^{34,35,36,37,38,39,40,41,42,43,44,45,46} This indication is extended to pediatric patients aged 10 years and older for Bydureon BCise (exenatide synthetic, extended release), Victoza (liraglutide), and Trulicity (dulaglutide).^{35,36,37,40} Victoza (liraglutide), Trulicity (dulaglutide), Ozempic (semaglutide) are also indicated to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease.^{37,40,43} The weight reduction product Wegovy (semaglutide) also has a MACE-related indication. Additional details are provided in Table 1.

Table 1. Currently Marketed Glucagon-like Peptide-1 Receptor Agonists in the United States				
Product Name NDA/BLA Applicant	Active Ingredient(s), Formulation	Indication(s)	Dosage Ranges	Approval Date
Byetta 021773 AstraZeneca AB*	Exenatide synthetic, SC Inj	T2DM in adults	5 mcg to 10 mcg twice daily	4/28/2005
Byetta 021919 AstraZeneca AB*	Exenatide synthetic, SC Inj	T2DM in adults	5 mcg to 10 mcg twice daily	10/30/2009
Bydureon BCise 209210 AstraZeneca AB	Exenatide synthetic, extended release, SC Inj	T2DM in adults, pediatrics ≥ 10 years	2 mg every 7 days	10/20/2017
Victoza 022341	Liraglutide recombinant,	T2DM in adults,	0.6 mg titrated to 1.8 mg daily	1/25/2010

Novo Nordisk Inc.	SC Inj	pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM and established CVD		
Saxenda 206321 Novo Nordisk Inc.	Liraglutide recombinant, SC Inj	Weight management in adults [†] , pediatrics ≥ 12 years [‡]	0.6 mg titrated to 3 mg daily	12/23/2014
Xultophy 100/3.6 208583 Novo Nordisk Inc.	Insulin degludec, liraglutide, SC Inj	T2DM in adults	10 units titrated to 50 units daily	11/21/2016
Trulicity 125469 Eli Lilly and Co.	Dulaglutide, SC Inj	T2DM in adults, pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM and established CVD or multiple CV risk factors	0.75 mg titrated to 4.5 mg weekly	9/18/2014
Soliqua 100/33 208673 Sanofi-Aventis US	Insulin glargine, lixisenatide, SC Inj	T2DM in adults	15 units titrated to 60 units daily	11/21/2016
Ozempic 209637 Novo Nordisk Inc.	Semaglutide, SC Inj	T2DM in adults; reduce the risk of MACE in adults with T2DM and established CVD	0.25 mg titrated to 1 mg weekly	12/5/2017
Rybelsus 213051 Novo Nordisk Inc.	Semaglutide, oral tablet	T2DM in adults	3 mg titrated to 14 mg daily	9/20/2019
Wegovy 215256 Novo Nordisk Inc.	Semaglutide, SC Inj	Weight management in adults [§] , pediatrics ≥ 12 years ; reduce the risk of MACE in adults with established CVD and either obesity or overweight	0.25 mg titrated to 2.4 mg weekly	6/4/2021
Mounjaro 215866 Eli Lilly and Co.	Tirzepatide, SC Inj	T2DM in adults	2.5 mg titrated to 5 mg weekly	5/13/2022
Zepbound 217806 Eli Lilly and Co.	Tirzepatide SC Inj	Weight management in adults [¶]	2.5 mg titrated to 15 mg weekly	11/8/2023

Source: Drugs@FDA

* On April 3, 2014, FDA acknowledged receipt of NDA transfer of ownership for Byetta (NDAs 021773 and 021919) from Bristol-Myers Squibb to AstraZeneca AB.^{47,48,49,50,51,52}

† Adults with BMI of 30 kg/m² or greater (obesity), or BMI 27 kg/m² or greater (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia)
‡ Pediatrics with body weight > 60 kg and initial BMI corresponding to 30 kg/m² for adults (obese)
§ Adults with BMI of 30 kg/m² or greater (obese), or BMI 27 kg/m² or greater (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia)
|| Pediatrics with an initial BMI at the 95th percentile or greater standardized for age and sex (obesity)
Abbreviations: BLA=Biologics License Application, BMI=body mass index, CV=cardiovascular, CVD=cardiovascular disease, Inj=injection, MACE=major adverse cardiovascular events, NDA=New Drug Application, SC=subcutaneous, T2DM=type 2 diabetes mellitus

1.3 RELEVANT PRODUCT LABELING^{53,54,55,56}

Relevant product labeling for GLP-1 RAs is listed in Table 2 below.

Table 2. Relevant Product Labeling for Alopecia in United States Marketed Glucagon-like Peptide-1 Receptor Agonists		
Active Ingredient(s) (Product Name)	6.1 Adverse Reactions: <i>Clinical Trials Experience</i>	6.2 Adverse Reactions: <i>Postmarketing Experience</i>
Exenatide synthetic (Byetta)	x	Alopecia*†
Exenatide synthetic, extended release (Bydureon BCise)	x	Alopecia
Liraglutide (Victoza)	x	x
Liraglutide (Saxenda)	x	x
Insulin degludec, liraglutide (Xultophy 100/3.6)	x	x
Dulaglutide (Trulicity)	x	x
Lixisenatide (Adlyxin)	x	x
Insulin glargine, lixisenatide (Soliqua 100/33)	x	x
Semaglutide (Ozempic)	x	x
Semaglutide (Rybelsus)	x	x
Semaglutide (Wegovy)	Hair loss	x
Tirzepatide (Mounjaro)	x	x
Tirzepatide (Zepbound)	Hair loss	x
x indicates no relevant information in respective section of the United States Prescribing Information. * Alopecia was added to Byetta USPI on October 29, 2010 † SPL changes based on Medical Officer Review (Pratt VS. Division of Metabolism and Endocrinology Products Review, NDA 21773, Exenatide (Byetta), September 30, 2010.		

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Case Definition

The case definition of alopecia requires the following in this review:

- Patient or healthcare provider reported scalp hair loss, alopecia, balding, or synonym thereof

2.2 CAUSALITY CRITERIA

Causality was assessed using a modified World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment (Table 3). A conservative approach to assessing causality was used in this review. Cases were excluded if causality was determined to be unlikely or unassessable.

Table 3. Causality Categories and Criteria Adapted from the WHO-UMC System	
Category	Criteria
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to drug withdrawal clinically reasonable • Rechallenge satisfactory, if necessary
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that make a relationship improbable (but not impossible) • Disease or other drugs provide more plausible explanations • No response to drug withdrawal
Unassessable	• Cases cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.3 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategies described in Tables 4 and 5. Please note that our initial scoping search strategy that did not restrict to serious outcome or direct reports retrieved 1,277 reports. DPV-I and DDLO met to discuss the review search strategy on May 8, 2023, and determined that for the purpose of this review, we would restrict our search strategy to reports with a serious regulatory outcome (Table 4) and direct reports (Table 5).

Table 4. FAERS Search Strategy*	
Date of search	August 21, 2023
Time period of search	October 21, 1988 [†] to August 20, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	Therapeutic drug class “GLP-1 Receptor Agonist [EPC]”

Table 4. FAERS Search Strategy*	
MedDRA search terms (Version 26.0)	<i>Alopecias (HLT)</i>
Other Criteria	Serious Outcome
* See Appendix A for a description of the FAERS database. † Earliest GLP-1 RA approval: Byetta (exenatide) injection (NDA 021773) Abbreviations: EPC=Established pharmacologic class, GLP-1 RA=Glucagon-like peptide-1 receptor agonist, HLT=High Level Term, MedDRA=Medical Dictionary for Regulatory Activities	

Table 5. FAERS Search Strategy*	
Date of search	August 21, 2023
Time period of search	October 21, 1988 [†] to August 20, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	Therapeutic drug class “GLP-1 Receptor Agonist [EPC]”
MedDRA search terms (Version 26.0)	<i>Alopecias (HLT)</i>
Report Type	Direct
* See Appendix A for a description of the FAERS database. † Earliest GLP-1 RA approval: Byetta (exenatide) injection (NDA 021773) Abbreviations: EPC=Established pharmacologic class, GLP-1 RA=Glucagon-like peptide-1 receptor agonist, HLT=High Level Term, MedDRA=Medical Dictionary for Regulatory Activities	

2.4 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Tables 6 and 7.

Table 6. Literature Search Strategy	
Date of search	October 18, 2023
Database	PubMed

Table 6. Literature Search Strategy	
Search terms	(secretin [tw] OR incretins [mh] OR incretins [tw] OR incretin [tw] OR exenatide [tw] OR “exendin 4” [tw] OR “exendin-4”[tw] OR exenatidine [tw] OR liraglutide [tw] OR lixisenatide [tw] OR dulaglutide [tw] OR semaglutide [tw] OR tirzepatide [tw] OR albiglutide [tw] OR “GLP-1RA” [tw] OR “glp 1 RA” [tw] OR “GLP-1RAS” [tw] OR “GLP 1RAS” [tw] OR “GLP1-RA” [tw] OR “GLP1 RA” [tw] OR “GLP1-RAS” [tw] OR “GLP1 RAS” [tw] OR “GLP-1R agonist” [tw] OR “GLP 1R agonist” [tw] OR “GLP-1R agonists” [tw] OR “GLP 1R agonists” [tw] OR “glucagon-like peptide 1 receptor agonist*” [tw] OR “glucagon like peptide 1 receptor agonist*” [tw] OR “glucagon-like peptide 1 agonist*” [tw] OR “glucagon like peptide 1 agonist*” [tw] OR “glucagon-like peptide 1 analog*” [tw] OR “glucagon like peptide 1 analog*” [tw] OR “GLP-1 receptor agonist*” [tw] OR “GLP 1 receptor agonist*” [tw] OR “glp1 receptor agonist*” [tw] OR “GLP-1 agonist*” [tw] OR “GLP 1 agonist*” [tw] OR “glp1 agonist*”[tw] OR “GLP-1 analog*” [tw] OR “GLP 1 analog*” [tw] OR “GLP1 analog*” [tw] OR "Glucagon-Like Peptide-1 Receptor/agonists"[Mesh] OR "Glucagon-Like Peptide 1/agonists"[Mesh] OR "Glucagon-Like Peptide 1/analogs and derivatives"[Mesh] OR “glucagon-like peptide 1” [mh] OR “glucagon-like peptide 1” [tw] OR “glucagon like peptide 1” [tw] OR “GLP-1” [tw] OR “GLP 1” [tw] OR GLP1 [tw] OR “glucose-dependent insulintropic polypeptide receptor agonist*” [tw] OR “glucose dependent insulintropic polypeptide receptor agonist*” [tw] OR “glucose dependent insulintropic polypeptide” [tw] OR “glucose-dependent insulintropic polypeptide” [tw] OR “glucose dependent insulintropic peptide” [tw] OR “glucose-dependent insulintropic peptide” [tw] AND “receptor agonist” [tw]) OR (“glucose dependent insulintropic peptide” [tw] AND “receptor agonist” [tw]) OR “gastric inhibitory polypeptide” [tw] OR (“gastric inhibitory polypeptide” [tw] AND “receptor agonist” [tw]) OR “gastric inhibitory peptide” [tw] OR (“gastric inhibitory peptide” [tw] AND “receptor agonist” [tw])) AND (Alopecia [mh] OR alopecia [tw] OR hypotrichosis [tw] OR “hair loss” [tw] OR “telogen effluvium” [tw] OR atrichosis [tw] OR baldness [tw] OR “hairlessness” [tw] OR “mucinosis follicularis” [tw] OR “mucinosis, follicular” [tw] OR hair [mh] OR hair [tw] OR “hair follicle” [tw] OR “hair follicles” [tw])
Years included in search	1988*-2023
*Earliest GLP-1 RA approval: Byetta (exenatide) injection (NDA 021773) Abbreviations: GLP-1 RA=Glucagon-like peptide-1 receptor agonist	

Table 7. Literature Search Strategy	
Date of search	October 18, 2023
Database	Embase

Table 7. Literature Search Strategy	
Search terms	(secretin OR incretin OR incretins OR exenatide OR 'exendin 4' OR 'exendin-4' OR exenatidine OR liraglutide OR lixisenatide OR dulaglutide OR semaglutide OR tirzepatide OR albiglutide OR 'glp-1ra' OR 'glp 1ra' OR 'glp-1ras' OR 'glp 1ras' OR 'glp1-ra' OR 'glp1 ra' OR 'glp1-ras' OR 'glp1 ras' OR 'glp-1r agonist' OR 'glp 1r agonist' OR 'glp-1r agonists' OR 'glp 1r agonists' OR 'glucagon like peptide 1 receptor agonist'/exp OR 'glucagon like peptide 1 receptor agonist*' OR 'glucagon-like peptide 1 receptor agonist*' OR 'glucagon-like peptide 1 agonist*' OR 'glucagon like peptide 1 agonist*' OR 'glucagon-like peptide 1 analog*' OR 'glucagon like peptide 1 analog*' OR 'glp-1 receptor agonist*' OR 'glp 1 receptor agonist*' OR 'glp1 receptor agonist*' OR 'glp-1 agonist*' OR 'glp 1 agonist*' OR 'glp1 agonist*' OR 'glp-1 analog*' OR 'glp 1 analog*' OR 'glp1 analog*' OR 'glucagon like peptide 1' OR 'glucagon-like peptide 1' OR 'glp1' OR 'glp-1' OR 'glp 1' OR 'glucose-dependent insulintropic polypeptide receptor agonist*' OR 'glucose dependent insulintropic polypeptide receptor agonist*' OR 'glucose dependent insulintropic polypeptide' OR 'glucose-dependent insulintropic polypeptide' OR 'gip-ra' OR 'gip ra' OR 'glucose dependent insulintropic peptide' OR 'glucose-dependent insulintropic peptide' OR 'glucose-dependent insulintropic peptide receptor agonist' OR 'glucose dependent insulintropic peptide receptor agonist' OR 'gastric inhibitory polypeptide' OR 'gastric inhibitory polypeptide receptor agonist' OR 'gastric inhibitory peptide' OR 'gastric inhibitory peptide receptor agonist' OR 'stomach inhibitory peptide' OR 'stomach inhibitory polypeptide') AND ('alopecia'/exp OR alopecia OR 'hypotrichosis'/exp OR 'hypotrichosis' OR 'hair loss'/exp OR 'hair loss' OR 'telogen effluvium'/exp OR 'telogen effluvium' OR 'atrichosis' OR 'baldness' OR 'hairlessness' OR 'mucinosi follicularis' OR 'mucinosi, follicular' OR 'hair'/exp OR hair OR 'hair follicle' OR 'hair follicles')
Years included in search	1988*-2023
*Earliest GLP-1 RA approval: Byetta (exenatide) injection (NDA 0217734) Abbreviations: GLP-1 RA=Glucagon-like peptide-1 receptor agonist	

2.5 INFORMATION REQUEST

On August 31, 2023, DDLO submitted an IR to Applicants with the following request:^{57,58,59,60,61,62,63,64}

- Starting from the international birth date (IBD) of your products, we request that you perform a cumulative review of all cases of alopecia/hair loss for Bydureon, Bydureon BCise, and Byetta. This analysis should include a review of the published scientific/medical literature, clinical trial data, data from spontaneous reports, and reports from studies. Include in your search the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): Alopecia; Alopecia areata; Diffuse alopecia; Seborrheic alopecia; Alopecia totalis; Alopecia universalis. At a minimum, include the

following information for each case: age, sex, time to onset, severity/seriousness, any reported weight loss, de-challenge and re-challenge information as appropriate, and reported indications of the suspected products as well as your assessment of causality. Group the narratives by PT. Also provide cases identified by reporter narrative search with the following phrases: hair loss, bald, or baldness. Where available, provide Individual Case Safety Reports (ICSRs) for the above reports. All reports should also be identified with Manufacturer Control Numbers and FAERS number, where applicable. Where applicable, data should be stratified according to indication for use (type 2 diabetes mellitus or for off-label use).

2.6 DRUG UTILIZATION

The Drug Use Team in DEPI-II used proprietary databases available to the Agency to assess the utilization of GLP-1 RAs to provide context for the signal evaluation. Full database descriptions and limitations are available in **Appendix B**.

Data Sources Used

We used the IQVIA, National Sales Perspectives™ (NSP) database to determine the setting(s) of care where GLP-1 RAs were sold from manufacturers to various U.S. channels of distribution in 2022.

We used the Symphony Health Metys® database to obtain the estimated number of prescriptions dispensed for GLP-1 RAs from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by molecule and product, from January 2013 through September 2023, calendar year.

We used the Syneos Health Research & Insights LLC., TreatmentAnswers™ to obtain the national estimates of drug use mentions for diagnoses associated with the use of GLP-1 RAs, stratified by molecule and product, as reported by surveys from U.S. office-based health care providers in 2022. We captured diagnoses data based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis codes. Estimates of drug use mentions are obtained from surveys of a sample of over 3,500 office-based health care providers. These survey data provide an insight into the prescriber intent but are not directly linked to dispensed prescriptions. The term “drug uses” to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a “drug use” does not necessarily result in a prescription being generated. Rather, the term indicates that a specific drug was mentioned during an office visit.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS searches retrieved 216 reports. After applying the case definition in Section 2.1, the causality criteria in Section 2.2, and accounting for duplicate reports, 82 cases were included in the case series of alopecia reported with GLP-1 RA use (see Figure 2).

Figure 2. FAERS Case Selection

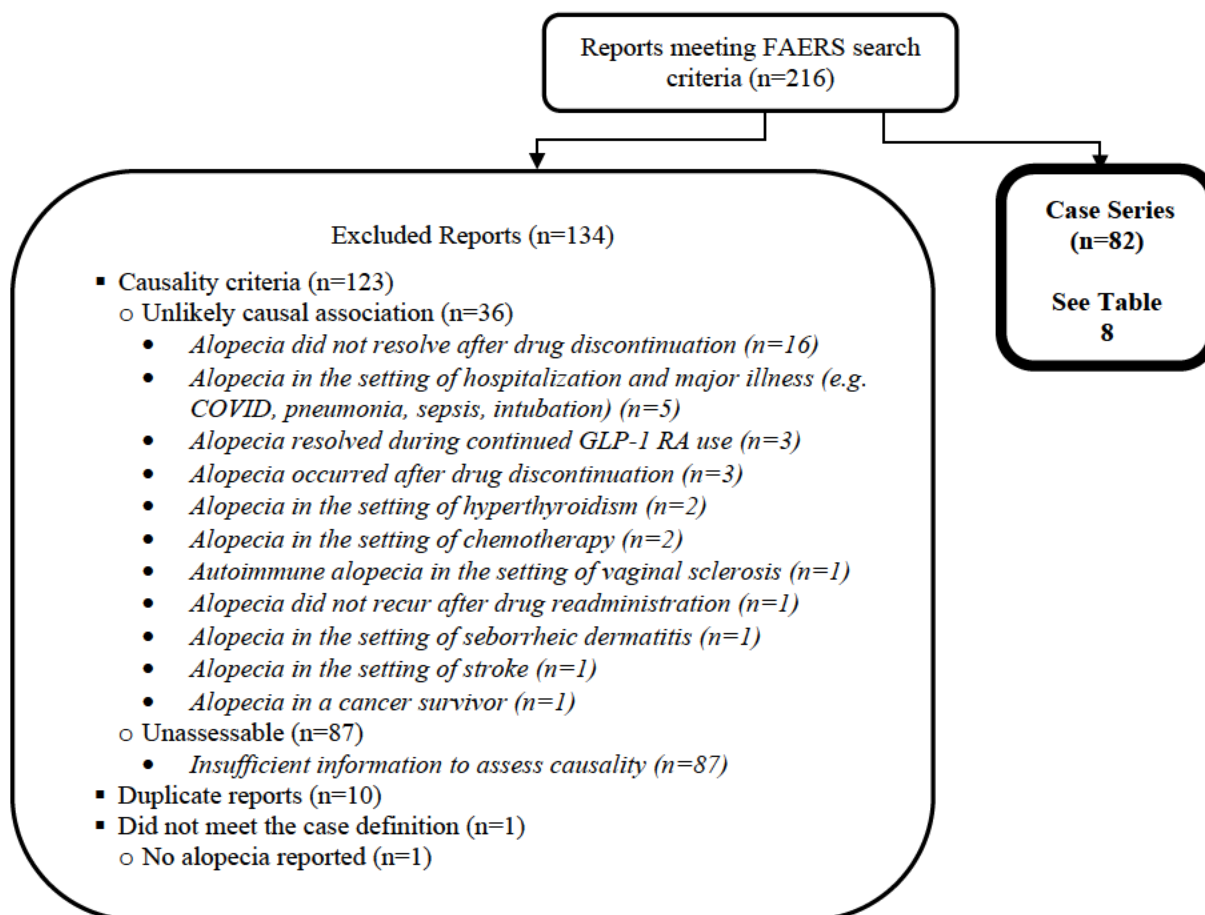


Table 8 summarizes the 82 FAERS cases of alopecia reported with GLP-1 RAs for this case series.

Appendix C contains a line listing of the 82 cases in this case series.

Table 8. Descriptive Characteristics of Alopecia with GLP-1 RAs in this FAERS Case Series Received by FDA through August 20, 2023 (N=82)

Characteristic	Exenatide			Liraglutide		Dulaglutide	Semaglutide		Tirzepatide	Albiglutide	Total
	Byetta (n=16)	Bydureon (n=2)	Bydureon BCISE (n=1)	Victoza (n=9)	Saxenda (n=4)	Trulicity (n=16)	Ozempic (n=23)	Wegovy (n=5)	Mounjaro (n=4)	Tanzeum (n=2)	NA (n=82)
Report type	n=16	n=2	n=1	n=9	n=4	n=16	n=23	n=5	n=4	n=2	n=82
Expedited	15	2	0	3	3	8	4	1	1	1	38
Periodic	0	0	0	2	0	0	0	1	0	0	3
Direct	1	0	1	4	1	8	19	3	3	1	41
Patient sex	n=16	n=2	n=1	n=8	n=4	n=15	n=22	n=5	n=3	n=2	n=78
Female	14	2	0	7	4	12	21	5	3	2	70
Male	2	0	1	1	0	3	1	0	NR	0	8
Age (years)	n=14	n=2	n=1	n=9	n=3	n=11	n=17	n=5	n=3	n=1	n=66
Median	57	70	58	54	46	53	49	55	52	58	53
Range	34-76	65-76	NA	28-67	44-46	36-82	36-76	35-61	24-54	NA	24-82
Country	n=16	n=2	n=1	n=9	n=4	n=16	n=23	n=5	n=4	n=2	n=82
United States	11	1	1	6	2	12	21	5	4	2	65
Foreign	5*	1†	0	3‡	2§	4	2¶	0	0	0	17
Reporter Type	n=16	n=2	n=1	n=9	n=4	n=16	n=23	n=5	n=4	n=2	n=82
Physician	7	2	0	2	0	2	1	1	1	0	16
Consumer	9	0	0	7	3	9	21	3	2	2	56
Pharmacist	0	0	1	0	0	3	1	1	0	0	6
HCP, NOS	0	0	0	0	1	2	0	0	1	0	4
Year received by FDA	n=16	n=2	n=1	n=9	n=4	n=16	n=23	n=5	n=4	n=2	n=82
2000-2010	9	0	0	0	0	0	0	0	0	0	9
2011-2020	7	2	0	9	1	5	1	0	0	2	27
2021-present	0	0	1	0	3	11	22	5	4	0	46
Reason for Use**	n=14	n=2	n=1	n=7	n=3	n=10	n=21	n=4	n=4	n=1	n=67**
Glycemic control	14	2	1	7	0	10	13	0	3	1	51
Weight management	0	0	0	1	3	0	8	3	2	0	17
Polycystic ovaries	0	0	0	0	0	0	1	0	0	0	1
Visible peristalsis	0	0	0	0	0	0	0	1	0	0	1
Serious outcome††	n=17	n=2	n=1	n=7	n=3	n=12	n=13	n=5	n=2	n=1	n=63
Death	0	0	0	0	0	0	0	0	0	0	0
Hospitalization	10	0	0	0	0	2	2	0	0	0	14
Life threatening	1	0	0	0	0	0	0	0	0	0	1
Disability	0	0	0	0	0	0	3	0	0	0	3
Required intervention	0	0	0	0	0	0	2	2	0	0	4
Other serious	6	2	1	7	3	10	6	3	2	1	41
Time to onset	n=6	n=1	n=0	n=6	n=3	n=7	n=16	n=3	n=3	n=0	n=45
Median (mo)	6	same day	NA	2	1	3	3	4	5	NA	3
Range (mo)	same day-35	NA	NA	0.5-5	0.5-2	1-4	0.75-11	1-4	4-7	NA	same day-35
GLP-1 RA disposition	n=13	n=1	n=1	n=5	n=4	n=13	n=21	n=5	n=3	n=2	n=68

Table 8. Descriptive Characteristics of Alopecia with GLP-1 RAs in this FAERS Case Series Received by FDA through August 20, 2023 (N=82)

Characteristic	Exenatide			Liraglutide		Dulaglutide	Semaglutide		Tirzepatide	Albiglutide	Total
	Byetta (n=16)	Bydureon (n=2)	Bydureon BCISE (n=1)	Victoza (n=9)	Saxenda (n=4)	Trulicity (n=16)	Ozempic (n=23)	Wegovy (n=5)	Mounjaro (n=4)	Tanzeum (n=2)	NA (n=82)
Dose decreased	2	0	0	0	0	0	0	0	0	0	2
Drug withdrawn	6	1	1	3	1	7	9	3	2	1	34
Drug continued	5	0	0	2	3	6	12	2	1	1	32
Patient disposition	n=10	n=1	n=1	n=6	n=3	n=4	n=11	n=1	n=0	n=1	n=38
Resolved	5	1	1	2	0	1	4	0	-	1	15
Resolving	1	0	0	1	1	0	1	1	-	0	5
Not resolved	4	0	0	3	2	3	6	0	-	0	18
Dechallenge	n=5	n=1	n=1	n=3	n=1	n=1	n=5	n=1	n=0	n=1	n=19
Positive	5	1	1	3	1	1	5	1	0	1	19
Negative	0	0	0	0	0	0	0	0	0	0	0
Positive Rechallenge	n=1	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=1
WHO causality	n=16	n=2	n=1	n=9	n=4	n=16	n=23	n=5	n=4	n=2	n=82
Probable	3	1	1	3	0	1	5	1	0	1	16
Possible	13	1	0	6	4	15	18	4	4	1	66
Baseline weight (kg)	n=7	n=2	n=0	n=3	n=3	n=4	n=15	n=4	n=2	n=1	n=41
Median	80	98	NA	86	110	94	83	90	66	108	85
Range	63-107	86-110	NA	85-104	98-141	86-107	64-124	67-117	63-69	NA	63-141
Final weight (kg)	n=1	n=0	n=0	n=1	n=0	n=0	n=0	n=1	n=1	n=0	n=4
Median	68	-	-	72	-	-	-	97	59	-	70
Range	NA	-	-	NA	-	-	-	NA	NA	-	59-97
Weight loss (kg)	n=7	n=0	n=0	n=1	n=2	n=2	n=1	n=3	n=2	n=2	n=20
Median	17	-	-	13	15	9	3	18	28	14	15
Range	10-18	-	-	NA	0.5-31	7-12	NA	11-63	27-29	10-18	0.5-63 ^{††}
Baseline BMI	n=1	n=1	n=0	n=1	n=2	n=0	n=2	n=2	n=0	n=0	n=9
Median	31	48	NA	38	44	-	25	33	-	-	37
Range	NA	NA	NA	NA	37-52	-	24-25	27-40	-	-	24-52
Final BMI	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=1	n=0	n=1
Median	-	-	-	-	-	-	-	-	22	-	22
Range	-	-	-	-	-	-	-	-	NA	-	NA

* Five foreign cases from Colombia (n=1), Great Britain (n=1), Italy (n=1), Japan (n=1), and Turkey (n=1)

† One foreign case from Australia (n=1)

‡ Three foreign cases from Sweden (n=1), and Turkey (n=1), and China (1)

§ Two foreign countries from Sweden (n=1) and United Kingdom (n=1)

|| Four foreign countries from Australia (n=1), Canada (n=1), United Kingdom (n=1), and Japan (n=1)

¶ Two foreign countries from Canada (n=1) and France (n=1)

** A case may report more than one reason for use

†† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, required intervention, or other serious important medical events.

A case may contain more than one serious outcome. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report.

Table 8. Descriptive Characteristics of Alopecia with GLP-1 RAs in this FAERS Case Series Received by FDA through August 20, 2023 (N=82)											
Characteristic	Exenatide			Liraglutide		Dulaglutide	Semaglutide		Tirzepatide	Albiglutide	Total
	Byetta (n=16)	Bydureon (n=2)	Bydureon BCISE (n=1)	Victoza (n=9)	Saxenda (n=4)	Trulicity (n=16)	Ozempic (n=23)	Wegovy (n=5)	Mounjaro (n=4)	Tanzeum (n=2)	NA (n=82)
Therefore, a serious outcome may not apply to all adverse events in a FAERS report. After hands-on review of the cases, we determine that Hospitalization outcomes were due to medical conditions other than alopecia, although in general, serious outcomes of Other were associated with alopecia.											
‡‡ Weight loss of 63 kg reported in a patient who received concomitant Xywav (calcium, magnesium, potassium, and sodium oxybates) and modafinil, which are labeled for weight decreased and anorexia, respectively.											
Abbreviations: BMI=body mass index, GLP1-RA=glucagon-like peptide-1 receptor agonist, HCP=health care provider, kg=kilogram, mo=month, NA=not applicable, NOS=not otherwise specified											

REPRESENTATIVE CASES

The representative cases below were selected because of relative strength of the causal association between the GLP-1 RA and alopecia, and where applicable, GLP-1 RA products marketed under different trade names for glycemic control or weight management indications.

Exenatide (Byetta)

FAERS 7888734 (United States, US-ELI_LILLY_AND_COMPANY-US201103008793, 2011, Expedited, Serious, Hospitalization):

A consumer reported a 47-year-old African American female with hypertension and gallstones who received exenatide (Byetta) 5-10 mcg twice daily for the treatment of T2DM. Concomitant medication included insulin aspart. An unknown time after starting exenatide, the patient experienced weight loss. The patient's dose of exenatide was decreased from 10 mcg BID to 5 mcg because the 10 mcg dose "was making her blood glucose levels too low." An unknown time after starting exenatide, the patient experienced alopecia, which she described as "male pattern baldness." The patient describes evaluation for alopecia including unspecified blood work, which were normal, and exclusion of medication as a cause for her alopecia, including exclusion of "valsartan/hydrochlorothiazide." She continued to experience hair thinning and alopecia. An unknown time later, the patient was hospitalized overnight and underwent a planned laparoscopic cholecystectomy. At her post-surgical follow-up, she reported having diarrhea, which the surgeon attributed to exenatide or the metformin but not from the surgery. The patient discontinued exenatide for 6 to 8 weeks; while off exenatide therapy, the patient's hair started to grow back but with a different texture. On an unknown date, the patient experienced a knee injury preventing the patient from exercising, resulting in increasing blood glucose levels. She was restarted on exenatide 10 mcg BID, and she experienced hair falling out again. After reviewing online blogs describing patients on exenatide experiencing alopecia and information regarding alopecia on Byetta.com, under her endocrinologist's care, she stopped exenatide and started pramlintide acetate. The patient reported her hair loss to the Byetta "CSC." The patient eventually recovered from her "alopecia/male pattern baldness/hair thinning/hair falling out." There was only 1 value reported for the patient's weight, 104.76 kg, and no height or BMI was reported. The weight was not correlated with exenatide exposure or alopecia findings at that time.

Reviewer comment: Resolution of alopecia upon discontinuation of exenatide supports a causal relationship between exenatide and alopecia. Recurrence of the event upon readministration of the drug supports a drug-event relationship. Although the time to onset was not reported in this case, the patient experienced alopecia after starting exenatide therapy, which supports the causal role of exenatide with alopecia. The patient had a negative work-up with unspecified blood testing. The first instance of exenatide associated alopecia occurred in relationship to post-cholecystectomy diarrhea, and therefore a weight-loss or nutritional component related to the cholecystectomy or the exenatide or both cannot be excluded. GLP-1 RA class labeling for acute gallbladder disease is contained within the WARNINGS AND PRECAUTIONS section. There is insufficient information provided to correlate the amount of weight loss or nutritional status to alopecia in this case. Despite the strengths of this case, it may have limited new regulatory significance, noting exenatide U.S. Prescribing Information (USPI) ADVERSE

REACTIONS Postmarketing Experience section is labeled for alopecia. This case was assessed as probable causality based on positive dechallenge and positive rechallenge information.

Liraglutide (Victoza)

FAERS Case 9722892 (China, CN-NOVOPROD-393315, 2013, Expedited, Serious, Other)⁶⁵

An endocrinologist reported a 67-year-old male experienced hair loss after receiving liraglutide (Victoza) 0.6 mg QD in the first week then increased to 1.2 mg QD in the second week for the treatment of T2DM. Medical history included T2DM for 15 years, gastric ulcer, chronic superficial gastritis for more than 20 years, allergy to alfacalcidol and aspirin, and no family history of hair loss. After 3 months, the patient experienced hair loss on top of the head, which “spread around,” and “aggravated gradually,” which was more obvious when combing and washing the hair. There was no redness, swelling, hotness, pain, pruritus on the scalp, increase in sebum secretion and “scurf”, or change in the color or elasticity of the hair. No obvious skin change or loss of hair was observed in other parts of the body. During treatment with liraglutide, the patient did not have his hair colored or permed. No lifestyle change or mental stress was reported and concomitant drugs remained unchanged. The patient discontinued liraglutide. After a half-month, the hair grew out gradually. A physical exam showed the surface of the scalp was smooth and covered with a little “scurf.” There was no inflammation, atrophy, or swelling. The hair was scant on top of the head and the gloss and elasticity of the hair were normal. No abnormalities were observed in the biochemical and trace element test. Liraglutide was discontinued and not reintroduced to the patient. There was only 1 value reported for the patient’s weight, which was 65 kg, and height was 170 cm, for a calculated BMI of 22.5 kg/m². The weight was not correlated with liraglutide exposure or alopecia findings at that time. The outcome was reported as recovered.

Reviewer comment: This patient experienced hair loss 3 months after receiving liraglutide to treat T2DM. The temporal relationship between the onset of hair loss and initiation of liraglutide supports a causal relationship between hair loss and liraglutide. Resolution of the event upon withdrawal of liraglutide supports a drug-event relationship. This patient reported negative work-up with blood testing. His concomitant medications remained unchanged prior to and during onset of the event. In addition, hereditary susceptibility or manipulation of hair were not risk factors for hair loss in this patient. There is insufficient information provided to correlate weight or nutritional status to alopecia in this case. This case was assessed as probable causality based on temporal association to liraglutide and positive dechallenge information.

Liraglutide (Saxenda)

FAERS 15676497 (United States, US-NOVOPROD-634779, 2018, Expedited, Serious, Other)

A female patient of unreported age was treated with liraglutide (Saxenda) due to an unreported indication. On an unreported date, the patient had “malnutrition ... extreme drop in weight” greater than 70 pounds while taking a 3 mg daily dose of Saxenda over the course of a year. The patient’s physician assistant “recently noticed” that the patient had hair loss on an exam. The patient also had thyroid disease, however, her current thyroid levels were within normal limits. The physician assistant associated the hair loss with the extreme drop in weight and believed it

may have also been associated with malnutrition. Action taken with Saxenda was reported as no change. The outcomes for the events of thyroid disease, hair loss, malnutrition, and extreme drop in weight were not recovered.

Reviewer comment: This patient experienced a 70-pound weight loss over 1 year after starting liraglutide, which suggests alopecia may have been a cascade effect related to GLP-1 associated weight loss leading to malnutrition, although there is no other supporting information regarding a nutritional deficiency. The patient's thyroid disease was stable during the onset of the event. The fact that alopecia was unlikely to be attributed to thyroid disease and the absence of an alternative etiology to explain the occurrence of the event supports a causal role of liraglutide with alopecia, perhaps with weight loss, malnutrition, or both within the causal pathway. This case lacks dechallenge information, and we cannot exclude the possibility that there is unreported information that may have contributed to alopecia in this patient. This case is assessed as having a possible causal association between liraglutide and alopecia.

Dulaglutide (Trulicity)

FAERS Case 18289975 (Australia, AU-ELI_LILLY_AND_COMPANY-AU202009003545, 2020, Expedited, Serious, Other)

A patient of unreported age, who was also nurse, reported that she received dulaglutide (Trulicity) (dose, frequency and route of administration unreported) on an unreported date for an unreported indication. Previously she was on empagliflozin and switched to dulaglutide by her endocrinologist; thereafter she lost 12 kg of weight over 6 to 8 weeks. She then experienced thinning of the scalp hair, which the reporter attributed “possibly” to the large weight loss. The patient reported that “specialist checked her for thyroid problems with no issues...”. The event of weight loss was considered serious due to medically significant reason. The outcome of the event, information regarding corrective treatment, and status of dulaglutide therapy were not provided.

Reviewer comment: This patient experienced weight loss that exceeded the Centers for Disease Control and Prevention (CDC) guidelines⁶⁶ of 1 to 2 pounds per week while treated with dulaglutide for an unreported indication. The patient had a negative workup for thyroid issues. The temporal association to dulaglutide, in conjunction with the absence of an alternative etiology to explain the occurrence of alopecia, supports a causal relationship between alopecia and dulaglutide. Although the outcome of the weight loss was unreported, it is plausible the rapid weight loss was a contributing factor to the development of hair loss in this patient. This case is assessed as having a probable causal association between dulaglutide and alopecia.

Semaglutide (Ozempic)

FAERS Case 20016815 (United States, 2021, Direct)

A female of unreported age noted mild generalized hair loss “a few weeks” after increasing her “Ozempic” dose from 0.25 mg weekly to 0.5 mg weekly to treat T2DM and weight loss. Thyroid testing showed she “was on the correct dose of my thyroid med.” Her “Ozempic” was continued, and the hair loss persisted and became more significant. Based on the patient’s “general searches”, the patient “decided to stop taking it ... Within several weeks, my hair loss had returned to my prior baseline. The only thing I changed at that time was to stop that medication. I am still diabetic, obviously, so that can't be the reason. I am completely convinced that it was due to the Ozempic. I easily lost half of my hair. This needs to be added as a side

effect, as if it has been, I would have stopped taking it much earlier, and would not have the end result.” This report contains no weight related information.

Reviewer comment: This direct report contains a very compelling personal account supporting probable causality, based on close temporal association to semaglutide, positive dechallenge, confirmation of euthyroid status, and no other likely cause reported. Moreover, the patient’s symptoms worsened after the dose of semaglutide was increased. This case is assessed as having a probable causal association between semaglutide and alopecia.

Semaglutide (Wegovy)

FAERS 21247805 (United States, 2022, Direct, Serious, Other, Required intervention)

“After 120 days use of the product, WEGOVY, (Dr. prescribed shot for for weight loss), ALL of my hair fell out. Literally FROM THE FOLLICLES! In the shower, sink, floor in my hands ,on my pillows... SIGH,...I went thick from shoulder length hair, to bald in less than 14 days...Devastating experience!!!. I have dated Photos, documentation from primary care, dermatologist, etc. as proof. I hesitated contacting the FDA because of the embarrassment. However, all health care professionals, patients and consumers must be warned. It's been a few months and my hair is barely peeking through the skin. I had a biopsy and have been diagnosed with alopecia (?). I'm really sure the diagnoses is NOT correct. Why, because research shows /predicted from dermatologist that the hair loss is PERMANENT and my hair will not grow back, but is slowly coming back. The devastation of suddenly losing all of my hair is horrifying, not to mention Excessively expensive....(Hair injections, wigs, medical expenses, laser helmets, etc.). Oh my God, Please WARN THE PUBLIC. AVOID OTHERS GOING THROUGH THIS NIGHTMARE! WEGOVY does not list excessive hair loss in the side effects. I will bet my last dollar and life that it is the cause of my baldness. I look as if I have gone through chemotherapy! Feel me to contact me for additional questions, documentation, etc.,. I still have unexpired prescriptions and medication ...” There was only 1 value reported for the patient’s weight, which was 72 kg, and no height was reported. The weight was not correlated with semaglutide exposure or alopecia findings at that time.

Reviewer comment: This patient experienced total scalp hair loss after starting semaglutide for weight reduction. Only the nonspecific terms “alopecia” is reported for the scalp biopsy obtained by the dermatologist. The improvement of alopecia upon cessation of semaglutide supports a drug-related effect. The hair loss experienced by this patient triggered psycho-social and emotional distress negatively impacting her quality of life. This case was assessed as probable causality based on temporal association to semaglutide and positive dechallenge data.

3.2 LITERATURE⁶⁷

DPV-I retrieved 116 literature citations from PubMed (n=9) and Embase (n=107), of which 4 were duplicates.

PubMed

DPV-I retrieved nine literature citations in PubMed for GLP-1 RAs and alopecia using the search criteria in Table 6. The titles and abstracts of the citations were reviewed to identify relevant articles reporting safety information. Of the nine citations, eight were excluded for the following reasons (the 9th citation is discussed in the paragraph below regarding List et al):

- one was a review article evaluating DPP-4 inhibitors
- one was a review article evaluating polycystic ovary syndrome (PCOS)
- one was a review article evaluating liraglutide to treat hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN)
- five articles did not pertain to the topic of this review

Embase

DPV-I retrieved 107 literature citations in Embase for GLP-1 RAs and alopecia using the search criteria in Table 7, of which 4 were also retrieved in our PubMed search. Of the 103 unique citations, all were excluded for the following reasons:

- 13 were review articles evaluating PCOS
- 6 were clinical trials evaluating the efficacy of
 - liraglutide to treat obesity (2) and diabetes (1)
 - albiglutide to treat gall bladder disease (1)
 - semaglutide to treat obesity (1)
 - tirzepatide to treat obesity (1)
- 6 were review articles evaluating DPP-4 inhibitors
- 4 were review articles evaluating GLP-1 RAs
- 3 were review articles evaluating diabetes mellitus
- 1 was an observational study evaluating liraglutide to treat diabetes mellitus
- 1 was a review article evaluating liraglutide to treat HAIR-AN
- 1 was a review article evaluating Cushing's disease
- 68 articles did not pertain to the topic of this review

DPV-I retrieved one publication by List et al. This citation is not a case report and is not included in our case series but discusses the role of GLP-1 and its receptor in folliculogenesis as demonstrated in an in-vitro animal-cell model. The expression of GLP-1 receptor and proglucagon in the skin of newborn mice (located in the hair follicles and cultures of skin-derived cells) express nestin, a marker of cultured cells that have dedifferentiated by epithelial to mesenchymal transition.⁶⁷ In the cultured skin cells, GLP-1 activates the MAPK/ERK signal transduction pathway, associated with cellular proliferation, differentiation, and cytoprotection. Moreover, redifferentiation of cultured skin-derived cells by incubation in differentiation medium containing GLP-1, induced expression of the proinsulin-derived peptide, C-peptide. This article does not discuss how GLP-1 could cause alopecia; however, the findings suggest a paracrine role for GLP-1 and its receptor in skin development, and possibly in folliculogenesis.

3.3 INFORMATION REQUEST^{68,69,70,71,72,73,74,75}

AstraZeneca (exenatide)

The Applicant noted that “Alopecia was updated to the USPI in Section 6 “Adverse reactions” for Byetta since 17 September 2010. Alopecia was updated to the USPI in Section 6 “Adverse reactions” of Bydureon and BCise since approval.”

Pooled clinical trial data for exenatide BID showed alopecia crude incidence rates in the adult population of 0.24%, 0.36%, and 0.16% for exenatide, placebo, and comparator groups, respectively. Pooled clinical trial data for exenatide weekly formulations showed alopecia crude incidence rates in the adult population of 0.49%, 0%, and 0.09% for exenatide, placebo, and comparator groups, respectively.

The cumulative safety database for Byetta contained 644 cases of alopecia, of which 187 were deemed medically confirmed. Forty-two cases reported positive dechallenge, of which 7 reported positive rechallenge. In all seven cases of positive rechallenge, the Applicant assessed the event of hair loss as possibly related to exenatide.

The Bydureon search identified 179 reports coded with the Preferred Terms *Alopecia* (n=178) or *Diffuse alopecia* (n=1). This included 15 cases with positive dechallenge and no cases with positive rechallenge. The Applicant deemed 50 reports as possibly due to exenatide therapy since time to onset was reported, but these cases contained contributory factors, such as concomitant drugs, underlying conditions, perimenopausal or geriatric age, or concurrent events of decreased appetite and weight loss.

Among reports within the cumulative safety database for Byetta and Bydureon, approximately half reported “contributory medical history /underlying medical conditions of stress, malnutrition, iron deficiency, polycystic ovarian syndrome, rheumatic disorder, thyroid disorder, systemic lupus erythematosus, weight loss and ageing and also had contributory concomitant drug usage of anticoagulants, antineoplastic drugs, antithyroid drugs, antihyperlipidemic drugs, anti-hypertensives.” Weight loss was reported as a concurrent adverse event in 23.1% of the cases. Bald and/or baldness was reported in only 3% of the cases. Ninety-nine percent of the alopecia related events were nonserious.

Novo Nordisk (semaglutide and liraglutide)^{71,72,73,74,75}

The Applicant concluded the following:

GLP-1 RA for weight management (WM) (Saxenda, Wegovy)

Wegovy and oral semaglutide for WM: Hair loss is an identified risk.

Clinical trial data:

Alopecia was observed with semaglutide (Wegovy, 3%; oral semaglutide for WM, 6.9%) compared to placebo/active comparator (Wegovy-placebo, 1.4%, comparator, 2.2%; oral semaglutide for WM-placebo, 2.7%).

Alopecia is included in the Wegovy label as hair loss and reported more frequently in patients with greater weight loss ($\geq 20\%$). The current evaluation does not warrant a label update.

Saxenda: The totality of data evaluated in the current assessment do not suggest an increased risk of alopecia.

Clinical trial data:

No increased risk of alopecia was observed with Saxenda, which may be explained by lower weight loss generally observed with Saxenda when compared to Wegovy and oral semaglutide for WM.

GLP-1 RA for T2DM (Rybelsus, Xultophy, Ozempic, or Victoza)

No increased risk of alopecia was identified with Rybelsus, Xultophy, Ozempic, or Victoza based on the current evaluation of data, although the Applicant did note that most postmarketing cases of drug-associated alopecia recover within 3-6 months from drug discontinuation.

Lilly (dulaglutide)⁶⁸

The Glycemic Control Study in Patients with Chronic Kidney Disease (GBDX) reported 1.8% ‘any alopecia’ in the dulaglutide arm and 0% placebo. A small numerical imbalance for alopecia was also reported in the REWIND trial with 0.45% for dulaglutide and 0.32% for placebo.

The review of the postmarketing data for alopecia identified 401 cases reporting 403 events of alopecia, and the Applicant calculated a reporting rate of 0.0022 (403 events/18,010,000 patients). Most cases were coded with the Preferred Term *Alopecia* (n=395; 98%), followed by *Alopecia areata* (AA) (n=5; 1.2%). The analysis of the 182 evaluable cases (i.e., those containing medical history and concomitant medication information) found that 79% involved female patients. About 58% of cases reported at least 1 risk factor for alopecia, with 12.6% of cases describing weight loss. Among 17 reports quantifying weight loss, the minimum weight loss reported was 7.3 kg, the maximum was 72.6 kg, and the median and mean were 18.0 kg and 19.2 kg, respectively. Only three of these cases described a baseline bodyweight, and of these three, only one described the timeframe of the weight loss.

A limited number of evaluable cases (3.3%) described baldness. There were 17 cases of positive dechallenge. Only one case described a possible biologically plausible timeframe for washout from dulaglutide treatment and hair regrowth to be observed. Narratives of the three positive rechallenge cases (US201908013842, US202004012245, US201510007051) were assessed by the Applicant as providing insufficient information on potential confounders, timing of hair loss, or timing of regrowth to sufficiently establish causality. Based on the information in the narrative, DPV-I assessed these rechallenge cases as possible WHO-UMC causality, although the reports do not provide information on weight loss. These three reports were excluded from our series as they are non-serious reports (i.e., periodic reports). Our FAERS search criteria included only serious and/or direct reports.

The Applicant concluded that evidence does not support a causal association between dulaglutide and alopecia/hair loss.

Lilly (tirzepatide)⁷⁶

The incidence of alopecia/hair loss observed in the tirzepatide group was greater than the comparator group in the T2DM clinical trials (0.38% and 0.13%) and chronic weight

management (CWM) clinical trials (4% and 0.7%). Among the patients who reported alopecia/hair loss in T2DM clinical trials, the majority reported weight loss, although this was variable; of the 25 alopecia/hair loss adverse events, 40% (n=10) were in participants experiencing weight loss between 0% to <10%, 40% (n=10) were in participants experiencing weight loss between 10% to <20%, and 20% (n=5) were in participants experiencing weight loss 20% to ≤30%. There were no alopecia/hair loss events in participants experiencing weight loss >30%.

Of an estimated postmarketing exposure of 2,646,000 patients, there were 151 alopecia/hair loss reports, although only 22.5% specified an indication of T2DM. Weight loss during treatment with tirzepatide was not specified in 121 (80.1%) of these reports. There were no cases of baldness or scarring reported, although two reported a bald spot as a descriptive term. Nine reports were assessed as having a possible causal relationship, including four with a positive dechallenge and one with a positive rechallenge. Unspecified weight loss was mentioned in the rechallenge case and one of the dechallenge cases reported a 6-pound weight loss in 1 week. The remaining 142 reports were considered unassessable or unlikely.

The Applicant concluded to not include alopecia/hair loss as an adverse drug reaction (ADR) for the T2DM indication in the tirzepatide core data sheet. The marketing authorization holder will continue to review events of alopecia/hair loss through routine pharmacovigilance, while noting alopecia/hair loss is already recognized as an ADR for the CWM indication secondary to substantial weight loss.

Sanofi (lixisenatide)⁶⁹

In the clinical trials, 30 (0.42%) participants in the lixisenatide arm (n=7166) experienced alopecia/AA/diffuse alopecia as compared to 15 (0.31%) participants in the placebo arm (n=4876) and 1 (0.35%) participant in the active comparator arm (n=289). Of these, most of the alopecia related events were reported with mild intensity. The Applicant concluded no imbalance was observed for lixisenatide with alopecia/hair loss.

The Applicant assessed their pharmacovigilance database and cumulatively retrieved eight non-serious cases. Of the eight cases, four used the drug for T2DM/diabetes mellitus, three were unknown, and one used the drug for the off-label use to prevent diabetes in a non-diabetic patient. Six cases were classified as having compatible chronology (three with identified relevant confounding factors and three cases with limited information), and the remaining two had unclassified causality. The overall reporting rate was assessed as lower than the general population. All cases had manufacturer control numbers of 2016 or earlier and none were from the United States.

The Applicant concluded that there is insufficient information to support a causal association between lixisenatide or the fixed ratio combination (insulin glargine + lixisenatide) and alopecia/hair loss.

3.4 DRUG UTILIZATION

Settings of Care

Based on the manufacturer sales distribution data in 2022^a, approximately 80%, 11%, and 9% of total packages^b of GLP-1 RAs were sold to U.S. outpatient retail pharmacies^c, mail-order/specialty pharmacies, and non-retail^d settings (mostly clinics), respectively. Therefore, we focused our analyses on utilization from U.S. outpatient retail and mail-order/specialty pharmacies.

U.S. Outpatient Retail and Mail-Order/Specialty Prescription Utilization

Figure 3 below and **Table 10** in **Appendix D** provide the annual estimates of prescriptions dispensed for GLP-1 RAs from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by molecule and product, from January 2013 through September 2023, calendar year. An estimated total of 35 million GLP-1 RA prescriptions were dispensed from U.S. outpatient retail and mail-order/specialty pharmacies in 2022. Of these total 35 million GLP-1 RAs dispensed prescriptions in 2022, semaglutide accounted for the highest proportion at approximately 45% (15.9 million prescriptions), followed by dulaglutide (35%, 12.4 million prescriptions), liraglutide (9%, 3.1 million prescriptions), tirzepatide (7%, 2.6 million prescriptions), exenatide (2%, 0.6 million prescriptions), insulin glargine/lixisenatide (1%, 0.4 million prescriptions), insulin degludec/liraglutide (<1%, 97,000 prescriptions), and lixisenatide (<1%, 1,600 prescriptions). No utilization was captured for albiglutide (discontinued in July 2017)⁷⁷ in 2022.

The estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022. Semaglutide dispensed prescriptions increased from 0.4 million prescriptions in 2018 to 15.9 million prescriptions in 2022. Similarly, dulaglutide dispensed prescriptions increased from 4,000 prescriptions in 2014 to 12.4 million prescriptions in 2022. Liraglutide dispensed prescriptions increased from 2.6 million prescriptions in 2013 to 4.8 million prescriptions in 2018, then decreased to 3.1 million prescriptions in 2022. Exenatide dispensed prescriptions remained relatively steady from 2013 through 2019 (1.4 million prescriptions), then decreased to 0.6 million prescriptions in 2022. Insulin glargine/lixisenatide dispensed prescriptions increased from 86,000 prescriptions in 2017 to 0.4 million prescriptions in 2022. Insulin degludec/liraglutide dispensed prescriptions steadily increased from 19,000 prescriptions in 2017 to 0.1 million prescriptions in 2020, then decreased to 97,000 prescriptions in 2022. Lixisenatide dispensed prescriptions increased from 700 prescriptions in 2017 to 2,500 prescriptions in 2021, then decreased to 1,600 prescriptions in 2022. Albiglutide dispensed prescriptions increased from 20,000 prescriptions in 2014 to 0.6 million prescriptions in 2016, then decreased to 1,700 prescriptions in 2019. A negligible use of albiglutide was captured in 2020.

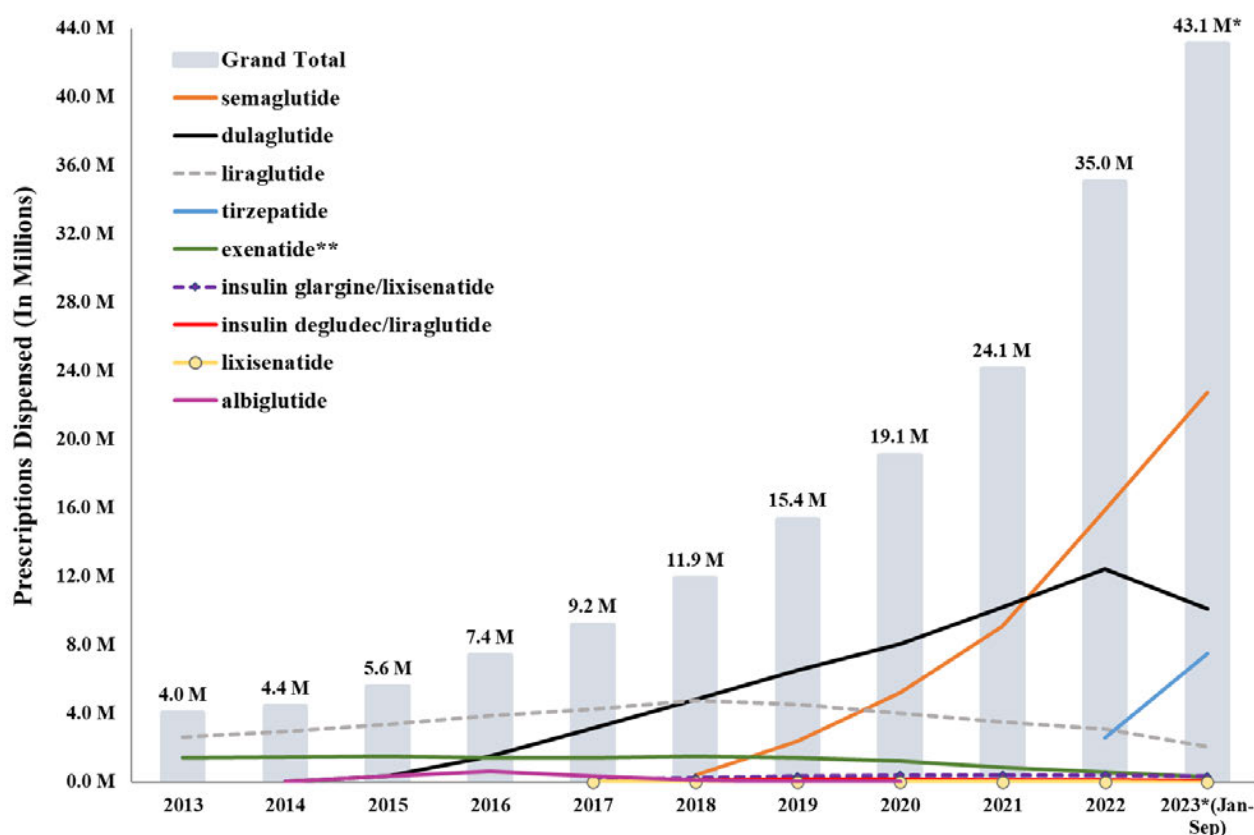
^a Source: IQVIA™ National Sales Perspectives (NSP). 2022. Extracted August 2023. File: IQVIA NSP 2023-5482 GLP-1 RAs 08-21-2023 .xlsx

^b Packages include auto-injectors, pens, and bottles.

^c Retail settings include chain drug stores, independent drug stores, mass merchandisers, food stores, and mail-order services.

^d Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

Figure 3: Estimated Number of Prescriptions Dispensed for GLP-1 RAs from U.S. Outpatient Retail and Mail-Order/Specialty Pharmacies, Stratified by Molecule, January 2013 through September 2023, Calendar Year



Source: Symphony Health Metys® Data years January 2013 – September 2023. Data Extracted October 2023. File: 2023-5971 GLP-1 RAs chart 10-23-2023.xlsx

*Includes January to September 2023

**Includes exenatide (immediate-release) and exenatide microsphere (extended-release) molecules

Figure 4 below shows estimated number of prescriptions dispensed for semaglutide and liraglutide from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by product, 2013 through 2022, calendar year. We are displaying data stratified by product^e for semaglutide and liraglutide only due to the differences in the labeled indication(s) among their products. All other GLP-1 RAs molecules and their products in this review are currently labeled for T2DM only. Complete data for all GLP-1 RAs molecule stratified by product are shown in **Appendix E**.

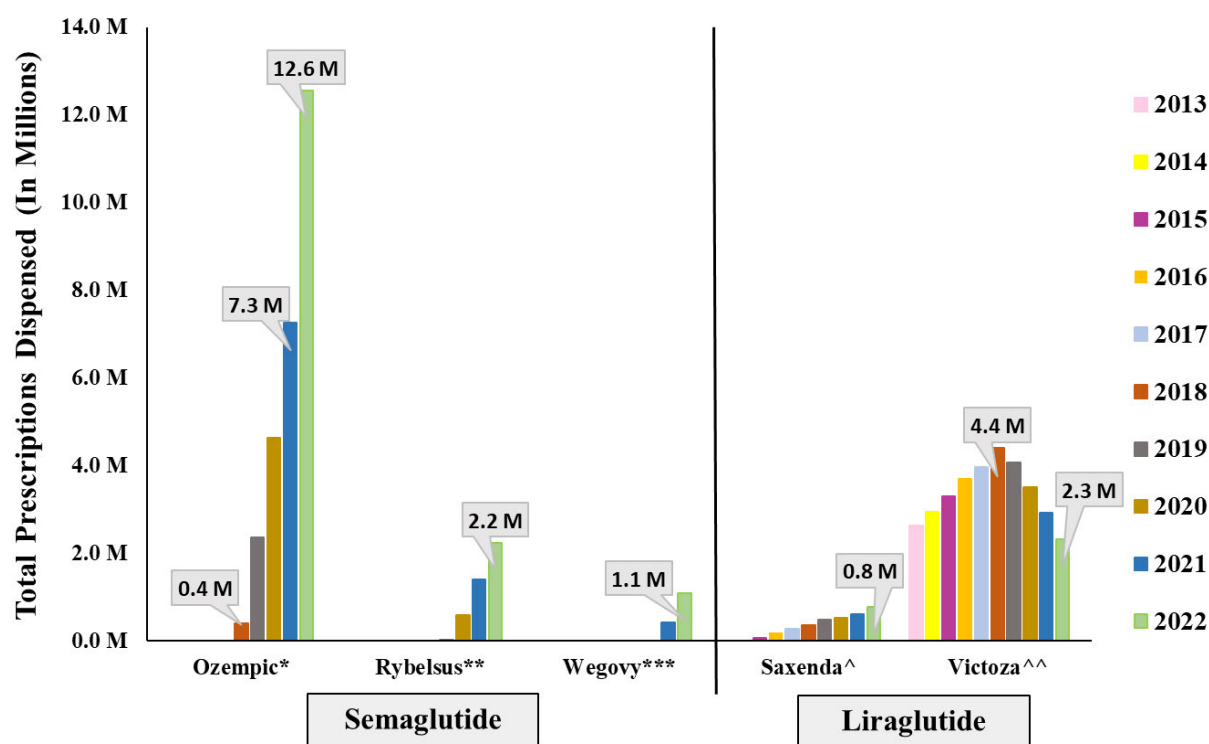
Of the estimated total 15.9 million semaglutide prescriptions dispensed in 2022, Ozempic accounted for the highest proportion (79%, 12.6 million prescriptions), followed by Rybelsus (14%, 2.2 million prescriptions), and Wegovy (7%, 1.1 million prescriptions). We observed similar patterns for semaglutide products in 2021. Prescriptions dispensed for all semaglutide products increased during the study period examined: Ozempic increased from 0.4 million prescriptions in 2018 to 12.6 million prescriptions in 2022, Rybelsus increased from 17,000

^e Tirzepatide is not included due to its weight management indication approval in November 2023.

prescriptions in 2019 to 2.2 million prescriptions in 2022, and Wegovy increased from 0.4 million prescriptions in 2021 to 1.1 million prescriptions in 2022.

Of the estimated total 3.1 million liraglutide prescriptions dispensed in 2022, Victoza accounted for the highest proportion at 75% (2.3 million prescriptions), while Saxenda accounted for 25% (0.8 million prescriptions). Victoza dispensed prescriptions steadily increased from 2.6 million prescriptions in 2013 to 4.4 million prescriptions in 2018, then decreased to 2.3 million prescriptions in 2022. Since the approval of Saxenda in December 2014, Saxenda dispensed prescriptions gradually increased from 54,000 prescriptions in 2015 to 0.8 million prescriptions in 2022.

Figure 4: Estimated Number of Prescriptions Dispensed for Semaglutide and Liraglutide from U.S. Outpatient Retail and Mail-Order/Specialty Pharmacies, Stratified by Product, 2013 through 2022, Calendar Year



Source: Symphony Health Metys™. Data years January 2013 – December 2022. Data Extracted August 2023. File: 2023-5971 GLP-1 RAs chart 10-23-2023.xlsx

*Ozempic approved in December 2017

**Rybelsus approved in September 2019

***Wegovy approved in June 2021

^Saxenda approved in December 2014

^^ Victoza approved in January 2010

Office-Based Prescriber Survey Data

Table 9 below shows the top 3 diagnoses associated with the use of GLP-1 RAs, as reported by surveys from U.S. office-based health care providers in 2022. T2DM was the top diagnosis reported for GLP-1 RAs in 2022, accounting for approximately 82% of total use mentions. This

was followed by overweight and obesity, and elevated blood glucose, accounting for 11% and 6% of total use mentions, respectively.

Semaglutide (59% of use mentions), dulaglutide (28%), and liraglutide (5%) were the top mentioned GLP-1 RAs for T2DM. Semaglutide (58% of use mentions) and liraglutide (35%) were the top mentioned GLP-1 RAs for overweight and obesity. Among the semaglutide use mentions reported for overweight and obesity, Wegovy comprised the highest proportion (44% of use mentions), followed by Ozempic (38%), and Rybelsus (18%). Among the liraglutide use mentions reported for overweight and obesity, Saxenda accounted for the vast majority (96% of use mentions), while Victoza accounted for 4%. Tirzepatide product Mounjaro accounted for 4% of use mentions and dulaglutide accounted for 3% of use mentions reported for the overweight and obesity diagnosis. Of note, the use mentions reported below 100,000 may not represent national use, given the small sample size and low precision associated with the estimates.

Table 9. Top Three Diagnoses Associated with the Use of GLP-1 RAs, as Reported by Surveys from U.S. Office-Based Health Care Providers, in 2022

	2022		
	Uses	95% CI	%
Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%
Type 2 diabetes mellitus	10,624,000	9,831,000 - 11,416,000	82.1%
Semaglutide	6,313,000	5,702,000 - 6,924,000	59.4%
Ozempic	4,516,000	3,999,000 - 5,033,000	71.5%
Rybelsus	1,791,000	1,466,000 - 2,117,000	28.4%
Wegovy	5,000	<500 - 23,000	0.1%
Dulaglutide (Trulicity)	2,941,000	2,524,000 - 3,358,000	27.7%
Liraglutide	553,000	372,000 - 734,000	5.2%
Victoza	548,000	368,000 - 728,000	99.1%
Saxenda	5,000	<500 - 22,000	0.9%
Insulin glargine/lixisenatide (Soliqua)	388,000	237,000 - 540,000	3.7%
Exenatide	328,000	189,000 - 468,000	3.1%
Byetta	154,000	59,000 - 250,000	47.0%
Bydureon BCise	148,000	55,000 - 242,000	45.2%
Bydureon	26,000	<500 - 65,000	7.8%
Insulin degludec/liraglutide (Xultophy)	71,000	6,000 - 137,000	0.7%
Tirzepatide (Mounjaro)	30,000	<500 - 71,000	0.3%
Overweight and obesity	1,426,000	1,136,000 - 1,717,000	11.0%
Semaglutide	821,000	601,000 - 1,042,000	57.6%
Wegovy	362,000	215,000 - 508,000	44.0%
Ozempic	312,000	176,000 - 448,000	38.0%
Rybelsus	147,000	54,000 - 241,000	18.0%
Liraglutide	506,000	333,000 - 678,000	35.4%
Saxenda	485,000	315,000 - 654,000	95.9%
Victoza	21,000	<500 - 56,000	4.1%
Tirzepatide (Mounjaro)	53,000	<500 - 109,000	3.7%
Dulaglutide (Trulicity)	46,000	<500 - 99,000	3.2%
Elevated blood glucose level	716,000	510,000 - 922,000	5.5%
All other diagnoses	178,000	75,000 - 280,000	1.4%

Source: Syneos Health Research & Insights, LLC, Treatment Answers™. Year 2022. Data Extracted: October 2023. File: 2023-5971 GLP-1 RAs Syneos 2022, 10-25-2023.xls

The projected use mentions below 100,000 estimates may not be representative of providers' prescribing habits at the national level.

Abbreviations: CI: confidence interval

4 DISCUSSION⁶⁷

This review identified 82 cases of alopecia reported with the use of GLP-1 RA medications. With the exception of lixisenatide, all GLP-1 RAs were represented in our case series. This difference may reflect the market share of these products and not a differential risk among these GLP-1 RAs. Our case series provides reasonable evidence for hair loss in the setting of GLP-1 RA use, whether or not weight loss was also reported. However, for reasons mentioned in Section 2.3, due to restricting our FAERS search to reports with serious regulatory outcome and direct reports, this review is not intended to assess a larger volume of reports not captured by this search strategy, which may have further added to our evidence.

Case Characteristics

The median time to onset in our series was 3 months (range same day to 35 months). In two cases where patients used Byetta or Bydureon to treat T2DM, a same day time to onset from initiation of the GLP-1 RA to the onset of alopecia was reported. We note that although both cases met our case definition and were deemed possibly related to the GLP-1 RA, one patient had breast cancer, but treatment for this condition was not reported and the other described resolution of hair loss 4 months after GLP-1 RA discontinuation. Although this short time to onset may conflict with a potential proposed mechanism of hair loss related to weight loss from these products, as discussed below, the biological mechanism(s) related to GLP-1 RAs and hair loss remains inconclusive at this time. The median patient age was 45 years with a predominance in females (70/78, 90%). Half of the cases were direct reports submitted by consumers reporting hair loss.

Causality Assessment

Sixteen cases in our series were assessed as probable causality, and this included all GLP-1 RAs except for liraglutide and tirzepatide. With the exception of three, all positive dechallenge cases reported a probable causality to GLP-RA. A single case reporting the use of exenatide (Byetta) reported a positive rechallenge, and was assessed as probable causality, as detailed within our representative cases. Adverse events included hair loss (n=14) and hair thinning followed by hair loss (n=2). Of the 14 cases reporting hair loss, half reported "severe" hair loss or losing "unusual" or "significant" amounts of hair. One of two cases reporting hair loss followed by hair thinning, reported "hair began thinning and then would completely fall out." Five cases reported exacerbation of symptoms with dose increases of the GLP-1 RA including semaglutide (Ozempic) (n=3), dulaglutide (n=1) and albiglutide (1). In all cases alopecia resolved upon discontinuation of the suspect drug.

Of the 82 cases in our series, most (66/82, 80%) were assessed as possible causality. These included hair loss (n=54), hair thinning followed by hair loss (n=6), hair thinning (n=5), and loss of eyelashes (n=1) after initiation of a GLP-1 RA. Of the 54 cases reporting hair loss,

approximately half reported losing “large” or “significant” amounts of hair in “handfuls” as well as hair falling out with showering, brushing, or combing. Cases were confounded by underlying disease (e.g., cancer, hypothyroidism, PCOS) or concomitant medications labeled for alopecia (e.g., levothyroxine, beta blockers, chemotherapy). In others, the discontinuation status or outcome of the hair loss was unreported. One case reported eyelashes falling out after the use of tirzepatide; however, the withdrawal status of the suspect drug and outcome of the event were unreported.

Alopecia Associated with Weight Loss Attributed to GLP-1 RA Use

Alopecia associated with concomitant weight loss was reported in 20 of our cases. In most cases, the indication or reason for use of the GLP-1 RA product was glycemic control. The most frequently reported GLP-1 RA was exenatide (Byetta). Two cases reported liraglutide (Saxenda) (n=1) and semaglutide (Wegovy) (n=1) used for the labeled indication of weight management. The median weight loss in our series was 15 kg (range 0.5 to 63 kg). In two cases, rapid weight loss was reported in the patient, including 12 kg in 2 months in 1 and 11 kg in 3 months in the other. The majority of cases reported withdrawal of GLP-1 RA where the outcome of weight loss and alopecia was unknown. Two cases reported resolution of alopecia upon discontinuation of GLP-1 RA; however, it was not reported if this correlated with weight gain or improved nutrition after GLP-1 RA discontinuation. Two cases reported hair loss with rapid weight loss associated with the use of liraglutide (Saxenda) (n=1) and dulaglutide (Trulicity) (n=1) reported for unknown indication. The temporal relationship with GLP-1 RA and the general absence of alternative etiologies for alopecia in these cases support a causal relationship between alopecia and weight loss related to the suspect drug.

Biological Plausibility

In our series, the reported weight loss induced by the GLP-1 RAs provides a plausible mechanism for the development of hair loss, as alopecia is a recognized complication of significant weight loss and caloric restriction, as discussed in Section 1.1.3. Our series, however, also described cases of hair loss with no reported concomitant weight loss, where the event resolved upon discontinuation of the suspect drug. List et al. describes the expression of proglucagon and GLP-1Rs in mouse skin, the latter concentrated in hair follicles, as discussed in Section 3.2. These findings suggest GLP-1 and their receptors may be involved in the regulation of folliculogenesis. Although this publication does not discuss alopecia-related mechanisms, it may be hypothesized that effects on the hair follicle trigger hair growth regression or move the hair follicles into the shedding stage, thereby causing alopecia. Other hypotheses have been proposed including disruption in hormonal pathways or androgen levels leading to drug-induced alopecia. On the contrary, GLP-1 agonists improve vasculature sensitivity to insulin, abating potential hair loss, by enhancing blood flow to the scalp. Despite conflicting hypotheses, the biological mechanism related to GLP-1 agonists and hair loss remains inconclusive at this time.⁷⁸

Drug Utilization Discussion

DEPI-II's utilization analyses from U.S. outpatient retail and mail-order/specialty pharmacies showed that the estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022. Semaglutide accounted for 45% of the total GLP-1 RAs prescriptions dispensed in 2022. Ozempic accounted for the majority of semaglutide dispensed prescriptions in 2022. Of note, we observed a sharp increase in Ozempic

dispensed prescriptions from 2021 to 2022. This may be attributed to factors such as the ongoing shortage (started in March 2022)⁷⁹ of Wegovy (another injectable semaglutide product) and new clinical data⁸⁰ suggesting the use of injectable semaglutide over liraglutide for weight loss in patients without diabetes. However, we did not examine the reasons behind the utilization patterns observed in our analyses. Office-based prescriber survey data showed that T2DM (82% of use mentions), overweight and obesity (11%), and elevated blood glucose (5%) were the top 3 diagnoses for GLP-1 RAs in 2022. Results from the survey data showed use of semaglutide products Ozempic and Rybelsus, liraglutide product Victoza, tirzepatide product Mounjaro, and dulaglutide for overweight and obesity, suggesting off-label use of these products. However, the use mentions reported for liraglutide product Victoza, tirzepatide product Mounjaro, and dulaglutide for the overweight and obesity diagnosis were too low (<100,000) and therefore, may not represent national use, given the small sample size and low precision associated with the estimates.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, we find an association between GLP-1 RA use and hair loss. We acknowledge our case series did not identify cases of hair loss in association with lixisenatide, which has represented less than 0.1% of the U.S. outpatient pharmacy market share. Wegovy and Zepbound contain the term hair loss in ADVERSE REACTIONS *Clinical Trials Experience*, and all exenatide products contain the term alopecia in ADVERSE REACTIONS *Postmarketing Experience*. Based on this review we recommend the following:

- Update ADVERSE REACTIONS *Postmarketing Experience* to reflect the potential risk of hair loss with all GLP-1 RAs, except exenatide, which includes the term alopecia within this section of labeling.*

* *Postmarketing Experience* alopecia labeling for Wegovy and Zepbound may not be required, as this information exists in *Clinical Trials Experience*, as noted above.

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~90% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys®

Powered by IDV®, Metys® is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys® accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 74% of all U.S. mail order prescriptions, 73% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys® Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

Syneos Health Research & Insights LLC., TreatmentAnswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,500 office-based physicians, physician assistants and nurse practitioners representing 32 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel

supplement surveys over 115 pain specialists' physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. In August 2019, the nurse practitioner and physician assistant specialties were added to the panel. This enhancement provides a more precise view of prescribing habits since nurse practitioners and physician assistants are increasingly playing an important role in patient care. All data collected, is projected nationally by physician specialty and region to reflect national prescribing patterns.

Drug Utilization Databases Limitations

The drug utilization findings from this review should be interpreted in the context of the known limitations of the databases used. Dispensed prescriptions are nationally projected based on a sample of prescription claims from U.S. outpatient retail and mail-order/specialty pharmacies. Summation of these projected estimates across time periods may lead to differences in prescription due to rounding attributable to the projection methodology utilized. Moreover, GLP-1 RAs utilization patterns in the outpatient settings might not represent GLP-1 RAs utilization patterns in other settings of care such, as clinics and hospitals, where these products may be used. Of note, the prescription data provided in this review are regardless of indication. Drug use mentions and diagnoses data were generated from surveys conducted for one day out a month for outpatient office visits from a sample of over 3,500 office-based providers and are not directly linked to dispensed prescriptions. Drug use mentions with diagnoses data did not necessarily result in dispensed prescriptions; rather they were the number of outpatient visits with a drug and diagnosis recorded. Use mentions below 100,000 do not represent sufficient portion of the population and are not representative of actual providers prescribing habits at a national level.

7.3 APPENDIX C. FAERS LINE LISTING OF GLP-1 RA ALOPECIA CASE SERIES N=82

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Bydureon									
1	04-APR-2018	14712787	1	AU-ASTRAZENECA-2018SE22229	Expedited (15-Day)	65.995	Female	AUS	OT
2	22-JAN-2016	11938375	7	US-ASTRAZENECA-2012BM13225	Expedited (15-Day)	76.331	Female	USA	OT
Bydureon BCISE									
3	05-JUL-2023	22677006	1	FDA-CDER-CTU-2023-49559	Direct	58	Male	USA	OT
Byetta									
4	18-SEP-2015	11524070	1	US-PFIZER INC-2015312450	Expedited (15-Day)		Female	USA	OT
5	21-JUL-2011	8048162	1	JP-ELI_LILLY_AND_COMPANY-JP201107002549	Expedited (15-Day)		Female	JPN	HO
6	26-OCT-2007	6452828	2	US-ELI_LILLY_AND_COMPANY-US200710004228	Expedited (15-Day)	34	Female	USA	HO
7	08-FEB-2008	6548559	4	US-ELI_LILLY_AND_COMPANY-US200801006403	Expedited (15-Day)	41.94	Female	USA	HO
8	02-FEB-2009	6898809	3	CO-ELI_LILLY_AND_COMPANY-CO200901005019	Expedited (15-Day)	47	Female	COL	HO
9	07-APR-2011	7888734	3	US-ELI_LILLY_AND_COMPANY-US201103008793	Expedited (15-Day)	47.48	Female	USA	HO
10	06-MAR-2009	6930109	1	GB-ELI_LILLY_AND_COMPANY-GB200902006305	Expedited (15-Day)	49	Male	GBR	OT
11	21-NOV-2006	6182365	2	2006PV024648	Expedited (15-Day)	53	Female	USA	HO
12	23-NOV-2016	12969976	1	US-ASTRAZENECA-2009BM09767	Expedited (15-Day)	55	Female	USA	LT, OT
13	27-JUL-2009	7063738	6	IT-ELI_LILLY_AND_COMPANY-IT200907003237	Expedited (15-Day)	60	Female	ITA	OT
14	19-SEP-2014	10464823	3	TR-BRISTOL-MYERS SQUIBB COMPANY-21394754	Expedited (15-Day)	61.563	Female	TUR	OT
15	31-AUG-2016	12700996	1	US-ASTRAZENECA-2008BM03626	Expedited (15-Day)	65	Female	USA	HO
15†	13-MAR-2008	6580358	2	US-ELI_LILLY_AND_COMPANY-US200803001892	Expedited (15-Day)	65.24	Female	USA	HO
16	05-FEB-2008	6554904	1	324540	Direct	66	Male	USA	OT
17	13-JAN-2011	7759128	1	US-ELI_LILLY_AND_COMPANY-US201101001501	Expedited (15-Day)	72	Female	USA	HO
18	27-OCT-2006	6168012	2	2006PV023207	Expedited (15-Day)	76	Female	USA	HO
19	18-SEP-2015	11524070	1	US-PFIZER INC-2015312450	Expedited (15-Day)		Female	USA	OT
19†	16-SEP-2015	11514827	1	US-ASTRAZENECA-2014SE08505	Expedited (15-Day)		Female	USA	OT

Mounjaro									
20	02-JUN-2023	22399194	1	US-ELI_LILLY_AND_COMPANY-US202305016639	Expedited (15-Day)		Female	USA	OT
21	16-FEB-2023	22005472	1	FDA-CDER-CTU-2023-13361	Direct	24.7	Female	USA	
22	28-JUN-2023	22654793	1	FDA-CDER-CTU-2023-48189	Direct	52	Female	USA	OT
23	15-MAR-2023	22103312	1	FDA-CDER-CTU-2023-20573	Direct	54		USA	
Ozempic									
24	25-FEB-2021	18941183	1	FR-NOVOPROD-778524	Expedited (15-Day)		Female	FRA	OT
25	29-OCT-2021	20008578	2	CA-RECORDATI-2020002101	Expedited (15-Day)			CAN	OT
26	03-JUN-2022	20909435	1	US-NOVOPROD-923990	Expedited (15-Day)		Female	USA	HO
27	14-FEB-2023	21995357	1	FDA-CDER-CTU-2023-12702	Direct		Female	USA	RI
28	08-MAY-2023	22294668	1	US-NOVOPROD-1059708	Expedited (15-Day)		Female	USA	HO
29	05-NOV-2021	20016815	1	FDA-CDER-CTU-2021-82806	Direct		Female	USA	
30	25-MAY-2023	22366964	1	FDA-CDER-CTU-2023-39148	Direct	36	Female	USA	
31	14-DEC-2021	20182480	1	FDA-CDER-CTU-2021-93819	Direct	38	Female	USA	
32	25-JAN-2022	20378593	1	FDA-CDER-CTU-2022-6803	Direct	42	Female	USA	
33	12-FEB-2023	21989313	1	FDA-CDER-CTU-2023-12068	Direct	43	Female	USA	
34	30-JUL-2022	21157373	1	FDA-CDER-CTU-2022-60424	Direct	44	Female	USA	
35	13-DEC-2022	21723555	1	FDA-CDER-CTU-2022-98954	Direct	45	Female	USA	DS
36	06-APR-2023	22181374	1	FDA-CDER-CTU-2023-25952	Direct	45	Female	USA	OT
37	12-AUG-2022	21208913	1	FDA-CDER-CTU-2022-64512	Direct	47	Female	USA	RI
38	12-MAY-2023	22323916	1	FDA-CDER-CTU-2023-35728	Direct	49	Female	USA	OT
39	10-AUG-2022	21200269	1	FDA-CDER-CTU-2022-63904	Direct	53	Female	USA	
40	01-JAN-2022	20280613	1	FDA-CDER-CTU-2022-216	Direct	54	Female	USA	
41	28-APR-2023	22270106	1	FDA-CDER-CTU-2023-31843	Direct	61	Female	USA	DS
42	09-DEC-2022	21715237	1	FDA-CDER-CTU-2022-98057	Direct	61	Male	USA	
43	29-DEC-2022	21800630	1	FDA-CDER-CTU-2022-103633	Direct	62	Female	USA	DS
44	29-APR-2020	17728417	1	FDA-CDER-CTU-2020-44914	Direct	67	Female	USA	OT
45	05-NOV-2022	21562078	1	FDA-CDER-CTU-2022-88665	Direct	71	Female	USA	OT
46	08-FEB-2022	20445551	1	FDA-CDER-CTU-2022-11035	Direct	76	Female	USA	
Saxenda									
47	30-NOV-2018	15676497	1	US-NOVOPROD-634779	Expedited (15-Day)		Female	USA	OT
48	31-MAY-2022	20894346	1	SE-NOVOPROD-919400	Expedited (15-Day)	44	Female	SWE	OT
49	04-NOV-2022	21552334	1	GB-NOVOPROD-974311	Expedited (15-Day)	46	Female	GBR	OT
50	19-OCT-2021	19968378	1	FDA-CDER-CTU-2021-77775	Direct	46.6	Female	USA	
Tanzeum									
51	27-AUG-2015	11427036	1	US-GLAXOSMITHKLINE-US2015GSK121802	Expedited (15-Day)		Female	USA	OT
52	19-DEC-2016	13040506	1	FDA-CDER-CTU-19696	Direct	58	Female	USA	

Trulicity									
53	22-JUL-2019	16609187	1	US-ELI_LILLY_AND_COMPANY-US201907007681	Expedited (15-Day)		Female	USA	HO
54	21-SEP-2020	18289975	1	AU-ELI_LILLY_AND_COMPANY-AU202009003545	Expedited (15-Day)		Female	AUS	OT
55	04-FEB-2022	20432187	1	GB-ELI_LILLY_AND_COMPANY-GB202201009264	Expedited (15-Day)		Female	GBR	OT
56	14-FEB-2022	20474030	1	FDA-CDER-CTU-2022-12481	Direct			USA	OT
57	13-MAR-2023	22092853	1	FDA-CDER-CTU-2023-19953	Direct		Female	USA	
58	26-SEP-2022	21385305	1	FDA-CDER-CTU-2022-76893	Direct	36	Female	USA	OT
59	02-AUG-2018	15231872	2	JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-070308	Expedited (15-Day)	39	Male	JPN	OT
60	25-APR-2021	19183979	1	FDA-CDER-CTU-2021-28312	Direct	42	Female	USA	
61	18-JUL-2021	19576102	1	FDA-CDER-CTU-2021-48642	Direct	45	Female	USA	
62	25-APR-2022	20749973	1	FDA-CDER-CTU-2022-31674	Direct	48	Male	USA	OT
63	12-FEB-2021	18884609	1	FDA-CDER-CTU-2021-10744	Direct	53	Female	USA	
64	23-MAR-2018	14676343	1	FDA-CDER-CTU-2018-27323	Direct	58	Female	USA	
65	09-FEB-2021	18869611	1	US-ELI_LILLY_AND_COMPANY-US202101013305	Expedited (15-Day)	61.582	Female	USA	OT
65†	12-OCT-2020	18372427	3	US-TAKEDA-2020TUS042242	Expedited (15-Day)		Female	USA	OT
66	25-JAN-2021	18786647	1	US-ELI_LILLY_AND_COMPANY-US202101006749	Expedited (15-Day)	62.904	Female	USA	OT
67	11-NOV-2019	17017226	1	CA-ELI_LILLY_AND_COMPANY-CA201911000341	Expedited (15-Day)	70	Female	CAN	OT
68	25-JUN-2021	19461840	2	US-ELI_LILLY_AND_COMPANY-US202106006666	Expedited (15-Day)	82.12	Male	USA	OT, HO
Victoza									
69	03-APR-2014	10058088	1	545501	Direct	28	Female	USA	OT
70	07-NOV-2013	9677454	1	529973	Direct	48		USA	
71	22-NOV-2017	14223978	1	FDA-CDER-CTU-2017-74628	Direct	51	Female	USA	
72	27-AUG-2012	9216716	2	354802	Periodic	53	Female	USA	OT
73	29-APR-2019	16255351	1	FDA-CDER-CTU-2019-49529	Direct	54	Female	USA	OT
74	28-OCT-2016	12894165	2	TR-NOVOPROD-516007	Expedited (15-Day)	56	Female	TUR	OT
75	16-FEB-2018	14540299	1	SE-NOVOPROD-585040	Expedited (15-Day)	62	Female	SWE	OT
76	12-AUG-2015	11369959	1	US-JNJFOC-20150700703	Periodic	63.23	Female	USA	OT
77	02-DEC-2013	9722892	2	CN-NOVOPROD-393315	Expedited (15-Day)	67	Male	CHN	OT
Wegovy									
78	05-JAN-2023	21825198	3	US-JAZZ-2022-US-016665	Expedited (15-Day)	35.69041	Female	USA	OT
79	13-JAN-2023	21860531	1	US-NOVOPROD-912118	Periodic	53	Female	USA	OT

80	29-JUL-2023	22766653	1	FDA-CDER-CTU-2023-55370	Direct	55	Female	USA	
81	23-AUG-2022	21247805	1	FDA-CDER-CTU-2022-67497	Direct	60	Female	USA	OT, RI
82	31-MAY-2023	22394476	1	FDA-CDER-CTU-2023-40380	Direct	61	Female	USA	RI
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome. † Duplicate Case Abbreviations: AUS=Australia, USA=United States, JPN=Japan, COL=Colombia, GBR=United Kingdom, ITA=Italy, TUR=Turkey, FRA=France, CAN=Canada, SWE=Sweden, CHN=China DE=death, HO=hospitalization, LT= life-threatening, DS= disability, RI=required intervention, OT=other medically significant									

7.4 APPENDIX D. TABLE 10: ESTIMATED NUMBER OF PRESCRIPTIONS DISPENSED FOR GLP-1 RAS FROM U.S. OUTPATIENT RETAIL AND MAIL-ORDER/SPECIALTY PHARMACIES, STRATIFIED BY MOLECULE AND PRODUCT, JANUARY 2013 THROUGH SEPTEMBER 2023, CALENDAR YEA

	2013		2014		2015		2016		2017		2018	
	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%
Grand Total	4,030,772	100.0%	4,428,689	100.0%	5,590,028	100.0%	7,394,460	100.0%	9,171,831	100.0%	11,879,037	100.0%
Semaglutide	-	-	-	-	-	-	-	-	-	-	387,504	3.3%
Ozempic ^a	-	-	-	-	-	-	-	-	-	-	387,504	100.0%
Dulaglutide (Trulicity^b)	-	-	4,292	0.1%	364,239	6.5%	1,488,583	20.1%	3,116,132	34.0%	4,788,089	40.3%
Liraglutide	2,626,207	65.2%	2,939,001	66.4%	3,353,403	60.0%	3,881,716	52.5%	4,224,620	46.1%	4,769,306	40.1%
Victoza [*]	2,626,207	100.0%	2,939,001	100.0%	3,299,208	98.4%	3,695,981	95.2%	3,957,592	93.7%	4,405,921	92.4%
Saxenda ^c	-	-	-	-	54,195	1.6%	185,735	4.8%	267,028	6.3%	363,385	7.6%
Exenatide^{**}	1,404,565	34.8%	1,465,342	33.1%	1,516,796	27.1%	1,409,224	19.1%	1,388,560	15.1%	1,505,202	12.7%
Bydureon Bcise ^d	-	-	-	-	-	-	-	-	456	<0.1%	376,336	25.0%
Byetta	756,600	53.9%	568,893	38.8%	428,377	28.2%	320,589	22.7%	255,894	18.4%	189,391	12.6%
Bydureon***	647,965	46.1%	896,449	61.2%	1,088,419	71.8%	1,088,635	77.3%	1,132,210	81.5%	939,475	62.4%
Insulin glargine/Lixisenatide (Soliqua 100-33^e)	-	-	-	-	-	-	-	-	85,912	0.9%	234,507	2.0%
Insulin degludec/Liraglutide (Xultrophy 100-3.6^f)	-	-	-	-	-	-	-	-	19,167	0.2%	101,128	0.9%
Lixisenatide (Adlyxin^g)	-	-	-	-	-	-	-	-	677	<0.1%	1,551	<0.1%
Albiglutide (Tanzeum^h)	-	-	20,054	0.5%	355,590	6.4%	614,937	8.3%	336,763	3.7%	91,750	0.8%

	2019		2020		2021		2022		2023 (Jan - Sep)	
	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%
Grand Total	15,355,658	100.0%	19,075,801	100.0%	24,135,468	100.0%	35,043,907	100.0%	43,095,732	100.0%
Semaglutide	2,377,781	15.5%	5,201,674	27.3%	9,062,532	37.5%	15,882,972	45.3%	22,738,333	52.8%
Ozempic ^a	2,360,999	99.3%	4,621,618	88.8%	7,250,119	80.0%	12,564,246	79.1%	16,534,172	72.7%
Rybelsus ⁱ	16,782	0.7%	580,056	11.2%	1,395,306	15.4%	2,240,269	14.1%	2,257,835	9.9%
Wegovy ^j	-	-	-	-	417,107	4.6%	1,078,457	6.8%	3,946,326	17.4%
Dulaglutide (Trulicity^b)	6,521,055	42.5%	8,039,261	42.1%	10,209,347	42.3%	12,439,669	35.5%	10,109,411	23.5%
Liraglutide	4,545,045	29.6%	4,033,504	21.1%	3,522,176	14.6%	3,094,823	8.8%	2,049,713	4.8%
Victoza [*]	4,066,394	89.5%	3,511,830	87.1%	2,922,237	83.0%	2,319,731	75.0%	1,437,419	70.1%
Saxenda ^c	478,651	10.5%	521,674	12.9%	599,939	17.0%	775,092	25.0%	612,294	29.9%
Tirzepatide (Mounjaro^k)	-	-	-	-	-	-	2,563,076	7.3%	7,499,720	17.4%
Exenatide^{**}	1,420,457	9.3%	1,246,180	6.5%	830,040	3.4%	557,401	1.6%	306,650	0.7%
Bydureon BCise ^d	590,817	41.6%	599,978	48.1%	641,292	77.3%	513,660	92.2%	283,120	92.3%
Byetta	133,516	9.4%	96,461	7.7%	64,385	7.8%	41,729	7.5%	23,283	7.6%
Bydureon***	696,124	49.0%	549,741	44.1%	124,363	15.0%	2,012	0.4%	247	0.1%
Insulin glargine/Lixisenatide (Soliqua 100-33^e)	337,200	2.2%	398,879	2.1%	389,231	1.6%	407,238	1.2%	326,793	0.8%
Insulin degludec/Liraglutide (Xultrophy 100-3.6^f)	150,372	1.0%	154,454	0.8%	119,669	0.5%	97,132	0.3%	65,075	0.2%
Lixisenatide (Adlyxin^g)	2,046	<0.1%	1,842	<0.1%	2,473	<0.1%	1,596	<0.1%	36	<0.1%
Albiglutide (Tanzeum^h)	1,702	<0.1%	7	<0.1%	-	-	-	-	1	<0.1%

Source: Symphony Health Metys™. Data years Jan 2013 – Sep 2023. Data Extracted October 2023. File: Symphony Health Metys 2023-5971 GLP-1 RAs 10-23-2023.xlsx

*includes Victoza 2-Pack and Victoza 3-Pack products

***includes Bydureon and Bydureon pen products

**includes exenatide and exenatide microsphere molecules

^aOzempic approved in December 2017

^dBydureon BCise approved in October 2017

^gAdlyxin approved in July 2016

^jWegovy approved in June 2021

^bTrulicity approved in September 2014

^eSoliqua 100/33 approved in November 2016

^hTanzeum approved in April 2014

^kMounjaro approved in May 2022

^cSaxenda approved in December 2014

^fXultrophy 100/3.6 approved in November 2016

ⁱRybelsus approved in September 2019

7.5 APPENDIX E. TABLE 11: DIAGNOSES ASSOCIATED WITH THE USE OF GLP-1 RAS, AS REPORTED BY SURVEYS FROM U.S. OFFICE-BASED HEALTH CARE PROVIDERS, STRATIFIED BY MOLECULE AND PRODUCT, IN 2022

	2022				2022		
	Uses	95% CI	%		Uses	95% CI	%
Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%	Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%
E11 Type 2 diabetes mellitus	10,624,000	9,831,000 - 11,416,000	82.1%	R73 Elevated blood glucose level	716,000	510,000 - 922,000	5.5%
Semaglutide	6,313,000	5,702,000 - 6,924,000	59.4%	Semaglutide	648,000	452,000 - 844,000	90.6%
Ozempic	4,516,000	3,999,000 - 5,033,000	71.5%	Ozempic	422,000	264,000 - 580,000	65.1%
Rybelsus	1,791,000	1,466,000 - 2,117,000	28.4%	Wegovy	226,000	111,000 - 342,000	34.9%
Wegovy	5,000	<500 - 23,000	0.1%	Dulaglutide (Trulicity)	68,000	4,000 - 131,000	9.4%
Dulaglutide (Trulicity)	2,941,000	2,524,000 - 3,358,000	27.7%	N18 Chronic kidney disease (CKD)	68,000	4,000 - 131,000	0.5%
Liraglutide	553,000	372,000 - 734,000	5.2%	Semaglutide (Ozempic)	68,000	4,000 - 131,000	100.0%
Victoza	548,000	368,000 - 728,000	99.1%	E10 Type 1 diabetes mellitus	50,000	<500 - 105,000	0.4%
Saxenda	5,000	<500 - 22,000	0.9%	Dulaglutide (Trulicity)	38,000	<500 - 86,000	75.8%
Insulin glargine/lixisenatide (Soliqua)	388,000	237,000 - 540,000	3.7%	Semaglutide (Ozempic)	7,000	<500 - 28,000	14.4%
Exenatide	328,000	189,000 - 468,000	3.1%	Exenatide (Byetta)	5,000	<500 - 22,000	9.8%
Byetta	154,000	59,000 - 250,000	47.0%	R63 Signs and symptoms concerning food and fluid intake	22,000	<500 - 58,000	0.2%
Bydureon BCise	148,000	55,000 - 242,000	45.2%	Liraglutide (Saxenda)	22,000	<500 - 58,000	100.0%
Bydureon	26,000	<500 - 65,000	7.8%	E88 Other metabolic disorders	21,000	<500 - 56,000	0.2%
Insulin degludec/liraglutide (Xultophy)	71,000	6,000 - 137,000	0.7%	Semaglutide (Ozempic)	21,000	<500 - 56,000	100.0%
Tirzepatide (Mounjaro)	30,000	<500 - 71,000	0.3%	Z79 Long term (current) drug therapy	17,000	<500 - 49,000	0.1%
E66 Overweight and obesity	1,426,000	1,136,000 - 1,717,000	11.0%	Insulin glargine/lixisenatide (Soliqua)	17,000	<500 - 49,000	100.0%
Semaglutide	821,000	601,000 - 1,042,000	57.6%				
Wegovy	362,000	215,000 - 508,000	44.0%				
Ozempic	312,000	176,000 - 448,000	38.0%				
Rybelsus	147,000	54,000 - 241,000	18.0%				
Liraglutide	506,000	333,000 - 678,000	35.4%				
Saxenda	485,000	315,000 - 654,000	95.9%				
Victoza	21,000	<500 - 56,000	4.1%				
Tirzepatide (Mounjaro)	53,000	<500 - 109,000	3.7%				
Dulaglutide (Trulicity)	46,000	<500 - 99,000	3.2%				

Source: Syneos Health Research & Insights, LLC, Treatment Answers™. Year 2022. Data Extracted: September 2023. File: 2023-5971 GLP-1 RAs Syneos 2022, 10-23-2023.xls
The projected use mentions below 100,000 estimates may not be representative of providers' prescribing habits at the national level.
Abbreviations: CI: confidence interval

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/s/

AMY I CHEN
07/24/2024 10:12:44 AM

MELISSA A REYES
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ZOYA RAMZAN
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DANIEL I WORONOW
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RAJDEEP K GILL on behalf of SHEHERYAR MUHAMMAD
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Signed on behalf of Sheheryar Muhammad

RAJDEEP K GILL
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: August 4, 2022

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DPV-I

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Product Name(s), Application Type/Number, Applicant:

Drug Name	Active Ingredient(s)	NDA/ BLA	Applicant
Byetta	Exenatide synthetic	021773	AstraZeneca AB
Byetta	Exenatide synthetic	021919	Amylin
Bydureon	Exenatide synthetic, extended release	022200	AstraZeneca AB

Bydureon BCise	Exenatide synthetic, extended release	209210	AstraZeneca AB
Victoza	Liraglutide recombinant	022341	Novo Nordisk Inc
Saxenda	Liraglutide recombinant	206321	Novo Nordisk Inc
Xultophy 100/3.6	Insulin degludec, liraglutide	208583	Novo Nordisk Inc
Tanzeum	Albiglutide	125431	GlaxoSmithKline
Trulicity	Dulaglutide	125469	Eli Lilly and Co
Adlyxin	Lixisenatide	208471	Sanofi-Aventis US
Soliqua 100/33	Insulin glargine, lixisenatide	208673	Sanofi-Aventis US
Ozempic	Semaglutide	209637	Novo Nordisk Inc
Rybelsus	Semaglutide	213051	Novo Nordisk Inc
Wegovy	Semaglutide	215256	Novo Nordisk Inc
Mounjaro	Tirzepatide	215866	Eli Lilly and Co

Subject: Cutaneous Amyloidosis

SS ID #: (b) (4)

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TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	3
1.1 Background	3
1.2 Regulatory History	4
1.3 Relevant Product Labeling.....	5
2 Methods and Materials.....	6
2.1 Case Definition.....	6
2.2 FAERS Search Strategy	7
2.3 Data Mining Search Strategy	7
2.4 Literature Search Strategy.....	8
2.5 Periodic Safety Reports.....	9
2.6 Drug Utilization.....	9
3 Results.....	10
3.1 FAERS Case Selection.....	10
3.2 Data Mining.....	11
3.3 Literature Cases.....	11
3.4 Periodic Safety Reports.....	12
3.5 Drug Utilization.....	12
4 Discussion	15
5 Conclusion	16
6 Recommendations.....	16
7 References.....	17
8 Appendices.....	19
8.1 Appendix A. FDA Adverse Event Reporting System (FAERS).....	19
8.2 Appendix B. FAERS Line Listing of Cutaneous Amyloidosis Associated with the Use of GLP-I RA Case Series.....	20
8.3 Appendix C. Drug Utilization Data Tables	21
8.4 Appendix D. Drug Utilization Database Descriptions.....	23

EXECUTIVE SUMMARY

The purpose of this Pharmacovigilance (PV) Review is for the Division of Pharmacovigilance-I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of cases of cutaneous amyloidosis associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS) database and medical literature. Information and recommendations from this review will aid DDLO in their decision on whether to update the labels for GLP-1 RAs with information regarding the potential risk for cutaneous amyloidosis.

On May 17, 2022, DDLO consulted DPV-I and opened Newly Identified Safety Signal (NISS) (SSID 1004842) for GLP-1 RAs and Cutaneous amyloidosis. This was based on a newly identified safety finding of cutaneous amyloidosis reported in the Development Safety Update Report (DSUR) under IND 73206 for Saxenda and Victoza. Review and assessment of the safety signal were also provided in the 2021 liraglutide Periodic Benefit-Risk Evaluation Report (PBRER). This signal was originally raised by the European Medicines Agency (EMA) in November 2021. Given that this could be an issue in the rest of the class, DDLO opened a NISS and consulted DPV-I to look at cases across the class.

DPV-I identified one case from FAERS of a patient who developed cutaneous amyloidosis with the use of liraglutide. Two cases were identified from the medical literature of patients who developed cutaneous amyloidosis with the use of liraglutide. These cases provide information to support the recent safety labeling change (SLC) for liraglutide (Saxenda and Victoza) to include the risk of cutaneous amyloidosis in the U.S. Prescribing Information (USPI). DPV-I did not identify any cases from FAERS or the medical literature of cutaneous amyloidosis associated with dulaglutide, exenatide, lixisenatide, or tirzepatide. However, in the semaglutide PBRER, the Applicant mentioned some cases of amyloidosis but did not specify the type of amyloidosis. In the dulaglutide Periodic Safety Update Report (PSUR), the Applicant listed one case of non-serious cutaneous amyloidosis with no details/assessment.

DEPI II drug utilization analysis shows that GLP-1 RAs are widely dispensed from the U.S. retail pharmacy settings. Overall, GLP-1 RA utilization increased from 2.4 million prescriptions dispensed in 2010 to 18.5 million prescriptions dispensed in 2020. During the cumulative period, approximately 39% of prescriptions were dispensed for liraglutide followed by dulaglutide (30%), exenatide (19%), and semaglutide (10%).

In conclusion, there appears to be a causal relationship between cutaneous amyloidosis and liraglutide use, and we concur with the Applicant's addition of cutaneous amyloidosis to Post-Marketing Experience of the Victoza and Saxenda USPIs. There is limited supportive information at this time for updating the labels of dulaglutide, exenatide, lixisenatide, semaglutide, and tirzepatide regarding the risk of cutaneous amyloidosis. Our case series did not identify cases of cutaneous amyloidosis associated with dulaglutide, exenatide, lixisenatide, semaglutide, or tirzepatide.

Based on this review, DPV-I recommends the following:

- Continue routine pharmacovigilance monitoring of dulaglutide, exenatide, lixisenatide, semaglutide, and tirzepatide and the potential risk of cutaneous amyloidosis.
- DPV-I concurs with the Applicant's inclusion within *Postmarketing Experience* of the USPI to reflect the risk of cutaneous amyloidosis with liraglutide.

1 INTRODUCTION

The purpose of this Pharmacovigilance (PV) Review is for the Division of Pharmacovigilance-I (DPV-I) to provide to the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of cases of cutaneous amyloidosis associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from the FDA Adverse Event Reporting System (FAERS) database and medical literature. Information and recommendations from this review will aid DDLO in their decision on whether to update the labels for GLP-1 RAs with information regarding the potential risk for cutaneous amyloidosis.

On May 17, 2022, DDLO consulted DPV-I and opened Newly Identified Safety Signal (NISS) (SSID 1004842) for GLP1-RAs and cutaneous amyloidosis. This was based on a newly identified safety finding of cutaneous amyloidosis reported in the Development Safety Update Report (DSUR) under IND 73206 for Saxenda and Victoza. Review and assessment of the safety signal were also provided in the 2021 liraglutide Periodic Benefit-Risk Evaluation Report (PBRER). This signal was originally raised by the European Medicines Agency (EMA) in November 2021. Given that this could be an issue in the rest of the class, DDLO opened a NISS and consulted DPV-I to look at cases across the class.

1.1 BACKGROUND

Amyloidosis and Cutaneous Amyloidosis¹

Amyloidosis consists of a constellation of disease entities characterized by the extracellular accumulation of misfolded proteins (i.e., amyloid fibrils) in various tissues and organs that may lead to the disruption of cellular function at the microscopic level and ultimately, may result in disruption of function of tissues or organs. Approximately 30 different types of amyloidosis exist, depending upon the specific protein misfolding.² The etiology of amyloidosis can be genetic or acquired. Amyloidosis can be categorized as primary when caused by plasma cell dyscrasia or as secondary to conditions such as rheumatoid arthritis. Amyloidosis can be further divided into localized and systemic forms. This review focuses on the localized cutaneous form of amyloidosis. Amyloidosis of the skin can occur at various layers of the skin and is divided into three types: nodular, macular, and lichen (or papular) cutaneous amyloidosis.³ The progression of local cutaneous disease to a systemic form is rare, but it has been reported for nodular amyloidosis.⁴

A DPV-I Pharmacovigilance Review in 2019 concluded that there is a potential risk for patients to develop Cutaneous Amyloidosis with chronic use of injectable insulin products. Subsequently, the U.S. Prescribing Information (USPI) of products that contain insulin for injection were revised to warn of the risk of cutaneous amyloidosis.

GLP-1 RAs Pharmacology

GLP-1 RAs activate the GLP-1 receptor on pancreatic beta cells, reducing blood glucose through stimulation of insulin secretion and decrease in glucagon secretion in a glucose-dependent manner. Although all the GLP-1 RAs have a similar mechanism of action, there are some differences in pharmacological and pharmacokinetic properties among the agents in the class. Exenatide and lixisenatide are derived from exendin-4 and show 53% homology to human

GLP-1, whereas dulaglutide, liraglutide, and semaglutide are modified from the active fragment of human GLP-1 and have higher homology to human GLP-1 (dulaglutide 90%, liraglutide 97%, semaglutide 94%).⁵ Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA.⁶ Exenatide (original formulation, Byetta) and lixisenatide are short-acting and provide short-lived GLP-1 receptor activation with half-lives ranging from 2 to 3 hours. Dulaglutide, liraglutide, semaglutide, and tirzepatide are long-acting GLP-1 RAs that activate the GLP-1 receptor continuously at their recommended doses and have a prolonged half-life ranging from 13 hours (liraglutide) to ~5 days (tirzepatide) to ~1 week (dulaglutide, semaglutide).^{5,7} Semaglutide (Rybelsus) is the only GLP-1 RA available as an oral formulation and is administered at higher doses than subcutaneous semaglutide due to very low oral bioavailability of 0.4% to 1% to provide similar levels of exposure as the subcutaneous formulation.⁸

1.2 REGULATORY HISTORY

There are six GLP-1 RAs approved by the FDA and currently marketed as adjunct therapy to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). The first GLP-1 RA product, Byetta (exenatide), was approved on April 28, 2005. Victoza (liraglutide), Trulicity (dulaglutide), and Ozempic (semaglutide) are also indicated to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease. There are currently two GLP-1 RAs approved by the FDA for chronic weight management in adult patients, Saxenda (liraglutide) and Wegovy (semaglutide), at higher daily doses compared to the glycemic control indicated products. The most recent GLP-1 RA product, Mounjaro (tirzepatide), was approved on May 13, 2022. Table 1 lists all the currently marketed GLP-1 RAs, including fixed ratio drug-drug combinations (FRC), in the U.S. Albiglutide, another GLP-1 RA, was previously marketed in the U.S. but currently is discontinued due to a business decision (low usage of the product) and not related to safety or efficacy.

Table 1. Currently Marketed Glucagon-like Peptide 1 Receptor Agonists in the U.S.				
Drug Name NDA/BLA Applicant	Active Ingredient(s), formulation	Indication	Dosage Ranges	Approval Date
Byetta 021773 AstraZeneca AB	Exenatide synthetic, sc inj	T2DM in adults	5 mcg to 10 mcg twice daily	4/28/2005
Byetta 021919 Amylin	Exenatide synthetic, sc inj	T2DM in adults	See above	10/30/2009
Bydureon 022200 AstraZeneca AB	Exenatide synthetic, extended release, sc, inj	T2DM in adults, pediatrics ≥ 10 yrs	2 mg every 7 days	1/27/2012
Bydureon BCise 209210 AstraZeneca AB	Exenatide synthetic, extended release, sc, inj	Same as Bydureon	Same as Bydureon	10/20/2017
Victoza 022341 Novo Nordisk	Liraglutide recombinant, sc inj	T2DM in adults, pediatrics ≥ 10 yrs; reduce the risk of MACE in adults	0.6 mg titrated to 1.8mg daily	1/25/2010

Table 1. Currently Marketed Glucagon-like Peptide 1 Receptor Agonists in the U.S.				
Drug Name NDA/BLA Applicant	Active Ingredient(s), formulation	Indication	Dosage Ranges	Approval Date
Saxenda 206321 Novo Nordisk	Liraglutide recombinant, sc inj	Weight management in adults and pediatrics ≥ 12 yrs*	0.6 mg titrated to 3 mg daily	12/23/2014
Xultophy 100/3.6 208583 Novo Nordisk	Insulin degludec, liraglutide, sc inj	T2DM in adults	10 units titrated to 50 units daily	11/21/2016
Trulicity 125469 Eli Lilly and Co	Dulaglutide, sc inj	T2DM in adults; reduce the risk of MACE in adults	0.75 mg titrated to 4.5 mg weekly	9/18/2014
Adlyxin 208471 Sanofi-Aventis	Lixisenatide, sc inj	T2DM in adults	10 mcg daily on day 15, 20 mcg daily	7/27/2016
Soliqua 100/33 208673 Sanofi-Aventis	Insulin glargine, lixisenatide, sc inj	T2DM in adults	15 units titrated to 60 units daily	11/21/2016
Ozempic 209637 Novo Nordisk	Semaglutide, sc inj	T2DM in adults; reduce the risk of MACE in adults	0.25 mg titrated to 1 mg weekly	12/5/2017
Rybelsus 213051 Novo Nordisk	Semaglutide, oral tablet	T2DM in adults	3 mg titrated to 14 mg daily	9/20/2019
Wegovy 215256 Novo Nordisk	Semaglutide, sc inj	Weight management in adults	0.25 mg titrated to 2.4 mg weekly	6/4/2021
Mounjaro 215866 Eli Lilly and Co	Tirzepatide, sc inj	T2DM in adults	2.5 mg titrated to 5 mg weekly	5/13/2022
Source: Drugs@FDA * pediatrics with body weight > 60 kg and BMI corresponding to 30 kg/m ² for adults Abbreviations: BLA=Biologics License Application, CV=cardiovascular, CVD=cardiovascular disease, inj=injection, MACE=major adverse cardiovascular events, NDA=New Drug Application, sc=subcutaneous, T2DM=type 2 diabetes mellitus, yrs=years				

1.3 RELEVANT PRODUCT LABELING

Cutaneous amyloidosis is listed in the USPI for liraglutide but not for any other single ingredient GLP-1 RA.^{9,10,11,12,13,14,15} Cutaneous amyloidosis is listed in the Dosage and Administration (2.2/2.1) and Post-Marketing Experience (6.2/6.3) sections of the Saxenda and Victoza USPIs; the safety labeling change (SLC) was approved June 10, 2022. The FRCs Soliqua 100/33 (insulin glargine and lixisenatide) and Xultophy 100/3.6 (insulin degludec and liraglutide) list cutaneous amyloidosis in the Dosage and Administration (2.5), Warnings and Precautions (5.4), and Postmarketing Experience (6.3) sections of the labeling.^{16,17} The USPIs for Soliqua 100/33 (insulin glargine and lixisenatide) and Xultophy 100/3.6 (insulin degludec and liraglutide) were updated to include cutaneous amyloidosis as part of a SLC for insulin products in 2019.

Sample from Victoza (liraglutide) labeling¹⁰

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Instructions

- Rotate injection sites within the same region in order to reduce the risk of cutaneous amyloidosis [see *Adverse Reactions* (6.3)]

6 ADVERSE REACTIONS

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of VICTOZA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Skin and subcutaneous tissue disorder: cutaneous amyloidosis

Sample from Soliqua 100/33 (insulin glargine and lixisenatide) labeling¹⁷

2 DOSAGE AND ADMINISTRATION

2.5 Important Administration Instructions

- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see *Warnings and Precautions* (5.2), *Adverse Reactions* (6)].

5 WARNINGS AND PRECAUTIONS

5.4 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

...Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to unaffected area) has been reported to result in hypoglycemia [see *Adverse Reactions* (6)]...Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia...

6 ADVERSE REACTIONS

6.3 Postmarketing Experience

(b) (4) Localized cutaneous amyloidosis at the injection site has occurred with insulins. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Case definition for cutaneous amyloidosis

Diagnosis of amyloidosis by histological evaluation from biopsy of cutaneous mass. Reports of cutaneous amyloidosis without histological confirmation were excluded because cutaneous amyloidosis is difficult to differentiate clinically from other injection site-related lesions.

Case selection criteria

Inclusion criteria:

1. Meets the case definition above for cutaneous amyloidosis and

2. History of injection of a GLP-1 RA product at the site of the cutaneous amyloidosis in the past two weeks

Exclusion criteria:

1. Duplicate report
2. Alternative etiology reported or other diseases (e.g., concomitantly on insulin, systemic amyloidosis) known to be associated with amyloid nodules
3. Insufficient information for causality assessment

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	May 25, 2022
Time period of search	Through May 24, 2022
Search type	Quick Query
Product terms	GLP-1 Receptor Agonist [EPC] (Therapeutic drug class)
MedDRA search terms (Version 24.1)	HLT: <i>Amyloidoses</i>
* See Appendix A for a description of the FAERS database. Abbreviations: GLP-1=Glucagon-like peptide-1, EPC=Established Pharmacologic Class, MedDRA=Medical Dictionary for Regulatory Activities, HLT=High Level Term	

2.3 DATA MINING SEARCH STRATEGY

DPV-I used the Empirica Signal software with the strategy described in Table 3 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”). If a drug-event combination has a score (EB05) of ≥ 2 , this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Table 3. Data Mining Search Strategy*	
Data refresh date	June 5, 2022
Product terms	liraglutide, dulaglutide, semaglutide, exenatide, lixisenatide
Empirica Signal run name	PAM (S)
MedDRA search strategy	HLT: <i>Amyloidoses</i>
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. Abbreviations: PAM=Product Active Moieties, MedDRA=Medical Dictionary for Regulatory Activities, HLT=High Level Term	

2.4 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Tables 4 and 5.

Table 4. Literature Search Strategy	
Date of search	May 23, 2022
Database	PubMed@FDA
Search terms	("liraglutid"[All Fields] OR "liraglutide"[MeSH Terms] OR "liraglutide"[All Fields] OR "liraglutide s"[All Fields] OR ("dulaglutide"[Supplementary Concept] OR "dulaglutide"[All Fields]) OR ("semaglutide"[Supplementary Concept] OR "semaglutide"[All Fields]) OR ("exenatide"[MeSH Terms] OR "exenatide"[All Fields] OR "exenatide s"[All Fields]) OR ("lixisenatide"[Supplementary Concept] OR "lixisenatide"[All Fields]) OR ("tirzepatide"[Supplementary Concept] OR "tirzepatide"[All Fields]) OR ("GLP-I"[All Fields] AND ("receptor"[All Fields] OR "receptor s"[All Fields] OR "receptors"[All Fields]) AND ("agonist"[All Fields] OR "agonist s"[All Fields] OR "agonistic"[All Fields] OR "agonistically"[All Fields] OR "agonistics"[All Fields] OR "agonists"[MeSH Subheading] OR "agonists"[All Fields])) OR (("glucagon like peptide 1"[MeSH Terms] OR "glucagon like peptide 1"[All Fields] OR "glp 1"[All Fields]) AND "RA"[All Fields])) AND ("amyloidosis"[MeSH Terms] OR "amyloidosis"[All Fields] OR "amyloidoses"[All Fields] OR (("cutaneous"[All Fields] OR "cutaneously"[All Fields] OR "cutanous"[All Fields]) AND ("amyloidosis"[MeSH Terms] OR "amyloidosis"[All Fields] OR "amyloidoses"[All Fields])))
Years included in search	All

Table 5. Literature Search Strategy	
Date of search	June 24, 2022
Database	Embase
Search terms	(('liraglutide'/exp OR liraglutide OR 'dulaglutide'/exp OR dulaglutide OR 'semaglutide'/exp OR semaglutide OR 'exenatide'/exp OR exenatide OR 'lixisenatide'/exp OR lixisenatide OR 'tirzepatide'/exp OR tirzepatide OR 'glp 1'/exp OR 'glp 1' OR 'glucagon like peptide 1 receptor agonist'/exp OR 'glucagon like peptide 1 receptor agonist') AND ('amyloidosis'/exp OR amyloidosis OR 'cutaneous amyloidosis'/exp OR 'cutaneous amyloidosis' OR (cutaneous AND ('amyloidosis'/exp OR amyloidosis))))
Years included in search	All

2.5 PERIODIC SAFETY REPORTS

DPV-I screened the following periodic safety reports for the Applicant's assessment of cutaneous amyloidosis with GLP-1 RA use:

- Byetta (exenatide twice daily [BID]) and Bydureon (exenatide once weekly [QW] and exenatide once weekly suspension [QWS]) PBRER. Reporting Period: April 1, 2021 to March 31, 2022.¹⁸
- Victoza and Saxenda (liraglutide) PBRER. Reporting period: January 1, 2021 to December 31, 2021.¹⁹
- Dulaglutide Periodic Safety Update Report (PSUR) in the Format of ICH E2C (R2). Reporting period: September 19, 2020 to September 18, 2021.²⁰
- Lixisenatide PBRER. Reporting period: January 8, 2021 to January 7, 2022.²¹
- Ozempic, Rybelsus, and Wegovy (semaglutide) PBRER. Reporting period: June 1, 2021 to November 30, 2021.²²

2.6 DRUG UTILIZATION

We used proprietary drug utilization databases available to the Agency to conduct the analyses in this review. Detailed database descriptions are included in Appendix D.

2.6.1 Data Sources Used

DEPI-II used the IQVIA National Sales Perspective™ database to determine the primary settings of care where GLP-1 RAs were sold from manufacturers to U.S. retail and non-retail institutions in 2020.

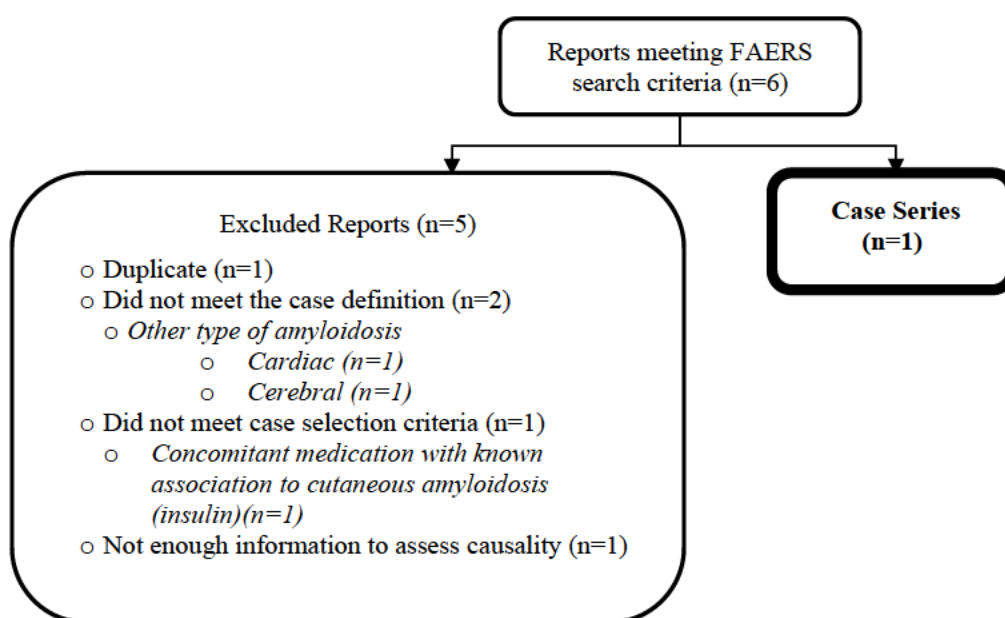
DEPI-II used the Symphony Health Metys™ database to obtain the estimated number of 1) dispensed prescriptions and 2) patients who received dispensed prescriptions for GLP-1 RAs from U.S. outpatient pharmacies, 2010 through 2020.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved six reports, which were all liraglutide cases, with the exception of a duplicate exenatide case. After applying the case definition in Section 2.1 and accounting for duplicate reports, one case was included in the case series of cutaneous amyloidosis reported with GLP-1 RA use (see Figure 1).

Figure 1. FAERS Case Selection



One case was included in the case series of cutaneous amyloidosis reported with GLP-1 RA use. This case is summarized below.

FAERS Case #15927186; 2019; USA; Expedited; Other:

Case reported by two medical doctors of a 58-year-old male patient who was treated with liraglutide from 2011 until date of report for T2DM. Past medical history included T2DM, hypertension, hyperlipidemia, follicular lymphoma, and sigmoid colon cancer. The patient had no family history of amyloidosis or related blood cancers. The patient experienced symptoms of intermittent diarrhea and weight loss since 2016. In November 2018, a magnetic resonance imaging (MRI) scan revealed an abdominal mass (3 inch x 2 inch x 0.5 inch). The biopsy result of the mass was positive for localized amyloidosis (subtype not listed). In January 2019, fat pad aspirations also found localized amyloidosis and an antibody test to glucagon was highly positive. The patient was treated with oral budesonide and the outcome for the event was reported as “recovering/resolving”. Action taken with liraglutide was reported as “no change”.

Follow up: DPV-I contacted the reporter and on July 14, 2022 they responded with clarification that this was a case of cutaneous amyloidosis not involving other organs.

Reviewer's Comments: The patient developed localized amyloidosis while injecting liraglutide as confirmed with biopsies from his abdominal mass as well as from fat pad aspirations with a seven-year time to onset. The patient also had a positive antibody test to glucagon. This case is consistent with cutaneous amyloidosis associated with liraglutide use. Liraglutide has new Postmarketing Experience labeling informing of the risk of cutaneous amyloidosis associated with liraglutide use.^{9,10}

Appendix B contains a line listing of the one case in this case series.

3.2 DATA MINING

Table 6 summarizes the results of the data mining search using Empirica Signal for Amyloidoses (HLT) reported with GLP-1 RA use.

Table 6. Data Mining Results Using Empirica Signal for Amyloidoses (HLT) Reported With GLP-1 RA Use					
Product active moieties	MedDRA Preferred Terms	N	EB05	EBGM	EB95
Liraglutide	Amyloidosis	3	0.329	0.884	2.015
<i>A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."</i>					

3.3 LITERATURE CASES

Using the search criteria in Table 4 in PubMed@FDA, four articles were retrieved from the medical literature. Titles and abstracts were reviewed to determine relevance. Two articles describe mouse models. One article does not discuss cutaneous amyloidosis associated with GLP-1 RA use. We summarized one article that was also assessed in the Applicant's PBRER below.

- Martins et al. published a case report of an 81-year-old man with a medical history including melanoma, diabetes and peripheral neuropathy. He was found to have amyloid deposits in the subcutaneous tissue at the time of melanoma resection. Serum studies and liquid chromatography-mass spectrometric analysis were performed, and the results indicated that the amyloid identified in the reported patient was the result of subcutaneously injected liraglutide and ruled out other known causes of systemic amyloidosis, including amyloid light-chain (AL) amyloidosis.²³

Using the search criteria in Table 5 in Embase, 44 citations were retrieved from the medical literature. Titles and abstracts, when available, were reviewed to determine relevance. Of the 44 citations, 42 citations did not provide additional cases because they were animal studies (n=2),

not primary literature (n=29), primary literature that does not describe cutaneous amyloidosis with GLP-1 RA use (n=10), and primary literature that describes cutaneous amyloidosis attributed to insulin (n=1). There were two case reports of cutaneous amyloidosis with use of GLP-1 RAs; one was described above by Martins et al.,²³ and the second one that was also assessed in the Applicant's PBRER is summarized below.

- Wat et al. published a case report of a 38-year-old female with a medical history of polycystic ovarian syndrome (PCOS) and family history of lymphoma who presented with cutaneous nodular amyloidosis of the right hip. The patient had been injecting liraglutide into the hip area for 10 years to treat insulin resistance. There was no mention of different injection sites on the hip. No confirmatory diagnostic details were available.²⁴

3.4 PERIODIC SAFETY REPORTS

The Applicant did not assess cutaneous amyloidosis with exenatide or lixisenatide in the periodic safety reports screened by DPV-I. In the semaglutide PBRER, the Applicant mentioned "amyloidosis" but did not specify the type of amyloidosis in both the Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials table and the Number of Adverse Reactions by Preferred Term from Post-Marketing Sources table. In the dulaglutide PSUR, the Applicant listed one case of non-serious cutaneous amyloidosis with no details/assessment. The safety signal for cutaneous amyloidosis was assessed in the liraglutide PBRER and conclusions are summarized below.

Victoza and Saxenda (liraglutide) PBRER. Reporting period: January 1, 2021 to December 31, 2021¹⁹

- "A thorough review and assessment of cutaneous amyloidosis was done with the available data from relevant sources (nonclinical, clinical trials, post marketing sources (incl. scientific literature) and review of labels of other marketed GLP-1 RAs). It was concluded that, a causal relationship between cutaneous amyloidosis and liraglutide cannot be ruled out. This was based on the confirmatory findings in the well documented index case (Martin et al.),²³ suggestive temporal relationship noted in three cases from postmarketing sources (including the index case), and the fact that liraglutide is intended for daily subcutaneous injections. Thus, the signal of cutaneous amyloidosis was validated and closed as a non-important identified risk for both liraglutide products ... (Victoza® and Saxenda®). Relevant information will be updated in the product labels for both products as well as the ... protocol and subject information in the informed consent form for the ongoing trial ... for liraglutide in weight management."¹⁹

3.5 DRUG UTILIZATION

3.5.1 Settings of Care

In 2020, sales distribution data showed that GLP-1 RAs were primarily sold to U.S. retail pharmacies with approximately 80% of total sales. Sales to mail and non-retail settings of care were approximately 12% and 8% of total sales, respectively.²⁵ Therefore, we focused our analyses on utilization of GLP-1 RAs in U.S. outpatient pharmacies. We did not conduct utilization analyses in non-retail settings of care in this review.

3.5.2 U.S. Retail Prescription Utilization

Figure 2 shows the estimated number of prescriptions for GLP-1 RAs stratified by molecule dispensed from U.S. outpatient pharmacies, 2010 through 2020. Dispensed prescriptions of GLP-1 RAs increased from approximately 2.4 million in 2010 to 7.3 million in 2016 mainly driven by the rising use of liraglutide. Thereafter, dispensed prescription utilization of GLP-1 RAs doubled from 9.0 million prescription in 2017 to 18.5 million prescriptions in 2020. During this time, utilization gradually shifted from liraglutide to dulaglutide. Dulaglutide prescriptions increased from 3.1 million prescriptions in 2017 to 8.3 million prescriptions in 2020; semaglutide utilization more than doubled from 2.4 million prescriptions in 2019 to 5.3 million prescriptions in 2020.

For the cumulative period, an estimated 84 million prescriptions were dispensed for GLP-1 RAs from U.S. outpatient pharmacies. Of these prescriptions, approximately 33 million prescriptions were dispensed for liraglutide followed by dulaglutide (25 million), exenatide (16 million), and semaglutide [8 million: 93% injectable; 7% oral (data not shown)²⁶]. Albiglutide and lixisenatide accounted for approximately 2 million prescriptions combined (see **Table 7 in Appendix C**).

Figure 2. Estimated number of prescriptions dispensed for GLP-1 RAs from U.S. outpatient pharmacies 2010 through 2020

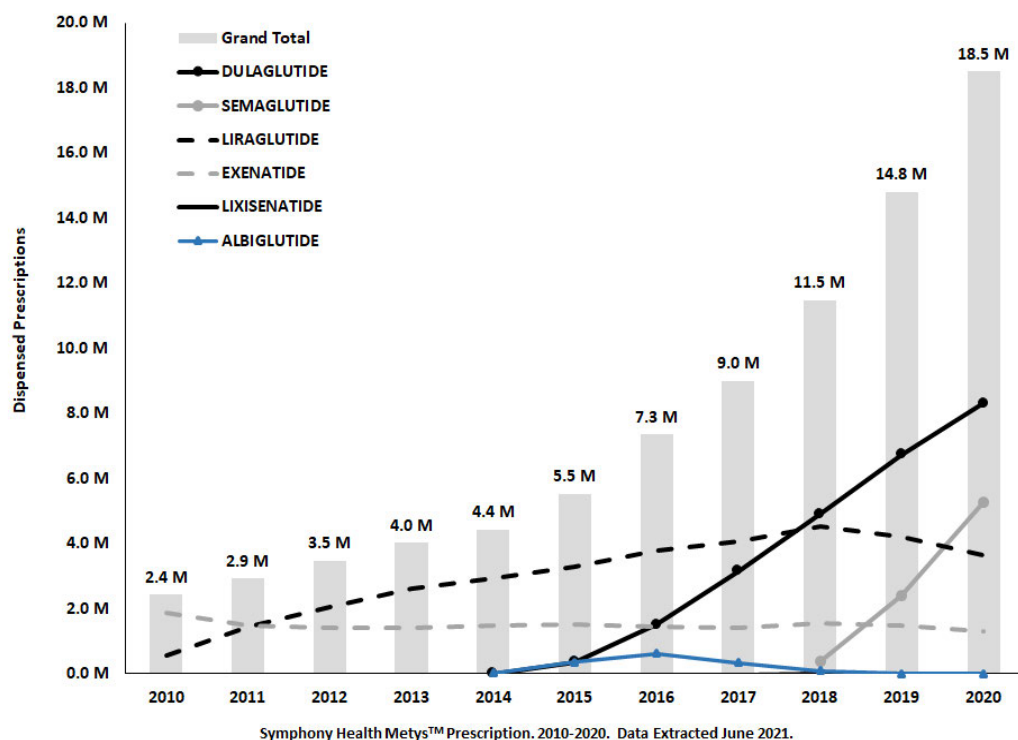
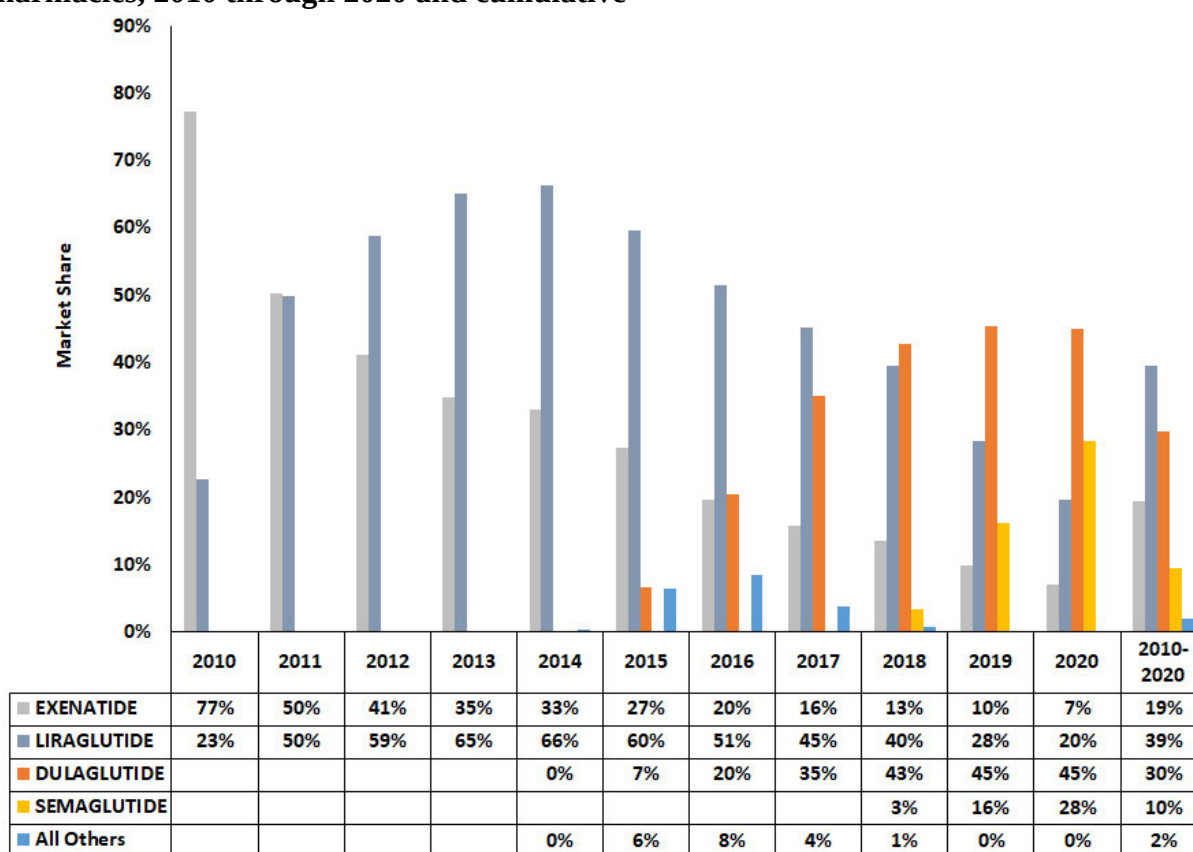


Figure 3 shows the proportion of prescriptions dispensed for GLP-1 RAs stratified by molecule from U.S. outpatient pharmacies from 2010 through 2020. The proportion of prescriptions dispensed for exenatide decrease from 77% of total prescriptions in 2010 to 33% of total prescriptions in 2014. Conversely, use of liraglutide gradually increased from 23% of total prescriptions in 2010 to 66% of total prescriptions in 2014.

Thereafter, utilization of liraglutide decreased from 60% of total prescriptions in 2015 to 20% of total prescriptions in 2020. Exenatide followed similar trends and decreased from 27% of total prescriptions to 7% of total prescriptions during the same time period. In contrast, dulaglutide market share increased from 7% of total prescriptions in 2015 to 45% of total prescriptions in 2020; semaglutide utilization increased from 16% of total prescriptions in 2019 to 28% of total prescriptions in 2020.

For the cumulative period, approximately 39% of prescriptions were dispensed for liraglutide followed by dulaglutide (30%), exenatide (19%), and semaglutide (10%). Albiglutide and lixisenatide accounted for approximately 2% of total prescriptions combined.

Figure 3: Proportion of prescriptions dispensed for GLP-1 RAs from U.S. outpatient pharmacies, 2010 through 2020 and cumulative



Symphony Health Metys™ Prescription. 2010-2020. Data Extracted June 2021.

3.5.3 Patient-Level Data

Table 8 in Appendix C shows the estimated number of patients with a dispensed prescription for GLP-1 RAs from U.S. outpatient pharmacies from 2010 through 2020. In 2015, approximately 1.2 million patients received a dispensed prescription for a GLP-1 RA, a 92% increase from 2010. Use of GLP-1 RAs increased from 1.5 million patients in 2016 to 3.5 million patients in 2020.

4 DISCUSSION

Case series and literature characteristics:

DPV-I identified one case from FAERS of a patient who developed cutaneous amyloidosis with the use of a GLP-1 RA product, specifically liraglutide. The patient experienced localized amyloidosis while taking liraglutide with confirmatory biopsies from his abdominal mass as well as fat pad aspirations with a seven-year time to onset. The patient also had a positive antibody test to glucagon. This case is consistent with cutaneous amyloidosis associated with liraglutide use.

DPV-I identified two case reports from the medical literature of patients who developed cutaneous amyloidosis with the use of a GLP-1 RA product, specifically liraglutide, that was also assessed in the liraglutide PBRER. Martins et al. was considered the well documented index case by the Applicant. The case report had plausible temporal relationship, positive immunohistochemistry, and mass spectrometry for glucagon (specifically, a peptide that is shared by glucagon, GLP1 and liraglutide, and a peptide that is unique to the sequence of liraglutide was detected).²³ Wat et al. described a case report with plausible temporal relationship and histopathological examination, and a metabolic panel ruled out other known causes of amyloidosis.²⁴

Biologic plausibility:

Liraglutide and other GLP-1 RAs are GLP1 mimetic peptide drugs and are administered subcutaneously for the management of diabetes. Like other peptide drugs such as insulin, repeated injections at the same site may lead to extensive localized amyloid deposition. This observation has two important implications. First, as has been described for insulin, once the amyloid plaque has developed, continued injection at the same site may lead to poor absorption, thereby reducing the drugs' effect. More importantly, liraglutide and other GLP-1 RA - associated cutaneous amyloidosis may be misdiagnosed and mismanaged as systemic amyloid light-chain amyloidosis.²³

Considerations for labeling:

Current labeling for liraglutide products (Saxenda and Victoza) and the FRCs Soliqua 100/33 (insulin glargine and lixisenatide) and Xultophy 100/3.6 (insulin degludec and liraglutide) reflect the potential risk of cutaneous amyloidosis with use of the products. The SLC for Saxenda and Victoza was approved June 10, 2022, and Soliqua and Xultophy USPIs were updated to include cutaneous amyloidosis as part of a SLC for all insulin products in 2019. DPV-I identified one case from FAERS and two cases from the medical literature that show cutaneous amyloidosis with use of liraglutide. This provides evidence to support the recent SLC updating the USPIs for Saxenda and Victoza to include the risk of cutaneous amyloidosis. DPV-I did not identify any cases from FAERS, or the medical literature of cutaneous amyloidosis associated with dulaglutide, exenatide, lixisenatide, semaglutide, or tirzepatide. Possible reasons may include that these products had lower usage than liraglutide which accounted for approximately 39% of GLP-1 RA prescriptions dispensed from 2010 to 2020. The next GLP-1 RA which accounted for approximately 30% of prescriptions, dulaglutide, is administered once weekly compared to liraglutide which is administered daily thus exposing the patient to less injections into the same site. Tirzepatide was just approved in 2022 and except for exenatide, liraglutide has been on the market longer than the other GLP-1 RAs. However, in the semaglutide PBRER, the Applicant

noted a few cases of amyloidosis but did not specify the type of amyloidosis. In the dulaglutide PSUR, the Applicant listed one case of non-serious cutaneous amyloidosis with no details/assessment.

5 CONCLUSION

In conclusion, we find some basis for a causal relationship between cutaneous amyloidosis and liraglutide use and concur with the Applicant's addition of cutaneous amyloidosis to Post-Marketing Experience of the Victoza and Saxenda USPIs. There is limited supportive information at this time for updating the labelings of dulaglutide, exenatide, lixisenatide, semaglutide, and tirzepatide regarding the risk of cutaneous amyloidosis. Our case series did not identify cases of cutaneous amyloidosis associated with dulaglutide, exenatide, lixisenatide, semaglutide, or tirzepatide.

6 RECOMMENDATIONS

Based on this review, DPV-I recommends the following:

- Continue routine pharmacovigilance monitoring of dulaglutide, exenatide, lixisenatide, semaglutide, and tirzepatide and the potential risk of cutaneous amyloidosis.
- DPV-I concurs with the Applicant's inclusion within *Postmarketing Experience* of the USPI to reflect the risk of cutaneous amyloidosis with liraglutide.

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26. Source: Symphony Health MetysTM PrescriptionTM. Years 2010-2020. Extracted July 2021. File: SH Metys GLP-1 RA TRx semaglutide by form 7-19-21.xlsx

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. FAERS LINE LISTING OF CUTANEOUS AMYLOIDOSIS ASSOCIATED WITH THE USE OF GLP-1 RA CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	06-FEB-2019	15927186	4	US- NOVOPROD- 644899	Expedited (15-Day)	58	MALE	USA	OT
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome. Abbreviations: OT=other medically significant									

8.3 APPENDIX C. DRUG UTILIZATION DATA TABLES

Table 7. Estimated number of prescriptions for GLP-1 RAs dispensed from U.S. outpatient pharmacies, 2010 through 2020 and cumulative

	2010		2011		2012		2013		2014		2015	
	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)
Grand Total	2,426,279	100%	2,922,701	100%	3,467,594	100%	4,030,907	100%	4,428,880	100%	5,535,845	100%
LIRAGLUTIDE	552,742	23%	1,454,913	50%	2,040,201	59%	2,626,292	65%	2,939,091	66%	3,299,216	60%
EXENATIDE	1,873,537	77%	1,467,788	50%	1,427,393	41%	1,404,615	35%	1,465,443	33%	1,516,800	27%
DULAGLUTIDE									4,292	<0.1%	364,239	7%
ALBIGLUTIDE									20,054	<0.1%	355,590	6%
	2016		2017		2018		2019		2020		Cumulative Total 2010-2020	
	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)	TRx	Share (%)
Grand Total	7,343,336	100%	8,992,340	100%	11,470,465	100%	14,798,456	100%	18,509,697	100%	83,926,500	100%
LIRAGLUTIDE	3,780,550	51%	4,064,665	45%	4,535,607	40%	4,206,811	28%	3,647,706	20%	33,147,794	39%
DULAGLUTIDE	1,504,241	20%	3,161,010	35%	4,901,873	43%	6,723,889	45%	8,313,573	45%	24,973,117	30%
EXENATIDE	1,438,634	20%	1,424,194	16%	1,547,592	13%	1,466,763	10%	1,291,026	7%	16,323,785	19%
SEMAGLUTIDE					390,059	3%	2,396,955	16%	5,255,463	28%	8,042,477	10%
ALBIGLUTIDE	619,911	8%	341,794	4%	93,738	1%	1,800	<0.1%	15	<0.1%	1,432,902	2%
LIXISENATIDE			677	<0.1%	1,596	<0.1%	2,238	<0.1%	1,914	<0.1%	6,425	<0.1%

Source: Symphony Health Metys™ Prescription. Years 2010-2020. Data Extracted June 2021. File: SH Metys GLP-1 RA TRx all retail 6-28-21.xlsx

*Retail: includes retail, mail-order, and long-term care outpatient pharmacies; TRx = dispensed prescriptions

Table 8. Estimated number of patients with a dispensed prescription for GLP-1 RAs from U.S. outpatient pharmacies, 2010 through 2020

	2010		2011		2012		2013		2014		2015	
	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)
Grand Total	617,687	100%	703,104	100%	808,503	100%	899,325	100%	972,177	100%	1,183,896	100%
LIRAGLUTIDE	203,041	26%	383,045	54%	499,145	62%	613,662	68%	661,350	68%	714,538	60%
EXENATIDE	454,014	74%	350,747	46%	343,258	38%	319,264	32%	337,813	35%	352,007	30%
DULAGLUTIDE									3,588	<0.1%	110,451	9%
ALBIGLUTIDE									11,664	1%	87,005	7%
	2016		2017		2018		2019		2020			
			Patients	Share (%)	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)	Patients	Share (%)
Grand Total			1,494,312	100%	1,792,081	100%	2,277,833	100%	2,874,653	100%	3,471,062	100%
DULAGLUTIDE			344,209	23%	642,722	36%	958,491	42%	1,269,329	44%	1,491,440	43%
SEMAGLUTIDE							146,158	6%	627,884	22%	1,191,288	34%
LIRAGLUTIDE			800,357	54%	875,867	49%	960,059	42%	873,515	30%	728,858	21%
EXENATIDE			331,246	22%	318,934	18%	357,479	16%	316,918	11%	261,941	8%
LIXISENATIDE					287	<0.1%	512	<0.1%	668	0%	441	<0.1%
ALBIGLUTIDE			126,757	8%	72,057	4%	23,327	1%	929	0%	15	

Source: Symphony Health Metys™ Patients. Years 2010-2020. Data Extracted June 2021. File: SH Metys GLP-1 RA Patients all retail 6-29-21.xlsx

*Retail: includes retail, mail-order, and long-term care outpatient pharmacies

Due to the projection methodology used in the database, summarization of patient estimates across time periods may lead to differences in patient count due to rounding. Therefore, summing across time periods is not advisable and will result in overestimates of patient counts.

8.4 APPENDIX D. DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys™

Metys™ Powered by IDV®, Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point — all while delivering insights faster than any other tool in the industry. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 84% of all U.S. retail prescriptions; 72% of all U.S. mail order prescriptions, 76% of all U.S. specialty prescriptions and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data are not projected to the national level.

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DIVISION OF BIOEQUIVALENCE ADDENDUM ASSESSMENT

ANDA No.	215503	
Drug Product Name	Liraglutide Injection, for subcutaneous use	
Strength(s)	18 mg/3 mL (6 mg/mL)	
Applicant Name	Hikma Pharmaceuticals USA Inc.	
Applicant Address	2 Esterbrook Lane Cherry Hill, NJ 08003	
Applicant Contact Name and Mailing Address	Jonathan Endo, Manager, Regulatory Affairs 2325 Camino Vida Roble, Suit B Carlsbad, CA 92011	
Applicant Contact Telephone Number & E-mail	(b) (6) usfdainj@hikma.com jendo@hikma.com	
Applicant Contact Fax Number	440-201-7640	
Original Submission Date(s)	09/08/2021 3/4/2022	
Submission Date(s) of Amendment(s) Under Review	06/30/2023	
Primary Reviewer	Yumei Ye, Ph.D.	
Secondary Reviewer	Tian Ma, Ph.D.	
Tertiary Reviewer	N/A	
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)¹ <u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) Error! Bookmark not defined.	
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor/DRL ☒ N/A (Review is Adequate)	

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: <u>11/2024</u> RLD Number: <u>NDA 022341²</u> ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 8, 12	Waiver	18 mg/3 mL (6 mg/mL)	☒ Adequate ☐ Inadequate

NOTE TO REGULATORY PROJECT MANAGER (RPM): The comments to the applicant in the amendment assessment dated 2/14/2024 remain the same. There is no additional information to be communicated to the applicant from the current addendum assessment.

² The product specific guidance (PSG) for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020; Revised Nov 2024)
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022341)

1 EXECUTIVE SUMMARY

This is an addendum to the bioequivalence (BE) amendment assessment dated 02/14/2024³. The purpose of this addendum is to address the impact of the revision of the Draft BE Guidance on Liraglutide Subcutaneous Solution for Injection Product (Recommended Mar 2020; Revised Nov 2024)⁴ on the BE outcome of current ANDA 215503.

In the current application, the applicant has requested a waiver of in vivo bioequivalence (BE) study requirements for its test product, Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), under 21 CFR § 320.22 (b)(1). The reference-listed drug (RLD) and Reference Standard (RS) product is Novo Nordisk Inc.'s Victoza® (liraglutide) Injection, for subcutaneous use, 18 mg/3 mL (NDA 022341, approved on Jan 25, 2010).⁵

Impact of the November 2024 Guidance Revision

The original and subsequent amendment BE assessments were based on the previous version of BE Guidance (Recommended Mar 2020)⁶ in which the following was recommended for the Request for waiver of in vivo bioequivalence study requirements:

“To qualify for a waiver of the in vivo bioequivalence study requirement on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic liraglutide subcutaneous solution for injection product must be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD).”

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”

³ GDRP: A215503N000DB-Review01-Amend-06302023.pdf

(<https://panorama.fda.gov/document/view?ID=65a1cad3000567748f8a23c473811d7c>)

⁴ The product specific guidance (PSG) for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

⁵ Orange Book & Drugs@FDA: Search term: 022341 (Last accessed: 10/10/2024)

Assessor's Note: Per the most recent Policy Alert List as of 20241206, this drug product has been accepted for Novel Complex Drug product review. The NC Team was created due to the following potential NC Issues: immunogenicity questions and difference in buffer. Potential need to revisit non-substantial response to CP from RLD holder on ability to approve ANDA. If similar assessment issues are encountered for other ANDAs to the RLD, contact the NC TL and RPM listed in the Notes column. Please check DLRS policy updates in the link [OGD Policy Alert - Home \(sharepoint.com\)](#).

⁶ Assessor's Note: In the previous PSG dated 03/2020 and current PSG for this drug product, the applicants are recommended to refer to FDA's guidance for industry, ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, for additional recommendations on when an application for generic liraglutide injection solution product should be submitted as an abbreviated new drug application (ANDA). The latter guidance has additional recommendation with respect to active ingredient sameness and impurities (<https://www.fda.gov/media/107622/download>).

The current drug product is presented in a prefilled pen injector. The previous PSG did not provide device-related recommendations. Per the PSG revision assessment for the current version of the PSG⁷, the primary purpose of this revision is to incorporate the recommendations for device-related language and user interface assessment statement. The current revised PSG includes the following Device and User Interface Language under the “Additional Information” section of the said PSG.

Device:

The Reference Listed Drug (RLD) is presented in a prefilled pen injector. The pen injector is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the Test (T) device including:

- *Single-patient-use, disposable pen injector with variable-dose format*
- *Dose selector and dose button*
- *Needle compatibility*

Per the original BE assessment dated 03/02/2022 and the amendment assessment dated 02/12/2024 on the current application, both the test and RLD/RS products are injectable solution for the subcutaneous route. The test product contains the same inactive ingredients in the same concentrations as the RLD product. The test formulation is Q1 and Q2 the same as the RLD product. In addition, the measured physicochemical properties, including pH and osmolality, of the test product are comparable to those of the RLD product.^{8, 9, 3}

Per consult response assessment dated 2/6/2024 from the Center for Devices and Radiological Health (CDRH), the device constituent of the combination product is approvable for the proposed indication.¹⁰

⁷ GDRP: LIRAGLUTIDE SUBCUTANEOUS SOLUTION NDA 022341 REVISION PSG Review RC.pdf (<https://panorama.fda.gov/document/view?ID=66abe453003b01ac27773ba759353539>)

⁸ GDRP: A215503N000DB-Review01-09082021.pdf (<https://panorama.fda.gov/document/view?ID=620dc46800d22f5ca409fdd5c3989933>)

⁹ **Assessor’s Note:** Per the label approved on 07/05/2023 for NDA 022341, VICTOZA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous). (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022341s039lbl.pdf). Per the PSG for this drug product, a biowaiver may be granted if the generic product is Q1/Q2 the same as the RLD, and applicants is referred to FDA’s guidance “Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin” for additional recommendations on when an application for generic liraglutide injection solution product should be submitted as ANDA. The latter guidance has additional recommendation with respect to active ingredient sameness and impurities.

¹⁰ GDRP: ANDA215503.CDRH-OPEQ Review.ICC2300588.technical device review.pdf (<https://panorama.fda.gov/document/view?ID=658069b2004204ff53709e4f5216a9a5>)

The Division of Clinical Review (DCR) of Office of Safety and Clinical Evaluation (OSCE) has completed the assessment of the comparative analyses and finds the proposed drug-device user interface for the current proposed generic product acceptable.¹¹

Per the Drug Product assessment dated 05/30/2024, the applicant's results demonstrate that the proposed Liraglutide Injection, 18 mg/3 mL (6 mg/mL) and RLD are pharmaceutically equivalent.¹²

Per the amendment assessment dated 02/14/2024, the current application is adequate per BE perspective. And the Division of Bioequivalence I (DBI) can grant the waiver of in vivo BE study requirements for the test product, Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL).³

Based on above information, the test product contains the same active and inactive ingredients in the same concentration as the RLD product. The test formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product, which remains in accordance with the current PSG. Therefore, there is no impact of the current PSG revision on the BE outcome of current ANDA from DBI's perspective. As mentioned above, the PSG revision is with regard to device, which is evaluated by the Division of Clinical Review (DCR) of Office of Safety and Clinical Evaluation (OSCE). Therefore, the impact of the PSG change regarding device on the current ANDA is deferred to the DCR.

Therefore, per BE perspective, the current application remains **adequate**.

NOTE TO REGULATORY PROJECT MANAGER (RPM): The comments to the applicant in the amendment assessment dated 2/14/2024 remain the same. There is no additional information to be communicated to the applicant from the current addendum assessment.

¹¹ GDRP: A215503N000DCR-Comparative Analyses Liraglutide Pen Injector Review01.pdf (<https://panorama.fda.gov/document/view?ID=6272a327000a7e88d343ae8b648dd57b>)

¹² GDRP: A215503 Drug Product R03-AQ.pdf (<https://panorama.fda.gov/document/view?ID=6614118000090a27395b1c0e3cfa22fc>)

2 OUTCOME

Completed Assignment for 215503 ID: 55431

Reviewer: Ye, Yumei **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description:

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
55431	6/30/2023	Parallel2024	Other (Addendum not for error correction) (0.5 per application) [0.5]	0.5	0.5
				Total:	0.5

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	215503	
Drug Product Name	Liraglutide Injection, for subcutaneous use	
Strength(s)	18 mg/3 mL (6 mg/mL)	
Applicant Name	Hikma Pharmaceuticals USA Inc.	
Applicant Address	2 Esterbrook Lane Cherry Hill, NJ 08003	
Applicant Contact Name and Mailing Address	Jonathan Endo, Manager, Regulatory Affairs 2325 Camino Vida Roble, Suit B Carlsbad, CA 92011	
Applicant Contact Telephone Number & E-mail	(b) (6) usfdainj@hikma.com jendo@hikma.com	
Applicant Contact Fax Number	440-201-7640	
Original Submission Date(s)	09/08/2021 3/4/2022	
Submission Date(s) of Amendment(s) Under Review	06/30/2023	
Primary Reviewer	Yumei Ye, Ph.D.	
Secondary Reviewer	Tian Ma, Ph.D.	
Tertiary Reviewer	N/A	
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) ¹
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor/DRL ☒ N/A (Review is Adequate)	

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: <u>3/2020</u> RLD Number: <u>NDA 022341²</u> ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 8, 12	Waiver	18 mg/3 mL (6 mg/mL)	☒ Adequate ☐ Inadequate

² The product specific guidance (PSG) for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020)
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022341)

1 EXECUTIVE SUMMARY

This is a review of amendment dated 06/30/2023.

The applicant has requested a waiver of *in vivo* bioequivalence (BE) study requirements for its test product, Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), under 21 CFR § 320.22 (b)(1). The reference-listed drug (RLD) and Reference Standard (RS) product is Novo Nordisk Inc.'s Victoza® (liraglutide) Injection, for subcutaneous use, 18 mg/3 mL (NDA 022341, approved on Jan 25, 2010).³

Per the original BE review dated 03/02/2022, both the test and RLD/RS products are injectable solution for the subcutaneous route. The test product contains the same inactive ingredients in the same concentrations as the RLD product. The test formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product. In addition, the measured physicochemical properties, including pH and osmolality, of the test product are comparable to those of the RLD product. However, the application is inadequate due to the deficiencies related to the active pharmaceutical ingredient (API) sameness issued by the Office of Pharmaceutical Quality (OPQ) and related to the device component by the Center for Devices and Radiological Health (CDRH).^{4, 5}

Per the current CDRH consult response review dated 2/6/2024, the device constituent of the combination product is approvable for the proposed indication.⁶

The Division of Clinical Review (DCR) of Office of Safety and Clinical Evaluation (OSCE) has completed the review of the comparative analyses and finds the proposed drug-device user interface for the current proposed generic product acceptable.⁷

³ Orange Book & Drugs@FDA: Search term: 022341 (Last accessed: 01/12/2024)

⁴ GDRP: A215503N000DB-Review01-09082021.pdf
(<https://panorama.fda.gov/document/view?ID=620dc46800d22f5ca409fdd5c3989933>)

⁵ **Assessor's Note:** Per the label approved on 07/05/2023 for NDA 022341, *VICTOZA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).* (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022341s039lbl.pdf). Per the PSG for this drug product, a biowaiver may be granted if the generic product is Q1/Q2 the same as the RLD, and applicants is referred to FDA's guidance "*Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin*" (May 2021) for additional recommendations on when an application for generic liraglutide injection solution product should be submitted as ANDA. The latter guidance has additional recommendation with respect to active ingredient sameness and impurities.

⁶ GDRP: ANDA215503.CDRH-OPEQ Review.ICC2300588.technical device review.pdf
(<https://panorama.fda.gov/document/view?ID=658069b2004204ff53709e4f5216a9a5>)

⁷ GDRP: A215503N000DCR-Comparative Analyses Liraglutide Pen Injector Review01.pdf
(<https://panorama.fda.gov/document/view?ID=6272a327000a7e88d343ae8b648dd57b>)

Per the most recent OPQ's assessment dated 02/06/2024⁸ and the email communication between the OPQ and the Division of Bioequivalence I (DBI) on the same day⁹, the API sameness still has not been adequately demonstrated for the current application, which is pending the applicant's response to the deficiencies that impact the API aggregation and impurities.¹⁰

As mentioned above, the determination of API sameness is pending. Based on the current OB practice, from DBI's perspective, the DBI can grant the waiver of *in vivo* BE study requirements for the test product, Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL).¹¹ In addition, based on the current OB practice, the OPQ will inform the DBI if the waiver for the current test product needs to be retrieved in the future due to API sameness issue.

The current application is **adequate** per BE perspective.

⁸ GDRP: A215503 Drug Product R02-IQ.docx

(<https://panorama.fda.gov/document/view?ID=659bf5480003eb2191de47945252b7e8>)

⁹ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\ANDA 215503 Liraglutide Injection\RE API Sameness for ANDA 215503.msg

¹⁰ GDRP: A215503 Executive Summary_R02-CR.pdf

(<https://panorama.fda.gov/document/view?ID=64ac36c8000e1a2da65c97ff6728dcc8>)

¹¹ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\ANDA 215503 Liraglutide Injection\RE API Sameness for ANDA 215503 - OB Policy.msg

2 SUBMISSION SUMMARY

2.1 Drug Product Information¹²

Test Drug Product and Strength(s)	Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL)
Reference Standard (RS) and Strength(s)	VICTOZA® (liraglutide) Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
Reference Listed Drug (RLD) and Strength(s)	VICTOZA® (liraglutide) Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
RS and RLD Holder; NDA/ANDA Number; Approval Date	Novo Nordisk Inc., NDA 022341, 01/25/2010

2.2 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	There is a PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020)¹³  PSG_022341.pdf FDA's guidance "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021)¹⁴  GUI_FINAL_Highly Purified Synthetic Pep
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2.3 Review of Amendment Submission Dated 06/30/2023

Bioequivalence Deficiency Comment:

Your waiver request of in-vivo bioequivalence (BE) study requirements for your test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), cannot be granted at this time. There are deficiencies related to the active ingredient sameness and device components of your proposed drug product, which should be communicated to you by the Office of Pharmaceutical Quality

¹² Orange Book: Search term: 022341 (Last accessed: 01/212/2024)

(https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022341)

¹³ The PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

¹⁴ FDA's Guidance for Industry: "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021) (<https://www.fda.gov/media/107622/download>)

(OPQ). Please address all outstanding deficiencies and communicate with OPQ for further evaluation.

Applicant's Response:

Hikma acknowledges the Agency comment. The Hikma Complete Response included in this amendment fully and completely addresses each of the Office of Pharmaceutical Quality (OPQ) concerns as communicated in the FDA Complete Response Letter dated July 7, 2022. All deficiencies communicated by OPQ related to the active ingredient sameness and device components of the proposed drug product have been fully responded to.

Based upon the above, Hikma believes the proposed Liraglutide Injection drug product meets the requirement for a waiver of the in vivo bioequivalence (BE) study requirement on the basis that BE is self-evident under 21 CFR 320.22(b) based on the following:

- The proposed drug product is qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD) according to the data provided in Module 3.2.P.1 (Sequence 0001).*
- As discussed in the FDA Guidance for Industry, ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, active ingredient sameness has been demonstrated through the comparability studies of the peptide higher order (secondary and tertiary structures), oligomer/aggregation profile, impurity profile, biological activity and immunogenicity studies on the three drug product exhibit batches at the end of shelf life and RLD batches at similar sample age. Please refer to Module 3.2.S.3.1 for Report RD03-I-HY034-0015-01 Pharmaceutical Equivalence of the Proposed Liraglutide Injection, 18 mg/3 mL (6 mg/mL) at the end of shelf life to Victoza the Reference Listed Drug.*

Assessor's Comment:

The applicant acknowledges the Agency's comment and has submitted the complete response to address the outstanding deficiencies related to active ingredient sameness and device components.

Per the most recent OPQ's assessment dated 06/08/2022, the current application remains inadequate and the drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(l) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). And the outcome of the CDRH consult/evaluation remains inadequate.¹⁵

¹⁵ GDRP: A215503 Drug Product R01a-IQ.docx
(<https://panorama.fda.gov/document/view?ID=61af74c30016e624475bc3a944bbe60f>)

Per the current CDRH consult response review dated 2/6/2024, the device constituent of the combination product is approvable for the proposed indication.¹⁶

Per the most recent OPQ's assessment dated 02/06/2024¹⁷ and the email communication between the OPQ and the DBI on the same day¹⁸, the API sameness still has not been adequately demonstrated for the current application, which is pending the applicant's response to the deficiencies that impact the API aggregation and impurities.¹⁹

As mentioned above, the determination of API sameness is pending. Based on the current OB practice, from DBI's perspective, the DBI can grant the waiver of *in vivo* BE study requirements for the test product, Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL).²⁰ In addition, based on the current OB practice, the OPQ will inform the DBI if the waiver for the test product needs to be retrieved in the future due to API sameness issue.

Therefore, the application is **adequate**, per BE perspective.

¹⁶ GDRP: ANDA215503.CDRH-OPEQ Review.ICC2300588.technical device review.pdf
(<https://panorama.fda.gov/document/view?ID=658069b2004204ff53709e4f5216a9a5>)

¹⁷ GDRP: A215503 Drug Product R02-IQ.docx

(<https://panorama.fda.gov/document/view?ID=659bf5480003eb2191de47945252b7e8>)

¹⁸ \\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\ANDA 215503 Liraglutide Injection\RE API Sameness for ANDA 215503.msg

¹⁹ GDRP: A215503 Executive Summary_R02-CR.pdf

(<https://panorama.fda.gov/document/view?ID=64ac36c8000e1a2da65c97ff6728dcc8>)

²⁰ [\\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\ANDA 215503 Liraglutide Injection\RE API Sameness for ANDA 215503 – OB Policy.msg](mailto:\\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO1\Email Reference\ANDA 215503 Liraglutide Injection\RE API Sameness for ANDA 215503 - OB Policy.msg)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 215503

APPLICANT: Hikma Pharmaceuticals USA Inc.

DRUG PRODUCT: Liraglutide Injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL)

The Division of Bioequivalence I (DBI) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Utpal Munshi, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3 Completed Assignment for 215503 ID: 52819

Reviewer: Ye, Yumei

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description:

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
52819	6/30/2023	Parallel2023	Other (Minor amendment - original or supplement) [1]	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	215503		
Drug Product Name	Liraglutide Injection, for subcutaneous use		
Strength(s)	18 mg/3 mL (6 mg/mL)		
Applicant Name	Hikma Pharmaceuticals USA Inc.		
Applicant Address	2 Esterbrook Lane Cherry Hill, NJ 08003		
Applicant Contact Name and Mailing Address	Sarah Ansell, Director Regulatory Affairs Hikma Pharmaceuticals USA Inc. 2 Esterbrook Lane Cherry Hill, NJ 08003		
Applicant Contact Telephone Number & E-mail	(b) (6) usfdainj@hikma.com		
Applicant Contact Fax Number	440-201-7640		
Original Submission Date(s)	09/08/2021		
Submission Date(s) of Amendment(s) Under Review	03/04/2022		
Primary Reviewer	Yumei Ye, Ph.D.		
Secondary Reviewer	Dapeng Cui, Ph.D.		
Tertiary Reviewer	N/A		
Office of Study Integrity and Surveillance (OSIS) status	<table border="0"> <tr> <td> <u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)¹ </td> <td> <u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent)¹ </td> </tr> </table>	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) ¹
<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) ¹		
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☐ Adequate ☒ Inadequate (Pending for API sameness)		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☒ Minor/DRL ☐ N/A (Review is Adequate)		

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: _____ RLD Number: _ NDA 022341 ² _____ ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 8	Waiver	18 mg/3 mL (6 mg/mL)	☐ Adequate ☒ Inadequate

² The product specific guidance (PSG) for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

1 EXECUTIVE SUMMARY

This is a review of amendment dated 03/04/2022.

The applicant has requested a waiver of *in vivo* bioequivalence (BE) study requirements for its test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), for subcutaneous use, under 21 CFR § 320.22 (b)(1). The reference-listed drug (RLD) and Reference Standard (RS) product is Novo Nordisk Inc.'s Victoza® (liraglutide) Injection, 18 mg/3 mL, for subcutaneous use (NDA 022341, approved on Jan 25, 2010).³

Per the original BE review dated 03/02/2022, both the test and RLD/RS products are injectable solution for the subcutaneous route. The test product contains the same inactive ingredients in the same concentrations as the RLD product. The test formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product. In addition, the measured physicochemical properties, including pH and osmolality, of the test product are comparable to those of the RLD product. However, the application is inadequate due to the deficiencies related to the active pharmaceutical ingredient (API) sameness issued by the Office of Pharmaceutical Quality (OPQ) and related to the device component by the Center for Devices and Radiological Health (CDRH).^{4, 5}

Per the most recent OPQ's assessment dated 06/08/2022, the current application remains inadequate and the drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(l) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). And the outcome of the CDRH consult/evaluation remains inadequate.⁶ Please note that the Division of Clinical Review (DCR) of Office of Safety and Clinical Evaluation (OSCE) has completed the review of the comparative analyses and finds the proposed drug-device user interface for the current proposed generic product acceptable.⁷

³ Orange Book & Drugs@FDA: Search term: 022341 (Last accessed: 06/21/2022),

⁴ GDRP: A215503N000DB-Review01-09082021.pdf
(<https://panorama.fda.gov/document/view?ID=620dc46800d22f5ca409fdd5c3989933>)

⁵ **Assessor's Note:** Per the label approved on 06/10/2022 for NDA 022341, *VICTOZA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).* (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf). Per the PSG for this drug product and FDA's guidance "*Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin*" (May 2021), a biowaiver may be granted if the generic product contains the same active and inactive ingredients in the same concentrations as the RLD, and also demonstrate active ingredient sameness and impurities comparison to the RLD.

⁶ GDRP: A215503 Drug Product R01a-IQ.docx
(<https://panorama.fda.gov/document/view?ID=61af74c30016e624475bc3a944bbe60f>)

⁷ GDRP: A215503N000DCR-Comparative Analyses Liraglutide Pen Injector Review01.pdf
(<https://panorama.fda.gov/document/view?ID=6272a327000a7e88d343ae8b648dd57b>)

Therefore, at this time, the Division of Bioequivalence I (DBI) cannot grant the waiver of *in vivo* BE study requirements for the test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), due to the deficiencies related to API sameness and device performance.

As a result, the application is **inadequate**, pending for the review outcomes of API sameness and device equivalence by OPQ and CDRH.

2 TABLE OF CONTENTS

1	Executive Summary	3
2	Table of Contents	4
3	Submission Summary.....	5
3.1	Drug Product Information.....	5
3.2	OGD Recommendations for Drug Product	5
3.3	Review of Amendment Submission Dated 04/26/2022	5

3 SUBMISSION SUMMARY

3.1 Drug Product Information⁸

Test Drug Product and Strength(s)	Liraglutide Injection, 18 mg/3 mL (6 mg/mL)
Reference Standard (RS) and Strength(s)	VICTOZA® (liraglutide) injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
Reference Listed Drug (RLD) and Strength(s)	VICTOZA® (liraglutide) injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
RS and RLD Holder; NDA/ANDA Number; Approval Date	Novo Nordisk Inc., NDA 022341, 01/25/2010

3.2 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	There is a PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020)⁹  PSG_022341.pdf FDA's guidance "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021)¹⁰  GUI_FINAL_Highly Purified Synthetic Pep
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3.3 Review of Amendment Submission Dated 04/26/2022

DBI Deficiency Comment:

Your waiver request of in-vivo bioequivalence (BE) study requirements for your test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), cannot be granted at this time. There are deficiencies related to the active ingredient sameness and device components of your proposed drug product, which should be communicated to you by the Office of

⁸ Orange Book & Drugs@FDA: Search term: 022341 (Last accessed: 01/28/2022),

⁹ The PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

¹⁰ FDA's Guidance for Industry: "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021) (<https://www.fda.gov/media/107622/download>)

Pharmaceutical Quality (OPQ). Please address all outstanding deficiencies and communicate with OPQ for further evaluation.

Applicant's Response:

Hikma acknowledges the Agency's comment and will work to address the outstanding deficiencies related to active ingredient sameness and device components.

Assessor's Comment:

The applicant acknowledges the Agency's comment and will work to address the outstanding deficiencies related to active ingredient sameness and device components.

Per the most recent OPQ's assessment dated 06/08/2022, the current application remains inadequate and the drug product deficiencies have been classified as MAJOR because of insufficient data to demonstrate drug substance sameness as noted in Appendix A, Section A(2)(I) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). And the outcome of the CDRH consult/evaluation remains inadequate.¹¹

Please note that the DCR of OSCE has completed the review of the comparative analyses and finds the proposed drug-device user interface for the current proposed generic product acceptable.¹²

Therefore, the application is **inadequate**, pending for the review outcomes of API sameness and device equivalence by OPQ and CDRH.

¹¹ GDRP: A215503 Drug Product R01a-IQ.docx

(<https://panorama.fda.gov/document/view?ID=61af74c30016e624475bc3a944bbe60f>)

¹² GDRP: A215503N000DCR-Comparative Analyses Liraglutide Pen Injector Review01.pdf

(<https://panorama.fda.gov/document/view?ID=6272a327000a7e88d343ae8b648dd57b>)

Assessor's Note: The DCR of OSCE concludes the following in the said Comparative Analyses Review for the current test product: *"from a clinical safety perspective, there are minor and other acceptable design differences between the RLD and the proposed drug delivery device (color, dimensions, shape of pen; design of pen components - cap, cartridge holder, needle connector, dose selector, dose display features, pointer; color, art design and layout of pen and carton labeling; see table above for details). Therefore, DCR concludes this generic combination product can be substituted for the RLD without the intervention of a healthcare professional and/or without additional training prior to use of the generic combination product, and that the design differences as compared to RLD do not alter the clinical effect or safety profile of this proposed ANDA product under the conditions of use as specified in the labeling. In summary, DCR finds the proposed drug-device user interface for the proposed generic product acceptable."*

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 215503

APPLICANT: Hikma Pharmaceuticals USA Inc.

DRUG PRODUCT: Liraglutide Injection, 18 mg/3 mL (6 mg/mL), for subcutaneous use

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

- Your waiver request of in-vivo bioequivalence (BE) study requirements for your test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), cannot be granted at this time. There are deficiencies related to the active ingredient sameness and device components of your proposed drug product, which should be communicated to you by the Office of Pharmaceutical Quality (OPQ). Please address all outstanding deficiencies and communicate with OPQ for further evaluation.

Sincerely yours,

Utpal Munshi, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4 Completed Assignment for 215503 ID: 48501

Reviewer: Ye, Yumei

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description:

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score Subtotal</i>	
48501	3/4/2022	BIO	ANDA Amendment [1]	1	1
48501	3/4/2022	Parallel	Minor Amendment (Original or Supplement) [1]	1	1
				Total: 2	

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	215503		
Drug Product Name	Liraglutide Injection, for subcutaneous use		
Strength(s)	18 mg/3 mL (6 mg/mL)		
Applicant Name	Hikma Pharmaceuticals USA Inc.		
Applicant Address	2 Esterbrook Lane Cherry Hill, NJ 08003		
Applicant Contact Name and US Mailing Address	Sarah Ansell, Director Regulatory Affairs Hikma Pharmaceuticals USA Inc. 2 Esterbrook Lane Cherry Hill, NJ 08003		
Applicant Contact Telephone Number & E-mail	(b) (6) usfdainj@hikma.com		
Applicant Contact Fax Number	440.201.7640		
Original Submission Date(s)	09/08/2021		
Submission Date(s) of Amendment(s) Under Review	--		
Primary Reviewer	Yumei Ye, Ph.D.		
Secondary Reviewer	Dapeng Cui, Ph.D.		
Tertiary Reviewer	Qing Liu, Ph.D.		
Office of Study Integrity and Surveillance (OSIS) status	<table border="0"> <tr> <td> <u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)¹ </td> <td> <u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent)¹ </td> </tr> </table>	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) ¹
<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☐ Complete ☒ N/A (Waiver/Deem Bioequivalent) ¹		
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A		
QC Dissolution	☐ Pending ☐ Adequate ☐ Inadequate ☒ N/A		
Formulation	☐ Adequate ☒ Inadequate (Pending for API sameness)		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☒ Minor/DRL ☐ N/A (Review is Adequate)		

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: _____ RLD Number: _ NDA 022341 ² _____ ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1	Waiver	18 mg/3 mL (6 mg/mL)	☐ Adequate ☒ Inadequate

² The product specific guidance (PSG) for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

1 EXECUTIVE SUMMARY

The applicant, Hikma Pharmaceuticals USA Inc, has requested a waiver of *in vivo* bioequivalence (BE) study requirements for its test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), for subcutaneous use, under 21 CFR § 320.22 (b)(1). The reference-listed drug (RLD) and Reference Standard (RS) product is Novo Nordisk Inc.'s Victoza® (liraglutide) Injection, 18 mg/3 mL, for subcutaneous use (NDA 022341, approved on Jan 25, 2010).

Per the RLD label, VICTOZA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use.³ Per the product specific guidance (PSG) for this drug product and FDA's guidance "*Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin*" (May 2021)⁴, a biowaiver may be granted if the generic product contains the same active and inactive ingredients in the same concentrations as the RLD, and also demonstrate active ingredient sameness and impurities comparison to the RLD. The active ingredient sameness and impurities were evaluated by the Office of Pharmaceutical Quality (OPQ). Based on OPQ's review on the current ANDA, there were deficiencies identified related to the API which are included in the Quality Discipline Review Letter (DRL).⁵ Therefore, pharmaceutical equivalence cannot be demonstrated at this time. The applicant will be asked to address the deficiencies communicated by OPQ regarding the active ingredient sameness.

Based on the information/data provided by the applicant, both the test and RLD/RS products are injectable solution for the subcutaneous route. The test product contains the same inactive ingredients in the same concentrations as the RLD product. The test formulation is qualitatively (Q1) and quantitatively (Q2) the same as the RLD product. In addition, the measured physicochemical properties, including pH and osmolality, of the test product are comparable to those of the RLD product.

The RLD product is a drug-device combination product. Per FDA's guidance: "*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry*" (Issued January 2017)⁶, multi-dose pen injector is considered as a drug-device

³ Drugs@FDA: The label approved on 11/20/2020 for NDA 022341

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022341s036lbl.pdf)

⁴ FDA's Guidance for Industry: "*Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin*" (May 2021) (<https://www.fda.gov/media/107622/download>)

⁵ GDRP: ANDA-215503-ORIG-1»Drug Product Quality Review

(<https://panorama.fda.gov/task/view?ID=6139ff8d0099466dd8d746059d457590>)

Quality DRL: <https://panorama.fda.gov/task/view?ID=6139ff8d0099479b7f19d12579bc3768>; not archived as of 2/23/2022

A215503 Drug Product R01-IQ.docx (Draft, not finalized as of 02/16/2022)

(<https://panorama.fda.gov/document/view?ID=61af74c30016e624475bc3a944bbe60f>)

⁶ FDA Guidance for Industry: *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)

combination product and is expected to be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product. Currently, the device equivalence is pending the review by Division of Clinical Review (DCR) of Office of Safety and Clinical Evaluation (OSCE)⁷. In addition, there are deficiencies related to device component per the evaluation by the Center for Devices and Radiological Health (CDRH) which are included in the Quality DRL.⁵

Therefore, at this time, the Division of Bioequivalence I (DBI) cannot grant the waiver of *in vivo* BE study requirements for the test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), due to the deficiencies related to API sameness and device performance.

As a result, the application is **inadequate**.

(<https://www.fda.gov/files/drugs/published/Comparative-Analyses-and-Related-Comparative-Use-Human-Factors-Studies-for-a-Drug-Device-Combination-Product-Submitted-in-an-ANDA--Draft-Guidance-for-Industry.pdf>)

⁷ GDRP: ANDA-215503-ORIG-1»Combination Product Comparative Analyses Review
(<https://panorama.fda.gov/task/view?ID=617990fb007264a30f2db0d18d251bfe>)

2 TABLE OF CONTENTS

1	Executive Summary	3
2	Table of Contents	5
3	Submission Summary.....	6
3.1	Drug Product Information	6
3.2	PK/PD Information	6
3.3	OGD Recommendations for Drug Product	7
3.4	Formulation	12
3.5	Waiver Requests.....	12
3.6	Deficiency Comments.....	12
4	Appendix	13
4.1	Formulation Data	13
4.1.1	Test Formulation.....	13
4.1.2	RLD formulation	14
4.1.3	Comparison on Test and Reference Formulations.....	14
4.2	Consult Reviews.....	17
4.3	Additional Attachments.....	17
4.4	Attachments	17

3 SUBMISSION SUMMARY

3.1 Drug Product Information⁸

Test Drug Product and Strength(s)	Liraglutide Injection, 18 mg/3 mL (6 mg/mL)
Reference Standard (RS) and Strength(s)	VICTOZA® (liraglutide) injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
Reference Listed Drug (RLD) and Strength(s)	VICTOZA® (liraglutide) injection, for subcutaneous use, 18 mg/3 mL (6 mg/mL), NDA 022341
RS and RLD Holder; NDA/ANDA Number; Approval Date	Novo Nordisk Inc., NDA 022341, 01/25/2010

3.2 PK/PD Information⁹

Most recent RLD label	 022341s036lbl.pdf
Indication	VICTOZA is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated: • as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus. • to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. <u>Limitations of Use:</u> • Not for treatment of type 1 diabetes mellitus. • Should not be coadministered with other liraglutide-containing products
Boxed warning	WARNING: RISK OF THYROID C-CELL TUMORS • Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1). • VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors
Bioavailability	Absorption -Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_{max}) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg VICTOZA, the average steady state concentration of liraglutide over 24 hours was approximately 128

⁸ Orange Book & Drugs@FDA: Search term: 022341 (Last accessed: 01/28/2022),

⁹ Drugs@FDA: The label approved on 11/20/2020 for NDA 022341

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022341s036lbl.pdf)

	ng/mL. AUC _{0-∞} was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC _{0-∞} from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.
Food Effect	N/A
T_{max}	Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing.
Metabolism	During the initial 24 hours following administration of a single [³ H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.
Excretion	Following a [³ H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours, making VICTOZA suitable for once daily
Half-life	A plasma half-life of 13 hours after subcutaneous administration.
Maximum Daily Dose	1.8 mg/day

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	There is a PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020)¹⁰  PSG_022341.pdf FDA's guidance "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021)¹¹  GUI_FINAL_Highly Purified Synthetic Pep	
Summary of OGD or DB History	Approved ANDAs:	No
	Pending ANDAs:	Yes, numerous
	Controls:	Yes (several from the current applicant, please see comment below)

¹⁰ The PSG for Liraglutide Subcutaneous Solution for Injection Product (referencing NDA 022341) (Recommended Mar 2020) (https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022341.pdf)

¹¹ FDA's Guidance for Industry: "Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin" (May 2021) (<https://www.fda.gov/media/107622/download>)

	Protocols:	No
	Pending Citizen Petitions and other legal and regulatory issues: ¹² If yes, please comment.	☒ Yes ☐ No (see comment below)

Assessor's Comments:

Controlled Correspondences (CCs) from Current Applicant:

The applicant submitted the following CCs for the development of current generic product of Liraglutide Injection, 18 mg/3 mL (6 mg/mL):

CC #	Applicant	Submission	Question	Status	Completion
01606 ¹³	Hybio Pharmaceutical Co. Ltd	01/22/19	Q1/Q2	Completed	02/28/19
10691 ¹⁴	Hybio Pharmaceutical Co. Ltd.	04/06/20	Device Evaluation	Completed	06/04/20
12118 ¹⁵	Hybio Pharmaceutical Co. Ltd.	06/05/20	(b) (4)	Completed	07/28/20
12332 ¹⁶	Hybio Pharmaceutical Co. Ltd.	06/15/20	Q1/Q2	Completed	08/07/20

The applicant submitted CC# 01606 to seek the Agency's confirmation that the proposed formulation was qualitatively (Q1) and quantitatively (Q2) the same as the RLD, VICTOZA (Liraglutide Injection), 6 mg/mL, NDA 022341. Per OGD's evaluation, the applicant's proposed formulation was not Q1/Q2 the same as the RLD (b) (4)

The Agency responded the following to the applicant: *after reviewing your controlled correspondence submitted on January 22, 2019, the preliminary view of OGD is that, with respect to your proposed formulation, OGD would not likely grant a waiver of in vivo bioequivalence because bioequivalence would not be self-evident as per 21 CFR 320.22(b)(1). OGD has made a preliminary determination that it would likely refuse to receive your ANDA submitted pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and its implementing regulations.*¹⁷

¹² Please check DLRS policy updates in the link <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx>, policy alert as of February 14, 2022 (OGD Policy Alert List as of 20220214.pdf)

¹³ GDRP: Controlled Correspondence: LIRAGLUTIDE-NDA-022341-18mg per 3 mL (6mg per mL)-Q1/Q2 confirmation -01606 (<https://panorama.fda.gov/project/view?ID=5c45e58200d2c5d51b187ecaebf28637>)

¹⁴ GDRP: Controlled Correspondence: LIRAGLUTIDE-NDA-022341-Human Factor Study Waiver-10691 (<https://panorama.fda.gov/project/view?ID=5e8be0f900750316f14c3fb8ccec3c1e>)

CC 10691 Review.pdf (<https://panorama.fda.gov/document/view?ID=5ed13eef0007602a7bd4ef82b0c3545c>)

¹⁵ GDRP: Controlled Correspondence LIRAGLUTIDE NDA 022341 Packaging Requirements 12118

(<https://panorama.fda.gov/project/view?ID=5eda0e1603a66ab90de0e5a4ddd>)

C12118QLTYReview01.pdf

(<https://panorama.fda.gov/document/view?ID=5efdd848000671b167d50ae05d65c1a4>)

¹⁶ GDRP: Controlled Correspondence: LIRAGLUTIDE-NDA-022341-18mg per 3mL (6mg per mL)-Q1/Q2 confirmation-12332 (<https://panorama.fda.gov/project/view?ID=5ee7478f00c81ded74774c2dcc93bc95>)

¹⁷ GDRP: C28739650 Review.pdf

(<https://panorama.fda.gov/document/view?ID=5c61ccc9002118cddc1a473294af62ce>)

The applicant submitted CC #12332 to request the Agency's advice on the acceptability of its test formulation as compared to that of the RLD product. Per OGD's evaluation, the test formulation proposed in this CC was considered to be Q1/Q2 the same as the RLD (b) (4)

[REDACTED] The Agency responded the following to the applicant: *after reviewing your controlled correspondence submitted on June 15, 2020, with respect to your proposed test liraglutide injection formulation, OGD has made a preliminary determination that it would not likely refuse to receive your ANDA submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulations based on your proposed formulation pursuant to the requirements pertaining to inactive ingredients described in 21 CFR 314.101(d)(3) and 21 CFR 314.94(a)(9).*¹⁸ Please note that the test formulation in the current application ANDA 215503 is the same as that proposed in CC #12332.

The applicant submitted CC# 10691 to seek the Agency's confirmation that the proposed device was acceptable to the FDA for generic version of Victoza ® with respect to Information For Use (IFU) and mechanism perspective and can be submitted under section 505(j) of the FD&C Act. The Agency responded the following to the applicant: *after reviewing your controlled correspondence submitted on April 06, 2020, OGD's preliminary view is that the information submitted as part of your threshold analyses, including the sample devices provided, suggests your proposed device constituent may be appropriate for submission as part of an abbreviated new drug application (ANDA) referencing Victoza®, the reference listed drug (RLD). Based on the information you provided, we believe that the identified differences appear to be minor design differences, in that they would not be expected to impact an external critical design attribute involving the administration of the drug product, and therefore we agree that additional comparative human factors testing would not be warranted. However, the overall approvability of your proposed product, including the proposed test device constituent, will be determined during the scientific review of the ANDA. In addition, we recommend that you consider the following in the ANDA submission: although your proposed needle connector design appears reasonable,* (b) (4)

The applicant submitted CC# 12118 to seek the Agency's agreement on the number of samples, from these three exhibit batches packed to support testing the generic Liraglutide Injection expiration date. The Agency responded the following to the applicant: *based on the information provided in the controlled correspondence, your proposed plan to conduct the stability studies using a specified number of samples (per Table 2 of your correspondence) of each of the 3 exhibit batches of Liraglutide Injection generic product, packaged in the proposed commercial container closure system (i.e., pen) filled at 3.3 mL/pen, is considered acceptable. According to the FDA Guidance for Industry – ANDAs:*

¹⁸ GDRP: CC 12332 review.pdf

(<https://panorama.fda.gov/document/view?ID=5efc957a003cccea73a3c485cf44f4aa>)

(b) (4)

Pre-ANDA Meeting Request - ANDA-215503-PSUB-Meeting-17677:

#	Questions	Response ²²
1	Does FDA agree that our studies and/or study plan to demonstrate Drug Product equivalence to RLD based on the FDA Guidance's recommendations are in line with FDA expectations to support ANDA approval and equivalence claim of the proposed drug product to the RLD?	The Agency partially agrees with the proposed study plan to demonstrate drug product comparability with the RLD, (b) (4) (b) (4) (b) (4). It is recommended that you conduct a comparative impurity profile of the proposed product and the RLD. The need for additional characterization may be identified upon review of the complete ANDA submission. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) In addition, it is recommended that you compare the aggregation profile for your product under stress conditions such as increased temperature, agitation, light, freeze-thaw or humidity as indicated in the Draft Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin (October 2017). Please use at least two orthogonal validated methods of analysis for each comparability study class.
2	Does FDA agree that the immunogenicity assessment for Liraglutide	It is recommended that you conduct comparative characterizations on impurity profile using your test drug product on or near release and at the end of the proposed shelf life. (b) (4) (b) (4)

(<https://panorama.fda.gov/document/view?ID=600a1f3f006a2ae88fb7bceebb694255>)

	drug product is sufficient by the studies listed above?	(b) (4)
		(b) (5)

Pending Citizen Petition:

There is a pending citizen petition for BLA 208583, NDA #s. 206321 and 022341 (The RLD/RS for current ANDA, Liraglutide Injection, 18 mg/3 mL (6 mg/mL)) regarding referencing any of Novo Nordisk's liraglutide-containing drugs as the RLD as listed below.²³

Policy Alert Basis	Docket #	Action Requested or Issue Description	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes
Policy Issue - NSD / OGD to follow	FDA-2018-P-3401	Requests FDA refrain from receiving or approving any ANDA referencing any of Novo Nordisk's liraglutide-containing drugs as the RLD, and to require the sponsor of any ANDA or 505(b)(2) NDA that references an existing glucagon-like-peptide-1 (GLP-1) receptor agonist product to validate any immunoassays used in support of the application with clinical data and to implement a post-market surveillance program at least on par with current programs for VICTOZA as a condition of approval.	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence prior to contacting Policy Lead*	Petition response published, petition was denied. Filing no longer needs to contact Policy Lead if ANDA is filed for this drug product.

(b) (4)

²³ Please check DLRS policy updates in the link <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx>, policy alert as of February 14, 2022 (OGD Policy Alert List_as of 20220214.pdf)

(b) (4)

3.4 Formulation

Location in appendix	Appendix 4.1
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product bio-batch scored	N/A
Is the formulation acceptable?	NOT ACCEPTABLE
If not acceptable, why?	Deficiencies identified in the evaluation of API sameness by OPQ

3.5 Waiver Requests

Strengths for which waivers are requested, if applicable	18 mg/3 mL (6 mg/mL)
Proportional to strength tested in vivo?	N/A
Waiver regulation cited?	Yes [21 CFR § 320.22 (b)(1)]
Waivers granted?	NOT GRANTED
If not, then why?	Pending for evaluation of API sameness and device equivalence by OPQ and DCR.

3.6 Deficiency Comments

Please see deficiency letter.

4 APPENDIX

4.1 Formulation Data

4.1.1 Test Formulation²⁶

Ingredients	Function	Quality standard	Amount/3 mL	Concentration	% (w/v)	% (w/w)
Liraglutide	Active ingredient	In-house	(b) (4)	6 mg/mL	(b) (4)	(b) (4)
Disodium phosphate dihydrate	(b) (4)	USP-NF		1.42 mg/mL		
Propylene glycol		USP-NF		14 mg/mL		
Phenol		USP-NF		5.5 mg/mL		
Sodium hydroxide	pH modifier	USP-NF	Q.S to adjust pH of 8.15		(b) (4)	(b) (4)
Hydrochloric acid						
Water for injection	(b) (4)	USP	(b) (4)			

Per Module 2.3.P.1 of the original submission:

-
-
-
-

²⁶ [\\cdsesub1\evsprod\ANDA215503\0001\m2\23-qos](#) (Submitted on 09/08/2021)

4.1.2 RLD formulation²⁷

(Not to be released under FOIA)



(b) (4)

4.1.3 Comparison on Test and Reference Formulations

Ingredient	Function	Test Product (mg/mL)	RLD (mg/mL)	Difference (%) [=(R-T)x100/R]
Liraglutide	Active ingredient	6.00	6.00	0
Disodium (b) (4) Phosphate Dihydrate	(b) (4)	1.42	1.42	0
Phenol		5.50	5.50	0
Propylene glycol		14.00	14.00	0
Sodium hydroxide	pH modifier	(b) (4)		
Hydrochloric acid	pH modifier			

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	No
Comments on the drug product formulation:	The applicant's test product contains the same inactive ingredients in the same concentration as the RLD product. However,

²⁷ docuBridge: NDA 022341. Module 3.2.P.1. Description and Composition of the Drug Product. Received Date: 05/23/2008.

the test formulation is inadequate pending for evaluation of API sameness by the OPQ.

Comments on Formulation:

Active pharmaceutical ingredient (API): the API sameness was evaluated by the OPQ. Based on OPQ's review, there were deficiencies listed related to the API.²⁸ Therefore, pharmaceutical equivalence cannot be demonstrated at this time. Therefore, the applicant will be asked to address the deficiencies communicated via the OPQ regarding the API.

Inactive ingredients: the test product contains the same inactive ingredients in the same concentration as the RLD product. (b) (4)

Therefore, the test formulation is considered as Q1 and Q2 equivalent to the RLD product.

(b) (4)

Therefore, the test formulation is inadequate pending for the review outcomes of API sameness by the OPQ.

²⁸ GDRP: ANDA-215503-ORIG-1»Drug Product Quality Review
(<https://panorama.fda.gov/task/view?ID=6139ff8d0099466dd8d746059d457590>)
A215503 Drug Product R01-IQ.docx (Draft, not finalized as of 02/16/2022)
(<https://panorama.fda.gov/document/view?ID=61af74c30016e624475bc3a944bbe60f>)
(b) (4)

4.1.4 Overall Assessor's Comments:

- Per the RLD label, VICTOZA injection is a sterile, aqueous, clear, colorless or almost colorless solution for subcutaneous use. Each 1 mL of VICTOZA solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. VICTOZA has a pH of approximately 8.15, hydrochloric acid or sodium hydroxide may be added to adjust pH. Each pre-filled pen contains a 3 mL solution of VICTOZA equivalent to 18 mg liraglutide (free-base, anhydrous).³⁰
- The route of administration, dosage form, and strength of the test product are the same as those of the RLD product. The inactive ingredients of the test product are Q1 and Q2 the same as the RLD product.
- Per 2021 FDA's guidance "*Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Reference Peptide Drug Products of rDNA Origin*", the test product should also demonstrate active ingredient sameness and impurities comparison to RLD. The API sameness was evaluated by the OPQ. Based on OPQ's review, there were deficiencies listed related to the API sameness. Therefore, pharmaceutical equivalence cannot be demonstrated at this time. Therefore, the applicant will be asked to address the deficiencies communicated via the OPQ regarding the API.

-  (b) (4)

- Per RLD label, the pH of the RLD is approximately 8.15.  (b) (4)


. Therefore, the pH of the test and RLD product is comparable. In addition, another measured physicochemical property, osmolality, are also comparable between the test and RLD products as listed in the table below per the RLD results conducted by the applicant of current application.

³⁰ Drugs@FDA: The label approved on 11/20/2020 for NDA 022341
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022341s036lbl.pdf)

(b) (4)

Test	Test batches ³²				RLD batches ³³			
	Specification	3058200701	3058200702	3058200703	HS65B93	HS64Y06	JS68L85	JS68L68
pH	7.90-8.40	8.23	8.17	8.16	8.10	8.10	8.10	8.12
Osmolality (mOsm/kg)	253- 306	277	275	275	273	276	Not tested	

- The RLD product is a drug-device combination product. Per FDA’s guidance on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry*” (Issued January 2017), multi-dose pen injector is considered as a drug-device combination product and is expected to be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product. Currently, the device equivalence is pending the review by DCR³⁴. In addition, there are deficiencies related to device component per the evaluation by CDRH which are included in the Quality DRL.⁵
- Per 21 CFR § 320.22 (b)(1), the waiver request for the test formulation is not granted at this time, pending for the review outcomes of API sameness and device equivalence by the OPQ and DCR.

4.2 Consult Reviews

None

4.3 Additional Attachments

None

4.4 Attachments

None

³² \\cdsesub1\evsprod\ANDA215503\0001\m3\32-body-data\32p-drug-prod\Liraglutide-Injection-Injection\32p5-contr-drug-prod\32p54-batch-analys

³³ \\cdsesub1\evsprod\ANDA215503\0001\m2\23-qos

³⁴ GDRP: ANDA-215503-ORIG-1»Combination Product Comparative Analyses Review (<https://panorama.fda.gov/task/view?ID=617990fb007264a30f2db0d18d251bfe>)

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 215503

APPLICANT: Hikma Pharmaceuticals USA Inc.

DRUG PRODUCT: Liraglutide Injection, 18 mg/3 mL (6 mg/mL), for subcutaneous use

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

- Your waiver request of in-vivo bioequivalence (BE) study requirements for your test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), cannot be granted at this time. There are deficiencies related to the active ingredient sameness and device components of your proposed drug product, which should be communicated to you by the Office of Pharmaceutical Quality (OPQ). Please address all outstanding deficiencies and communicate with OPQ for further evaluation.

Sincerely yours,

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 Completed Assignment for 215503 ID: 47438

Reviewer: Ye, Yumei Date Completed:

Verifier: , Date Verified:

Division: Division of Bioequivalence

Description:

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
47438	9/8/2021	BIO	ANDA Original [1]	1	1
47438	9/ /2021	Parallel	Waiver Injectable (Per application) [1]	1	1
47438	9/8/2021	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total	2.25

CHAPTER VII: MICROBIOLOGY

Product Information	
ANDA Number	215503
Assessment Cycle Number	01
Drug Product Name / Strength	Liraglutide Injection / 18 mg/3 mL
Route of Administration	Subcutaneous injection
Applicant Name	Hikma Pharmaceuticals USA Inc.
Manufacturing Site	Hybio Pharmaceutical Co., Ltd. 2 nd Luhui Rd, Kengzi Jinsha Community, Pingshan District, Shenzhen, Guangdong 518118, China.
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is **recommended** for approval.

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: (Click link to view [Justification Statements](#))

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if “other” selected as theme.

Dates of Submission(s) Covered by this Review

Submit	Received	eCTD seq./Doc. #	Review Request	Assigned to Reviewer
09/08/2021	09/08/2021	#0000 / 1	N/A	09/21/2021
01/13/2022	01/13/2022	#0005 / 5	N/A	01/13/2022
04/14/2022	04/14/2022	#0010 / 10	N/A	05/09/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: No outstanding issues remain.

Remarks:

This is an electronic submission.
GDUFA goal date is 07/07/2022.
Mid Cycle date is 03/08/2022.

The 04/14/2022 submission is in response to microbiology deficiency conveyed to the applicant in the Agency's Quality Discipline Review Letter (DRL) dated 02/28/2022. The deficiencies are italicized.

Supporting Documents:

DMF (b) (4) (Type V): – (b) (4)

(b) (4)
was found adequate in the 06/20/2018 microbiology review.

DMF (b) (4) (Type V): – (b) (4)

(b) (4) site for (b) (4)
found adequate in the 05/08/2019 microbiology review.

(b) (4) site for (b) (4)
was found adequate in the 10/28/2019 microbiology review.

Select Number of Approved Comparability Protocols: 0**P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT**

Description of drug product –

(section 3.2.P.1: Description of dosage form).

Liraglutide Injection is a clear, colorless or almost colorless solution in a pre-filled, disposable and multi-dose pen injector containing 3 mL of drug product at a concentration of 6 mg/mL for subcutaneous injection, and delivering doses of 0.6 mg, 1.2 mg and 1.8 mg of Liraglutide, which is developed and designed in accordance with RLD (VICTOZA®, Novo Nordisk, NDA #022341).

Drug product composition –

(section 3.2.P.1: Description and composition of drug product).

Ingredients	Function	Concn.	Amount / cartridge
Liraglutide (in-house)	Active ingredient	6 mg/mL	18 mg
Disodium phosphate dihydrate, USP-NF	(b) (4)	1.42 mg/mL	(b) (4)
Propylene glycol, USP-NF		14 mg/mL	
Phenol, USP-NF		5.5 mg/mL	
Sodium hydroxide, USP-NF	pH modifier	Q.S to adjust pH of 8.15	

Hydrochloric acid, USP-NF	(b) (4)
Water for injection, USP	

Description of container closure system –
(section 3.2.P.1.4; section 3.2.P.7: Container closure system).

(b) (4)

(b) (4)

(b) (4)



QUALITY ASSESSMENT



(b) (4)

Adequate

(b) (4)

48 Pages have been withheld in full as b4
(CCI/TS) immediately following this page

**Adequate**

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, Ph.D., 05/31/2022

Secondary Assessor Name and Date

Elizabeth Berr, Ph.D., 05/31/2022



Eric
Adeeku

Digitally signed by Eric Adeeku

Date: 5/31/2022 03:48:35PM

GUID: 508da70b00028e3db199467cfbd47cb0



Elizabeth
Barr

Digitally signed by Elizabeth Barr

Date: 5/31/2022 03:50:00PM

GUID: 55370d1e00cfd67fc04d8bfbedbf3096

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Office of Surveillance and Epidemiology Review

Date: May 8, 2024

Reviewers: Courtney M. Suggs, PharmD, MPH Safety Evaluator
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Rajdeep Gill, PharmD
Deputy Director for Drug Utilization, DEPI-II

Wei Hua, MD, PhD, MHS, MS
Deputy Director, DEPI-I

Product Names, Application Type/Number, Applicant:

Product Name	Active Ingredient(s)	NDA/BLA	Applicant
Byetta	Exenatide synthetic	021773	AstraZeneca AB
Byetta	Exenatide synthetic	021919	Amylin

Bydureon	Exenatide synthetic, extended release	022200	AstraZeneca AB
Bydureon BCise	Exenatide synthetic, extended release	209210	AstraZeneca AB
Victoza	Liraglutide recombinant	022341	Novo Nordisk Inc.
Saxenda	Liraglutide recombinant	206321	Novo Nordisk Inc.
Xultophy 100/3.6	Insulin degludec, liraglutide	208583	Novo Nordisk Inc.
Tanzeum	Albiglutide	125431	GlaxoSmithKline
Trulicity	Dulaglutide	125469	Eli Lilly and Co.
Adlyxin	Lixisenatide	208471	Sanofi-Aventis US
Soliqua 100/33	Insulin glargine, lixisenatide	208673	Sanofi-Aventis US
Ozempic	Semaglutide	209637	Novo Nordisk Inc.
Rybelsus	Semaglutide	213051	Novo Nordisk Inc.
Rybelsus	Semaglutide	213182	Novo Nordisk Inc.
Wegovy	Semaglutide	215256	Novo Nordisk Inc.
Mounjaro	Tirzepatide	215866	Eli Lilly and Co.
Zepbound	Tirzepatide	217806	Eli Lilly and Co.

Subject: Completed Suicide, Suicide Attempt, and Suicidal Ideation

TTT Record ID: 2023-5971

SS ID#: 1005164

Acknowledgement: Thanks to Tracy Pham, PharmD for her assistance with the quality assurance/control check of the drug utilization data provided in this review and to Ian Dunne, PharmD, BCPS for his assistance with background information.

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	3
1.1 Background.....	3
1.2 Regulatory History.....	5
1.3 Relevant Product Labeling.....	7
2 Methods and Materials.....	8
2.1 Case Definition	8
2.2 Causality Criteria	8
2.3 FAERS Search Strategy.....	9
2.4 Data Mining Search Strategy.....	9
2.5 Case Report/Series Literature Search Strategy	10
2.6 Observational Studies And Pooled Analysis Literature Search Strategy.....	10
2.7 Periodic Safety Reports.....	11
2.8 Information Requests	11
2.9 Drug Utilization	11
3 Results.....	12
3.1 FAERS and Literature Case Selection.....	12
3.2 Data Mining	22
3.3 Periodic Safety Reports.....	23
3.4 Applicant Responses to FDA Information Requests	24
3.5 DEPI Literature Review.....	28
3.6 Drug Utilization	30
4 Discussion.....	35
5 Conclusion	39
6 References.....	40
7 Appendices.....	45
Appendix A. FDA Adverse Event Reporting System (FAERS)	45
Appendix B. Literature Search Strategy	46
Appendix C. Drug Utilization Database Descriptions And Limitations.....	50
Appendix D. FAERS Line Listing of Suicidal Ideation and Behavior Associated with GLP-1 RA Use Case Series	52
Appendix E. Narrative Case Summaries of Completed Suicides (n=18)	59
Appendix F: Tabular Summary of Observational Study and meta-analysis on association of depression and self-harm and GLP-1 RA exposure.....	66
Appendix G. Drug Utilization Tables.....	69

EXECUTIVE SUMMARY

The purpose of this joint pharmacovigilance and epidemiologic review is for the Division of Pharmacovigilance I (DPV-I) and the Division of Epidemiology I (DEPI-I) to provide the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of the relationship between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and completed suicide, suicide attempt, and suicidal ideation. DPV-I analyzed reports from the FDA Adverse Event Reporting System (FAERS), case reports and case series studies in medical literature, and information provided by the Applicants. DEPI-I provided an assessment of published observational studies and pooled analyses concentrating on the relationship between GLP-1 RAs and completed suicide, suicide attempt, and suicidal ideation. Additionally, the Division of Epidemiology II (DEPI-II) assessed utilization data for GLP-1 RAs to provide context to the signal evaluation. Information from this review will aid DDLO in their determination of whether any additional regulatory action is warranted regarding the safety signal of GLP-1 RAs and potential risk of suicidal ideation and behavior (SIB).

DPV-I identified 110 cases from FAERS of completed suicide (n=6), suicide attempt (n=6), or suicidal ideation (n=98) associated with GLP-1 RA use. Distribution of cases in our case series is consistent with market share of respective GLP-1 RA products. We assessed the cases included in our case series as having a possible causal relationship between GLP-1 RA use and SIBs, and therefore we cannot exclude the possibility that other conditions or drugs may have contributed to or caused the SIB events in these cases. Almost one-third (n=31) of our cases reported a pre-existing history of a psychiatric disorder and an additional 7 cases reported that a psychiatric medication had been started prior to initiation of the GLP-1 RA, despite the case not otherwise specifying an accompanying psychiatric disorder. Overall, our analysis of the FAERS cases was subject to significant limitations. SIBs are complex phenomena involving a dynamic interplay of biological, psychological, and social factors, and FAERS cases often lacked data pertinent to SIB risk.

The published observational or pooled studies on the relationship between GLP-1 RAs and suicide or suicidal ideation are inconclusive. DEPI-I identified one observational and one pooled analysis for review. The results from this pooled analysis are reported in the label for Saxenda. Both studies found a higher incidence of either SIB or depression and self-harm in GLP-1 RA users compared to placebo or sulfonylureas. However, differences in incidence between comparators and GLP-1RAs were small and might be explained by limitations in the analyses. As well, neither study had the sample size for SIB or self-harm for meaningful inference with statistical power.

The Drug Utilization analyses from United States outpatient retail and mail-order/specialty pharmacies showed that the estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022, with semaglutide accounting for the highest number of prescriptions dispensed in 2022.

In conclusion, we identified FAERS cases of patients who were taking GLP-1 RAs and had completed suicide, suicide attempt, and/or suicidal ideation. Implications of observational studies related to GLP-1 RAs and SIB are unclear at this time. Given the limitations of FAERS data and

available observational studies, the information contained in this analysis should be taken in context of other available evidence, including, but not limited to, clinical trial data, ongoing meta-analysis, and Sentinel System evaluations.

1 INTRODUCTION

The purpose of this joint pharmacovigilance and epidemiologic review is for the Division of Pharmacovigilance I (DPV-I) and the Division of Epidemiology I (DEPI-I) to provide the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) an evaluation of the relationship between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and completed suicide, suicide attempt, and suicidal ideation. DPV-I analyzed reports from the FDA Adverse Event Reporting System (FAERS), case reports and case series studies in medical literature, and information provided by the Applicants. DEPI-I provided an assessment of published observational studies and pooled analyses concentrating on the relationship between GLP-1 RAs and completed suicide, suicide attempt, and suicidal ideation. Additionally, the Division of Epidemiology II (DEPI-II) assessed utilization data for GLP-1 RAs to provide context to the signal evaluation. Information from this review will aid DDLO in their determination of whether any additional regulatory action is warranted regarding the safety signal of GLP-1 RAs and potential risk of suicidal ideation and behavior (SIB).

1.1 BACKGROUND

Suicide is a serious public health problem. In 2021, over 48,000 people committed suicide in the United States (U.S.), equivalent to about one death every 11 minutes. The number of people who experience suicidal ideation or attempted suicide is even higher. In 2021, an estimated 12.3 million adults in the U.S. seriously thought about suicide, and 1.7 million attempted suicide.¹ SIB includes suicidal ideation (thinking about ending one's life), suicide attempts (non-fatal suicidal behavior), and completed suicide (ending one's life). Collectively, these events will be referred to hereafter as SIB.

People of any age and sex can experience SIB; however, some age and demographic groups are at higher risk. In 2021, suicide was the second leading cause of death for people 10-14 and 20-34 years old. Overall, it is a leading cause of death and ranked within the top 9 causes for people 10-64 years old. Males experience significantly higher rates of suicide than females, and adults over the age of 85 have the highest rates of suicide out of all age groups.¹

Many factors have been identified that can put an individual at higher risk of suicide. Identifying these factors can aid in prevention and guide treatment decisions.² A prior history of attempted suicide is the strongest single predictor of future suicide. An estimated 10 to 40 non-fatal suicide attempts occur for every completed suicide.³ Certain psychiatric illnesses are also associated with increased risk for suicide. Psychiatric disorders most commonly associated with suicide include depression, bipolar disorder, alcoholism or other substance abuse, schizophrenia, personality disorders, anxiety disorders including panic disorder, posttraumatic stress disorder, and delirium. Patients who have multiple psychiatric comorbidities appear to be at higher risk than those with uncomplicated depression or an anxiety disorder. Suicide risk also increases with general medical illness, including asthma, cancer, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, spine disorders, stroke, recent surgery, and chronic or terminal disease. Chronic pain (e.g., back pain, cancer pain, and/or arthritis) is also prevalent in people who successfully commit suicide. Other risk factors for suicide include marital status, sexual orientation, military service, living alone, and loss of a loved one.²

A large meta-analysis of 54 observational cohort studies found that diabetes was associated with an increased risk of suicide (RR=1.56; 95% CI:1.29-1.89; $p<0.001$; $I^2 = 93.2\%$). Subgroup analysis by type of diabetes found an increase in relative risk of suicide associated with type 1 diabetes (T1DM) (RR=2.25; 95%CI: 1.50-3.38; $p<0.001$, $I^2=69.3\%$) compared to those without diabetes. The study also identified a marginal association between type 2 diabetes (T2DM) and suicide (RR = 1.65, 95% CI: 0.95–2.85; $P = 0.07$, $I^2 = 95.0\%$). Additional analysis of the causes of death in diabetic patients indicated death due to suicide in T1DM patients and T2DM patients was 7.7% (95% CI: 6.0–9.8; $I^2 = 67\%$) and 1.3% (95% CI: 0.6–2.6; $I^2 = 94\%$), respectively. Interpretation of these findings are limited by uncertainties from heterogeneity across study populations, low event sensitivity, and small sample size.⁴ The link between diabetes and SIB is concerning because the global diabetes prevalence is rising. In 2019, it was estimated to be 9.3% (463 million people) rising to an estimated 578 million people by 2030. T2DM is more common than T1DM.⁵

Suicidal behavior in patients with diabetes may be related to comorbid depression, and there appears to be a bidirectional relationship between diabetes and depression. Patients with diabetes are more likely to develop depression, and patients with depression are at higher risk of diabetes. The prevalence of depression is more than three-times higher in people with T1DM (12%, range 5.8-43.3% vs. 3.2%, range 2.7-11.4%) and nearly twice as high in people with T2DM (19.1%, range 6.5-33% vs. 10.7%, range 3.8-19.4%) compared to those without diabetes.⁶ The pathophysiology of depression and suicidality associated with diabetes is poorly understood and may be unique to the patient population. For example, depression and SIB in the diabetic population may be related to abnormalities in glucose metabolism. Studies suggest that both acute and chronic hyperglycemia have harmful effects on mood states and cognitive function. It has been shown that depressed mood and suicidal ideation are significantly related to higher hemoglobin A1C values. Another study has reported that cerebrospinal fluid insulin levels are higher among violent suicide attempters in comparison to non-violent suicide attempters.⁵

Summary of Events Leading to this Review

On July 11, 2023, the European Medicines Agency (EMA) issued a statement regarding the ongoing review of GLP-1 RAs. EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), is reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1 RAs, including Ozempic (semaglutide), Saxenda (liraglutide) and Wegovy (semaglutide). The review was triggered by the Icelandic Medicines Agency following reports of suicidal thoughts and self-injury in people using liraglutide and semaglutide.⁷ The FDA opened a Newly Identified Safety Signal (NISS, SS ID #1005164) for all GLP-1 RAs and suicidal ideation on July 12, 2023, which was moved to evaluation on July 14, 2023. On July 17, 2023, DDLO consulted DPV-I to review the FAERS database and medical literature for suicide and suicidal ideation in patients taking GLP-1 RAs.

Foreign Regulatory Agencies

In addition to EMA, a safety review on the potential risk of suicidal thoughts and self-harm with the use of GLP-1 RAs has been initiated by Singapore's Health Sciences Authority (HSA).⁸ The

United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) as well as Health Canada are also reviewing the association between GLP-1 RAs and the risks of suicide, self-harm, suicidal ideation, and self-injurious ideation.^{9,10}

1.2 REGULATORY HISTORY¹¹

Currently, there are six GLP-1 RAs approved by FDA and currently marketed under one or more tradenames (see Table 1 below). The first GLP-1 RA product, Byetta (exenatide synthetic, NDA 021773), was approved on April 28, 2005, in the U.S.

Tanzeum (albiglutide, BLA 125431) was previously marketed in the U.S. until July 2018, but currently has a voluntary “revoked” status due to a business decision (low usage of the product) and not related to safety or efficacy. Bydureon (exenatide extended release, NDA 022200) was previously marketed in the U.S., but the Applicant submitted a permanent withdrawal from sale for business reasons effective March 2021. Adlyxin (lixisenatide, BLA 208471) was previously marketed in the U.S., but the Applicant submitted a notification of permanent discontinuation for business reasons on February 22, 2023.

All GLP-1 RA products except for weight management formulations are indicated as adjunct therapy to diet and exercise to improve glycemic control in patients with T2DM. This indication is extended to pediatric patients aged 10 years and older with T2DM for Bydureon BCise (exenatide synthetic, extended release), Victoza (liraglutide), and Trulicity (dulaglutide). Victoza (liraglutide), Trulicity (dulaglutide), and Ozempic (semaglutide) are also indicated to reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease. Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) are indicated for chronic weight management in adults (at higher daily doses compared to their respective subcutaneous products of the same ingredients indicated for glycemic control and also pediatric patients aged 12 years and older for Saxenda and Wegovy).

Table 1 lists currently marketed FDA-approved GLP-1 RA products, including single-ingredient products and fixed ratio drug-drug combinations, in the U.S.

Table 1. Currently Marketed GLP-1 RAs in the U.S.				
Product Name NDA/BLA Applicant	Active Ingredient(s), Formulation	Indication(s)	Dosage Ranges	Approval Date
Byetta 021773 AstraZeneca AB	Exenatide synthetic, SC Inj	T2DM in adults	5 mcg to 10 mcg twice daily	4/28/2005
Bydureon BCise 209210 AstraZeneca AB	Exenatide synthetic, extended release, SC Inj	T2DM in adults, pediatrics ≥ 10 years	2 mg every 7 days	10/20/2017
Victoza 022341 Novo Nordisk Inc.	Liraglutide recombinant, SC Inj	T2DM in adults, pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM	0.6 mg titrated to 1.8 mg daily	1/25/2010

Table 1. Currently Marketed GLP-1 RAs in the U.S.				
		and established CVD		
Saxenda 206321 Novo Nordisk Inc.	Liraglutide recombinant, SC Inj	Weight management in adults*, pediatrics ≥ 12 years [†]	0.6 mg titrated to 3 mg daily	12/23/2014
Xultophy 100/3.6 208583 Novo Nordisk Inc.	Insulin degludec + liraglutide, SC Inj	T2DM in adults	10 units titrated to 50 units daily	11/21/2016
Trulicity 125469 Eli Lilly and Co.	Dulaglutide, SC Inj	T2DM in adults, pediatrics ≥ 10 years; reduce the risk of MACE in adults with T2DM and established CVD or multiple CV risk factors	0.75 mg titrated to 4.5 mg weekly [‡]	9/18/2014
Soliqua 100/33 208673 Sanofi-Aventis US	Insulin glargine + lixisenatide, SC Inj	T2DM in adults	15 units titrated to 60 units daily	11/21/2016
Ozempic 209637 Novo Nordisk Inc.	Semaglutide, SC Inj	T2DM in adults; reduce the risk of MACE in adults with T2DM and established CVD	0.25 mg titrated to 2 mg weekly	12/5/2017
Rybelsus 213051 Novo Nordisk Inc.	Semaglutide, oral tablet	T2DM in adults	3 mg titrated to 14 mg daily	9/20/2019
Wegovy 215256 Novo Nordisk Inc.	Semaglutide, SC Inj	Weight management in adults [§] , pediatrics ≥ 12 years	0.25 mg titrated to 2.4 mg weekly	6/4/2021
Mounjaro 215866 Eli Lilly and Co.	Tirzepatide, SC inj	T2DM in adults	2.5 mg titrated to 15 mg weekly	5/13/2022
Zepbound 217806 Eli Lilly and Co.	Tirzepatide SC inj	Weight management in adults [¶]	2.5 mg titrated to 15 mg weekly	11/8/2023
Source: Drugs@FDA * Adults with an initial BMI of 30 kg/m ² or greater (obese), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia) [†] Pediatrics with body weight > 60 kg and an initial BMI corresponding to 30 kg/m ² for adults (obese) [‡] In pediatrics, the maximum recommended dosage is 1.5 mg once weekly [§] Adults with an initial BMI of 30 kg/m ² or greater (obesity), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2DM, or dyslipidemia) Pediatrics with an initial BMI at the 95th percentile or greater for age and sex (obesity) [¶] Adults with an initial BMI of 30 kg/m ² or greater (obesity), or BMI 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, T2DM, obstructive sleep apnea, or CVD)				

Table 1. Currently Marketed GLP-1 RAs in the U.S.

Abbreviations: BLA=Biologics License Application, BMI=body mass index, CV=cardiovascular, CVD=cardiovascular disease, GLP-1 RA=glucagon-like peptide-1 receptor agonist, Inj=injection, MACE=major adverse cardiovascular events, NDA=New Drug Application, SC=subcutaneous, T2DM=type 2 diabetes mellitus, U.S.=United States

1.3 RELEVANT PRODUCT LABELING

The U.S. Prescribing Information (USPI) for the GLP-1 RA products approved for the treatment of chronic weight management, Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide), contain a WARNINGS AND PRECAUTIONS subsection relating to SIB; however, the GLP-1 RA products approved for glycemic control do not. This is because an imbalance in SIB was observed in Saxenda's adult clinical trial and one participant in a Saxenda pediatric trial died by suicide. This information is included in the Saxenda label; however, there was insufficient information to establish a causal relationship between suicidal ideation and Saxenda based on these data. There were no imbalances in events of SIB in clinical trials of Wegovy or Zepbound, which are the other two products approved for chronic weight management. Because of the potential for drugs in the same class (GLP-1 RAs) and approved for the indication of chronic weight management to have a similar risk of SIB (even though an increased risk was not seen), this potential risk was included in the labeling for the other GLP-1 RAs approved for chronic weight management.^{12,13,14}

Relevant excerpts from the Saxenda USPI are provided below:¹²

5.8 Suicidal Behavior and Ideation

In SAXENDA adult clinical trials, 9 (0.3%) of 3384 SAXENDA-treated patients and 2 (0.1%) of the 1941 placebo-treated patients reported suicidal ideation; one of these SAXENDA-treated patients attempted suicide.

In a SAXENDA pediatric clinical trial, 1 (0.8%) of the 125 SAXENDA-treated patients died by suicide. There was insufficient information to establish a causal relationship to SAXENDA.

Patients treated with SAXENDA should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue SAXENDA in patients who experience suicidal thoughts or behaviors. Avoid SAXENDA in patients with a history of suicidal attempts or active suicidal ideation.

8.4 Pediatric Use

In the pediatric clinical trial, there was one death due to suicide in a SAXENDA-treated patient [see *Warnings and Precautions* (5.8)]; one SAXENDA-treated patient had an event of pancreatitis [see *Warnings and Precautions* (5.2)]; more episodes of hypoglycemia confirmed by self blood glucose monitoring occurred in SAXENDA-treated patients compared to placebo [see *Warnings and Precautions* (5.4) and *Adverse Reactions* (6.1)]; and mean increases in resting heart rate of 3 to 7 bpm from

baseline were observed with SAXENDA- treated patients [*see Warnings and Precautions (5.5)*].

The safety and effectiveness of SAXENDA have not been established in patients less than 12 years of age.

The Wegovy and Zepbound USPIs contain nearly identical SIB labeling as excerpted below:^{13,14}

Wegovy (semaglutide)

5.9 Suicidal behavior and ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with WEGOVY for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue WEGOVY in patients who experience suicidal thoughts or behaviors. Avoid WEGOVY in patients with a history of suicidal attempts or active suicidal ideation.

Zepbound (tirzepatide)

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other chronic weight management products. Monitor patients treated with ZEPBOUND for the emergence or worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior. Discontinue ZEPBOUND in patients who experience suicidal thoughts or behaviors. Avoid ZEPBOUND in patients with a history of suicidal attempts or active suicidal ideation.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

DPV-I adapted case inclusion and exclusion criteria from the 2017 Suicidal Ideation and Behavior Office of Surveillance and Epidemiology (OSE) case definition.¹⁵ Cases were included if they reported a completed suicide, suicide attempt, and/or suicidal ideation.

2.2 CAUSALITY CRITERIA

Causality was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment (Table 2).¹⁶ Criteria for unlikely causal association have been modified to address concerns specific to SIB. Cases were excluded if causality was determined to be unlikely or unassessable.

Table 2. Causality Categories and Criteria Adapted from the WHO-UMC System	
Category	Criteria
Probable	• Event with reasonable time relationship to drug intake* • Unlikely to be attributed to other conditions or drugs • Response to withdrawal clinically reasonable
Possible	• Event with reasonable time relationship to drug intake • Could also be explained by other conditions or drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event with a time to drug intake that make a relationship improbable (but not impossible) • Other conditions or drugs provide more plausible explanations (e.g., traumatic brain injury, recent death of a spouse) • History of attempted suicide reported prior to GLP-1 RA initiation
Unassessable	• Cases cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
* There are no guidelines or consensus on timeline of temporal relationship between initiation of drug and onset of events for SIB events.	

2.3 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	August 28, 2023
Time period of search	January 1, 2013 to August 27, 2023
Search type	<i>RxLogix PV Reports Quick Query</i>
Product terms	GLP-1 RECEPTOR AGONIST [EPC] (Therapeutic drug class)
MedDRA search terms (Version 26.0)	PTs: <i>Completed suicide, Suicide attempt, Suicidal behaviour, Suicidal ideation</i>
Other Criteria	Serious cases only
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.4 DATA MINING SEARCH STRATEGY

DPV-I used the Empirica Signal software with the strategy described in Table 4 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”). If a drug-event combination has a score (EB05) of ≥ 2 , this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Table 4. Data Mining Search Strategy*	
Data refresh date	August 27, 2023
Product terms	PAM: Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Semaglutide, Tirzepatide
Empirica Signal run name	PAM(S)
MedDRA search strategy	PTs: <i>Completed suicide, Suicide attempt, Suicidal behaviour, Suicidal ideation</i>
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. Abbreviations: PAM: Product Active Moiety, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.5 CASE REPORT/SERIES LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Table 5 for case reports and case series studies.

Table 5. Literature Search Strategy	
Date of search	September 7, 2023
Database	Embase, PubMed@FDA
Search terms	See Appendix B
Years included in search	All
Limits	English, Human studies, Study types: case reports, case studies, case series, clinical trials, observational studies, reviews, systematic reviews and meta-analysis

2.6 OBSERVATIONAL STUDIES AND POOLED ANALYSIS LITERATURE SEARCH STRATEGY

DEPI-I conducted a literature search in PubMed for observational, pooled, or meta-analysis studies of GLP-1 RAs and suicidal ideation and suicide. The search criteria are detailed in Table 6.

Table 6. DEPI literature search strategy to identify human studies assessing GLP-1 RAs association with suicidal ideation and suicide.	
Date of search	August 3, 2023
Database	PubMed
Search terms	((("glucagon like peptides"[Supplementary Concept] OR "glucagon like peptides"[All Fields] OR "glucagon like peptide"[All Fields] OR "glucagon like peptides"[MeSH Terms] OR ("glucagon like"[All Fields] AND "peptides"[All Fields]) OR ("glucagon"[All Fields] AND "like"[All Fields] AND "peptide"[All Fields])) AND ("suicid"[All Fields] OR "suicidal ideation"[MeSH Terms] OR ("suicidal"[All Fields] AND "ideation"[All Fields]) OR "suicidal ideation"[All Fields] OR "suicidality"[All Fields] OR "suicidal"[All Fields] OR "suicidally"[All

	Fields] OR "suicidals"[All Fields] OR "suicide"[MeSH Terms] OR "suicide"[All Fields] OR "suicides"[All Fields] OR "suicide s"[All Fields] OR "suicided"[All Fields] OR "suiciders"[All Fields])) AND (humans[Filter])
Years included in search	All

2.7 PERIODIC SAFETY REPORTS

DPV-I screened the following recent periodic safety reports for currently marketed GLP-1 RAs for the Applicant's assessment of SIB with GLP-1 RA use:

- Tirzepatide (LY3298176) Periodic Safety Update Report - Reporting Period: November 14, 2022 - May 13, 2023¹⁷
- Dulaglutide (LY2189265) Periodic Safety Update Report - Reporting Period: September 19, 2021 - September 18, 2022¹⁸
- Semaglutide (Ozempic[®], Rybelsus[®] and Wegovy[®]) Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report – Reporting Period: June 1, 2022 - May 31, 2023¹⁹
- Byetta[™] (exenatide twice daily [BID]) and Bydureon[™] (exenatide once weekly [QW] and exenatide once weekly suspension [QWS]) Periodic Benefit-Risk Evaluation Report – Reporting Period: April 1, 2022 - March 31, 2023²⁰
- Lixisenatide Periodic Benefit Risk Evaluation Report – Reporting Period: January 8, 2020 - January 7, 2023²¹
- Liraglutide (Victoza[®] and Saxenda[®]) Periodic Safety Update Report/Periodic Benefit–Risk Evaluation Report – Reporting Period: January 1, 2022 - December 31, 2022²²

2.8 INFORMATION REQUESTS

On July 21, 2023, DDLO conveyed Information Requests (IRs) to the Applicants for their respective GLP-1 RA products. The Agency requested a cumulative review of all cases of depression and suicide/self-injury. The Applicant's analysis should include a review of the published literature, clinical trial data, data from spontaneous reports and reports from studies, as well as a discussion on possible biological plausibility and mechanism of this association. At a minimum, the Agency requested the following information for each case, as available: age, sex, history of suicidality, hospitalization status, current psychosocial stressors, and family history of suicide as well as overall medical history, concomitant medication, time to onset, dechallenge and rechallenge information as appropriate, and reported indications of the suspected products as well as the Applicant's assessment of causality. Where applicable, data should be stratified according to indication for use (T2DM or for off-label use).^{23,24,25,26,27,28,29,30,31}

2.9 DRUG UTILIZATION

The Drug Use Team in DEPI-II used proprietary databases available to the Agency to assess the utilization of GLP-1 RAs to provide context for the signal evaluation. Full database descriptions are available in Appendix C.

Data Sources Used

We used the IQVIA, National Sales Perspectives™ (NSP) database to determine the setting(s) of care where GLP-1 RAs were sold from manufacturers to various U.S. channels of distribution in 2022.

We used the Symphony Health Metys® database to obtain the estimated number of prescriptions dispensed for GLP-1 RAs from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by molecule and product, from January 2013 through September 2023, calendar year.

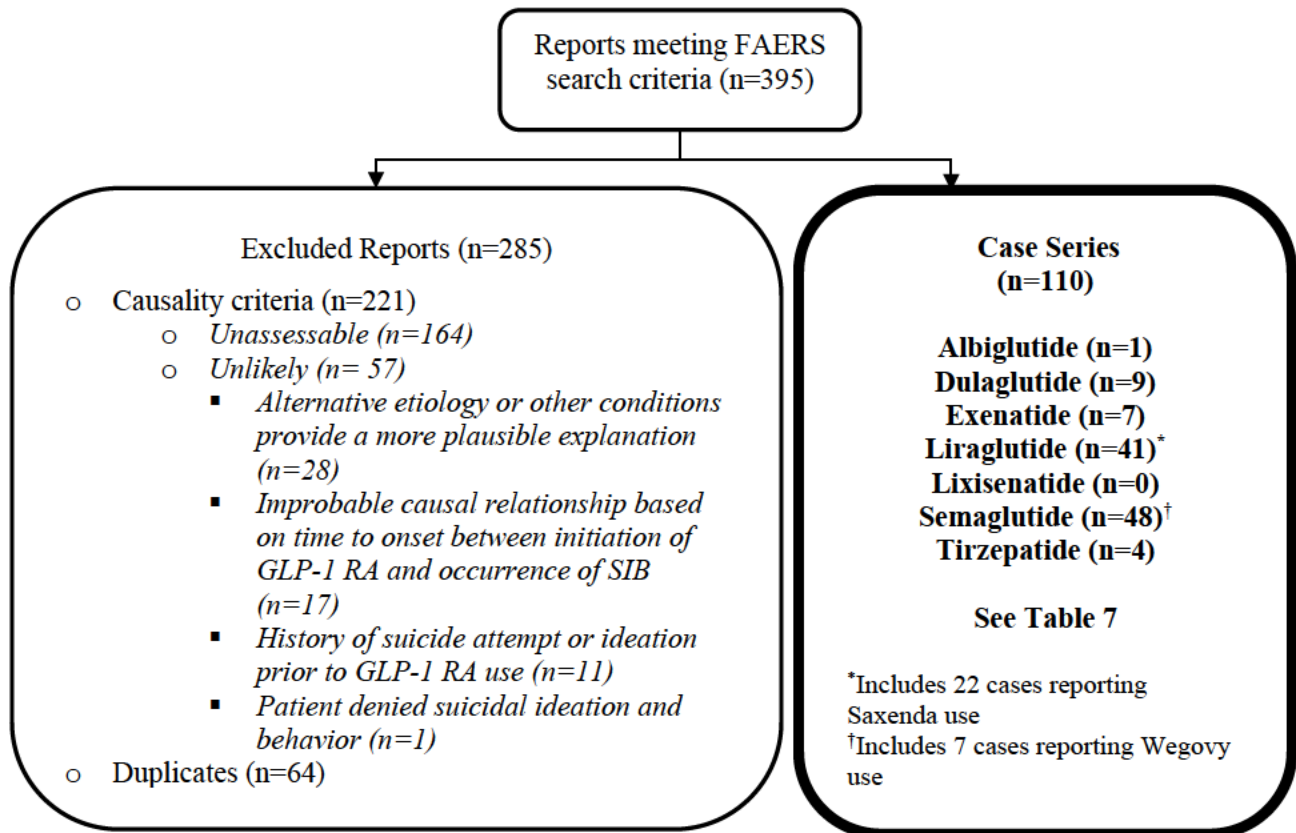
We used the Syneos Health Research & Insights LLC., TreatmentAnswers™ to obtain the national estimates of drug use mentions for diagnoses associated with the use of GLP-1 RAs, stratified by molecule and product, as reported by surveys from U.S. office-based health care providers in 2022. We captured diagnoses data based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis codes. Estimates of drug use mentions are obtained from surveys of a sample of 3,500 office-based health care providers. These survey data provide an insight into the prescriber intent but are not directly linked to dispensed prescriptions. The term “drug uses” refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a “drug use” does not necessarily result in a prescription being generated. Rather, the term indicates that a specific drug was mentioned during an office visit.

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

The FAERS search retrieved 395 reports. After applying the case definition in Section 2.1, the causality criteria in Section 2.2, and accounting for duplicate reports, 110 cases from FAERS were included in the case series of SIB reported with GLP-1 RA use (Figure 1). No additional case reports from the published medical literature were included in our case series.

Figure 1. FAERS Case Selection



Using the literature search strategy listed in Table 5, DPV-I retrieved 63 unique citations from the published medical literature. After DPV-I review of the titles and abstracts, all 63 citations were excluded from further review for the following reasons:

- 52 were review articles that lacked new safety information
- 3 were case reports also identified in FAERS
- 2 were clinical studies that lacked new safety information (1 related to the automatic detection of adverse events and the prediction of drug labeling changes and 1 related to the use of anti-obesity medications in people with mental illness as an adjunct to lifestyle interventions)
- 1 was a case report unrelated to the topic of GLP-1 RA use and suicidality
- 1 was a consensus guideline for recombinant human growth hormone therapy in Prader-Willi syndrome
- 1 was an editorial
- 1 was a book chapter
- 1 was a case report describing a suicide attempt by GLP-1 RA overdose in a patient with a history of previous suicide attempts and lack of a prescribed GLP-1 RA (liraglutide had been prescribed to the patient's partner)
- 1 was a case report that contained insufficient clinical details to make an assessment

Appendix D contains a line listing of the 110 cases in this case series.

Table 7 summarizes the 110 FAERS cases of SIB reported with GLP-1 RA use for this case series. It includes FAERS cases reporting the use of GLP-1 RAs FDA-approved for both glycemic control or chronic weight management.

Table 7. Descriptive Characteristics of Completed Suicide, Suicide Attempt, and Suicidal Ideation with GLP-1 RA Use in this FAERS Case Series, Received by FDA January 1, 2013 to August 27, 2023 (n=110)								
Characteristic	Categories	Dulaglutide (n=9)	Exenatide (n=7)	Liraglutide* (n=41)	Semaglutide† (n=48)	Tirzepatide (n=4)	Albiglutide (n=1)	Total (n=110)
Initial FDA received date or publication date	2013	--	2	--	--	--	--	2
	2014	--	--	2	--	--	--	2
	2015	--	1	7	--	--	--	8
	2016	1	--	5	--	--	1	7
	2017	--	1	4	--	--	--	5
	2018	1	1	6	1	--	--	9
	2019	1	2	2	2	--	--	7
	2020	3	--	3	2	--	--	8
	2021	--	--	2	6	--	--	8
	2022	3	--	3	6	2	--	14
	2023	--	--	7	31	2	--	40
Age (years) (n=77)	Median	71	53	49	45.5	48	--	50
	Mean	78	47	48	46	48	--	50
	Range	52-80	14-67	16-74	23-73	42-54	--	14-80
Sex	Male	4	3	14	19	2	--	42
	Female	4	4	27	28	2	1	66
	NR	1	--	--	1	--	--	2
Country	U.S.	6	5	24	26	4	1	66
	Foreign‡	3	2	17	22	--	--	44
FAERS Case Type	Expedited	9	6	25	33	2	1	76
	Direct	--	1	3	11	2	--	17
	Periodic	--	--	13	4	--	--	17
Serious outcome§	DE	2	--	1	3	--	--	6
	LT	2	1	7	13	2	--	25
	HO	1	1	6	1	--	--	9
	DS	--	--	1	6	--	--	7
	RI	--	--	--	6	--	--	6
	OT	6	5	31	36	3	1	82
Causality	Possible	9	7	41	48	4	1	110
Suicidal ideation or behavior category	Completed suicide	2	--	1	3	--	--	6
	Suicide attempt	1	--	4	1	--	--	6
	Suicidal ideation	6	7	36	44	4	1	98

Table 7. Descriptive Characteristics of Completed Suicide, Suicide Attempt, and Suicidal Ideation with GLP-1 RA Use in this FAERS Case Series, Received by FDA January 1, 2013 to August 27, 2023 (n=110)								
Characteristic	Categories	Dulaglutide (n=9)	Exenatide (n=7)	Liraglutide* (n=41)	Semaglutide† (n=48)	Tirzepatide (n=4)	Albiglutide (n=1)	Total (n=110)
Reason for use (a case may report more than one reason for use)	Diabetes	5	6	11	19	4	--	45
	Metabolic syndrome	--	1	--	--	--	--	1
	Weight management	--	1	15	20	--	--	36
	NR	4	--	17	10	--	1	32
GLP-1 RA Dose	Initiation [¶]	3	5	4	13	2	1	28
	Escalation ^{**}	5	--	12	20	2	--	39
	Maintenance ^{††}	1	1	2	2	--	--	6
	NR	--	1	23	13	--	--	37
Time to onset	0-<7 days	--	2	3	10	1	--	16
	7 days - <1 month	--	1	9	6	3	--	19
	1 - <3 months	3	--	2	7	--	1	13
	3 - <6 months	2	--	3	--	--	--	5
	>6 months	1	--	1	2	--	--	4
	NR	3	4	23	23	--	--	53
Potentially contributory concomitant medications (a case may report more than one)	NR	7	--	34	34	3	1	79
	Benzodiazepine	--	3	2	5	--	--	10
	Antidepressant	1	3	7	16	1	--	28
	Antiepileptic	--	1	3	1	1	--	6
	Lupron	1	--	--	--	--	--	1
	Antipsychotic	--	--	--	2	--	--	2
Psychiatric disorder prior to initiation of GLP-1 RA	Rx stimulant	--	--	1	3	--	--	4
	NR	8	3	33	32	2	1	79
GLP-1 RA Disposition	Psychiatric disorder (details provided below table)	1	4	8	16	2	--	31
	Discontinued ^{‡‡}	7	6	37	37	4	1	92
	Dose decreased	--	--	3	4	--	--	7
	Continued	2	1	--	5	--	--	8
Event outcome	NR	--	--	1	2	--	--	3
	Recovered	6	6	38	38	4	1	93
	Not Recovered ^{‡‡}	3	1	1	7	--	--	12
Rechallenge^{§§}	NR	--	--	2	3	--	--	5
	Positive	--	--	3	2	--	--	5
* Saxenda (n=22), Victoza (n=15), Xultophy (n=3), NR (n=1) † Ozempic (n=32), Rybelsus (n=5), Wegovy (n=7), NR (n=4)								

Table 7. Descriptive Characteristics of Completed Suicide, Suicide Attempt, and Suicidal Ideation with GLP-1 RA Use in this FAERS Case Series, Received by FDA January 1, 2013 to August 27, 2023 (n=110)								
Characteristic	Categories	Dulaglutide (n=9)	Exenatide (n=7)	Liraglutide* (n=41)	Semaglutide† (n=48)	Tirzepatide (n=4)	Albiglutide (n=1)	Total (n=110)
‡ Great Britain (n=15), France (n=4), Japan (n=4), Canada (n=4), Denmark (n=3), Australia (n=2), Poland (n=2), Sweden (n=2), Iceland (n=2), Turkey (n=1), Spain (n=1), Brazil (n=1), Germany (n=1), Netherlands (n=1), Norway (n=1) § For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical event. A case can have more than one serious outcome. Four of the WM cases reported people with BMI 24 kg/m² (n=2) and 25 kg/m² (n=2). Of these, one case reported dyslipidemia, and three cases did not report the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease). The remainder of the cases reporting WM as reason for use, reported BMI ≥ 30 kg/m² or did not report the BMI. ¶ FDA approved initial dosage **Dose between the FDA approved initial and maximum dose ††Maximum FDA approved dose ‡‡Includes 6 cases of completed suicide §§See Rechallenge subsection below for details. Abbreviations: BMI=body mass index, FAERS=FDA Adverse Event Reporting System, GLP-1 RA=glucagon-like peptide-1 receptor agonist, NR=not reported, Rx=prescription, WM=weight management								

DPV-I assessed the 110 cases in our case series as fulfilling WHO-UMC criteria for a possible causal association between GLP-1 RAs and SIB. A majority (n=81) of cases in our case series, reported SIB with a GLP-1 RA other than Saxenda or Wegovy. There were 6 cases reporting completed suicide (semaglutide (not associated with Wegovy use), n=3; dulaglutide, n=2; liraglutide (not associated with Saxenda use), n=1), 6 cases reporting suicide attempt (liraglutide (not associated with Saxenda use), n=4; dulaglutide, n=1; and semaglutide (not associated with Wegovy use), n=1), and 98 cases reporting suicidal ideation. Of the suicidal ideation cases, semaglutide (n=44) and liraglutide (n=36) accounted for the majority of the cases with exenatide, dulaglutide, tirzepatide, and albiglutide accounting for less than 7 cases each.

Completed Suicide

The FAERS search strategy in Table 3 retrieved 18 total reports of completed suicide among patients using GLP-1 RAs (Appendix E). Of the 18 reports, 6 (4 foreign and 2 domestic cases) were included in our case series. All six cases were reported in males, and all were assessed as possible causality. Five of the six cases reported a pre-existing mental health disorder (depression (n=3)) or a serious health condition such as end-stage renal disease (n=1) or proliferative diabetic retinopathy (n=1)). Of the 12 excluded completed suicide reports, 9 were judged unassessable causality because they lacked clinical details necessary to conduct an assessment of the report and 3 were assessed as unlikely causality as they included other conditions that provided more plausible explanations for the suicide (e.g., recent diagnosis of terminal pancreatic cancer, recent and significant occupational stress) or a time to onset from drug initiation to event occurrence that makes a causal relationship improbable (see details in Appendix E). A representative case of completed suicide that was included in our case series is summarized below:

FAERS Case #22518701, 2023, U.S., Direct, Serious Outcome: Death

This case was reported by the patient's sister on behalf of her brother. The reporter stated her brother (age not reported) was diagnosed with new onset "clinical depression" 13 months prior to committing suicide by firearm. Additional relevant past medical history included diabetes, high blood pressure, hypertriglyceridemia, and "hashimoto's disease". It was reported that he "was doing very well" after unspecified treatment for depression. Approximately 3-4 months prior to committing suicide, the patient was prescribed Ozempic (semaglutide) for T2DM by his family medicine physician. The patient was reportedly told to titrate upward at an undisclosed schedule to 1 mg weekly. The patient "had extreme weight-loss of 60 lbs. in a matter of months on Ozempic and no monitoring" according to the report. The patient's sister reported:

"He was on medications he had been on for years. He was not on anything new until Ozempic was prescribed. There were no outward reasons or any warning for this to happen. It seemingly was a spur of the moment decision he made. His life was very good. He was getting married in the fall – he said he was the happiest he had ever been. He had a great job, he was financially secure and had 4 beautiful children, and his second grandchild on the way. He had a very loving and close immediately and extended family. My family and I feel [Ozempic] could have caused the suicide or significantly contributed."

Reviewer Comments: This case, also reported by news media, was complicated by a history of "clinical depression."^{32,33,34} The patient's sister reported the patient was doing well after unspecified mental health treatment; however, the sister's recall may have been biased in

assigning causality to semaglutide in the wake of the patient's death. Depression is often a chronic condition with fluctuating symptom severity and episodic course, including periods of recovery, remission, and relapse, and it is possible the patient did not report ongoing or intermittent psychiatric symptoms to his sister. Although the report does not specify which "medications he had been on for years" it is implied that the patient was on antidepressant medications before and during treatment with semaglutide, and therefore it is difficult to determine semaglutide's contribution (or lack of) to this case with Preferred Term (PT) Completed suicide. A BOXED WARNING for SIB appears in antidepressant labeling.^{35,36} Additionally, the status of the patient's Hashimoto's thyroiditis was not reported. We note psychiatric manifestations, including depression, have been reported in association with Hashimoto's thyroiditis.³⁷

Suicide Attempt

Six cases (four males and two females) reported a suicide attempt. Three of the six cases reported a history of depression or a concomitant medication indicated for the treatment of depression prior to the initiation of the GLP-1 RA. All six cases reported a positive dechallenge with subsequent improvement after discontinuation of the GLP-1 RA. The following summary is a best representative case based on male sex and a positive dechallenge:

FAERS Case #15880466, 2019, U.S., Expedited, Manufacturer Control #US-NOVOPROD-643097, Serious Outcome: Other

A pharmacist reported a 36-year-old male was treated with Ozempic (semaglutide) for the treatment of T2DM. It was reported that the patient had, "no medical history of depression or thoughts of self-harm and no relevant family history." Concomitant medications included metformin, lisinopril, insulin glargine, and Bydureon (exenatide). Within "a few days" of starting semaglutide, the patient experienced suicidal thoughts and was depressed. The patient expressed feelings of "profound sadness and thoughts of self-harm on his blog." A "behaviorist... determined that the patient was not in imminent danger of harming himself." On an unreported date, thought to be within the same month, the patient took one dose of exenatide "in order to try to harm himself." Semaglutide was discontinued and the patient recovered from the suicidal thoughts and depression "within a few weeks."

Reviewer Comments: This case was assessed as possible causality based on the onset of SIB after initiation of semaglutide and subsequent recovery after discontinuation in the absence of prior history of self-harm, depression, or relevant family history. However, assessment of this case was limited by lack of information regarding other potential risk factors for suicide and any psychiatric treatment that could have facilitated recovery. Of note, it was not reported if the patient was taking exenatide concurrently with semaglutide; use of two GLP-1 RA simultaneously is not recommended.

Suicidal Ideation

Suicidal ideation was reported in 98 cases in our case series. Twenty-nine of the 98 cases specified use of Saxenda or Wegovy, which are labeled for SIB. The remaining 69 cases did not specify the trade name of the GLP-1 RA. Many cases contained incomplete information such as past medical or psychiatric history, concomitant medications, time to onset, disposition, and outcome. The narrative case summary below is the best representative case because it contains

information regarding the patient's medical history, concomitant medications, and GLP-1 RA disposition.

FAERS Case #19932827, 2021, Israel, Direct, Serious Outcomes: Disability, Life-threatening, Other, Required Intervention

A 39-year-old male dermatologist with a history of affective disorder, dyslipidemia, and gastroesophageal reflux disease self-reported that he initiated Ozempic (semaglutide) once weekly at an unknown dose for weight loss. Concomitant medications included escitalopram, reboxetine, clonazepam, famotidine, lansoprazole, finasteride, and simvastatin. "About two months" after initiation of semaglutide, he "began suffering from depressive symptoms." He had previously been diagnosed with an affective disorder but was "stable" for more than 16 years "under the same regimen of drugs." He reported, "Since diagnosis this was the first time I've ever suffered extremely bad symptoms up to serious suicidal thoughts." The symptoms were described as "devastating." He reported, "there were no external circumstances that could explain this unexpected aggravation." Semaglutide was discontinued. The outcome was not reported.

Reviewer Comments: Affective disorders include a broad range of conditions ranging from seasonal affective disorder to bipolar disorder.³⁸ The severity of the affective disorder in this physician patient was not reported, but he did report a stable multi-drug medication regimen for over a decade. Ozempic was being used off-label for weight loss. Suicidal ideation was reported about two months after initiation of semaglutide. Although suicidal ideation in this case is assessed as having a possible causal association with semaglutide, the above confounding factors including pre-existing affective disorder and self-prescribing are noteworthy.

Use of glycemic control products for weight management

Use of glycemic control products for weight management was reported in 17 cases (Ozempic, n=11; Rybelsus, n=2; Victoza, n=3; exenatide, n=1). Four cases reported more than one reason for use (e.g., diabetes and "uncontrolled obesity"). Over half (n=10) of the cases were initially reported to the FDA in 2023.

Psychiatric Disorder Prior to Initiation of GLP-1 RA

Thirty-one cases reported a psychiatric mental health history that preceded initiation of GLP-1 RA use. A case may have reported more than one psychiatric disorder. Depression was most commonly reported (n=16, including a case reporting major clinical depression and a case of severe depressive complaints in a 14-year-old with a prior psychiatric hospitalization). Other mental health disorders reported included anxiety (n=8), bipolar disorder (n=3), attention deficit hyperactivity disorder (n=1), autism (n=1), panic disorder (n=1), mania (n=1), affective disorder (n=1), and post-traumatic stress disorder (n=1). An additional seven cases reported the concomitant use of psychiatric medications, but lacked accompanying diagnosis in the case narrative, leading to an inferred psychiatric diagnosis. Two direct reports from FAERS reported patients who described suicidal ideation and feeling like their psychiatric medications were not working as well while receiving a GLP-1 RA. One case (FAERS Case #22625748) reported a 73-year-old female with history of "major clinical depression" and generalized anxiety who "plunged into severe depression and wanted to kill myself" after initiating Ozempic. The patient was also receiving duloxetine and alprazolam, the latter of which contains a Warning and Precaution for the potential to worsen depression and for SIB in the context of abuse and/or

misuse. The second case (FAERS Case #15761398) reported a male with a history of bipolar disorder experienced suicidal ideation 2.5 months after initiating liraglutide and reported his unnamed “meds for my bipolar and depression” were “depleted” and therefore caused [the patient] to become very suicidal. The outcome was not reported in either case.

Dosing Trends

No trends regarding dosage regimens were identified. Specifically, regarding the six completed suicide cases: two cases were on the FDA approved initiation dose at the time of the suicide, two cases reported taking the dulaglutide escalation dose, one reported taking the maximum Rybelsus (semaglutide) dose, and one case did not report the dose.

GLP-1 RA Disposition and Outcome

Overall, 99 cases reported the GLP-1 RA was discontinued (n=92) or the dose was decreased (n=7) following the occurrence of suicidal ideation or attempted suicide. Eight cases reported the patient continued using the GLP-1 RA after the occurrence of suicidal ideation. Five of the eight cases reported the patients had not recovered from the suicidal ideation and one case did not report the outcome. One case reported the patient recovered from the suicidal ideation while continuing to take the GLP-1 RA. One patient with a history of anxiety (FAERS Case # 22255819) reported that a “couple of hours” after the dose of semaglutide, she “felt extremely anxious and then started having suicidal thoughts”; the feelings subsided prior to the next dose and re-occurred after the next dose. Although suicidal ideation appears to have occurred in relationship to GLP-1 RA exposure, the immediate onset of anxiety and psychiatric symptoms after semaglutide injection suggests that the exacerbation of psychiatric symptoms may be more related to the patient's underlying psychiatric condition or a placebo-like effect with the act of injection itself.

Saxenda and Wegovy

Twenty-nine cases of SIB that specified Saxenda or Wegovy were included in our case series. All 29 cases reported suicidal ideation. Of these, 25 were female. No completed suicides or suicide attempts were reported. All 29 cases reported the product was discontinued or the dose was decreased with a subsequent recovery. The WHO-UMC causality was judged as possible for all 29 cases. Three of six Saxenda and four of five Wegovy cases reported in 2023 were reported following EMA's July 11, 2023, announcement they were investigating this potential safety issue and subsequent increased media coverage. (Zepbound is the tirzepatide product for chronic weight management and was approved November, 8, 2023, which is after the date of our FAERS search)

Rechallenge

Two Ozempic (semaglutide) cases reported a positive rechallenge (FAERS Case #'s 22803675 and 22821276). Both cases were directly reported to the FDA after July 11, 2023. FAERS Case #22803675 specified, “I heard a story on the news, and I heard Ozempic can cause these problems ... I quit taking my Ozempic for one month and all of the suicidal thoughts and self-harm behaviors went away. Then, as an experiment, I took my weekly prescribed dose last Thursday and had suicidal thoughts and self-harm behaviors return on Saturday until yesterday.” The medical history included bipolar disorder, panic disorder, and generalized anxiety disorder.

FAERS Case #22821276 specified, “I took several weeks off and went back on a 0.25mg dose yesterday, and the thoughts came back.”

Three Saxenda (liraglutide) cases reported a positive rechallenge. These were reported prior to 2023. FAERS Case #14402770 specified “medical history included depression,” and has insufficient information to determine the time interval between Saxenda discontinuation to reinitiation. FAERS Case #11624991 contains vague wording, but suggests the patient recovered from depression after the Saxenda 1.8 mg daily dose was discontinued for 2 days, and that the depression did not recur after reinitiation of Saxenda 0.6 mg daily. FAERS Case #19014613 stated, “patient discontinued Saxenda and after 1 week being off, her moral (mood) returned. But [approximately one week later], patient re-started Saxenda again and felt psychological distress returned.” Additional events after this are not reported. We cannot exclude the possibility that fluctuating or episodic symptoms for these cases may have occurred within the course of pre-existing mental illness, and not necessarily related to exposure or discontinuation of GLP-1 RA products.

3.2 DATA MINING

Table 8 summarizes the results of the data mining search using Empirica Signal for SIB reported with GLP-1 RA use.

	Product active ingredients (PAI)	Preferred Term (PT)	N	EB05	EBGM	EB95
1	Semaglutide	Suicidal ideation	122	1.576	1.833	2.122
2	Semaglutide	Suicidal behaviour	4	0.48	1.128	2.332
3	Liraglutide	Suicidal ideation	80	0.42	0.506	0.606
4	Semaglutide	Suicide attempt	17	0.292	0.441	0.644
5	Liraglutide	Suicide attempt	29	0.245	0.335	0.449
6	Semaglutide	Completed suicide	12	0.145	0.237	0.371
7	Liraglutide	Suicidal behaviour	3	0.14	0.374	0.848
8	Dulaglutide	Suicidal ideation	35	0.137	0.182	0.238
9	Tirzepatide	Suicidal ideation	13	0.134	0.214	0.329
10	Dulaglutide	Suicide attempt	18	0.122	0.181	0.262
11	Exenatide	Suicidal ideation	58	0.118	0.147	0.181
12	Liraglutide	Completed suicide	21	0.101	0.147	0.207
13	Dulaglutide	Suicidal behaviour	2	0.073	0.239	0.623
14	Exenatide	Suicide attempt	16	0.044	0.068	0.1
15	Albiglutide	Suicidal ideation	3	0.038	0.1	0.227

Table 8. Data Mining Results Using Empirica Signal for Suicidal Ideation and Behaviors Reported With GLP-1 RA Use, Sorted by Decreasing EB05						
	Product active ingredients (PAI)	Preferred Term (PT)	N	EB05	EBGM	EB95
16	Exenatide	Suicidal behaviour	1	0.015	0.075	0.255
17	Dulaglutide	Completed suicide	3	0.01	0.028	0.063
18	Exenatide	Completed suicide	5	0.008	0.018	0.034

A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background “expected.” The data mining search strategy described in Table 4 resulted in no GLP-1 RA with an EB05 of ≥ 2 for the PTs *Completed Suicide*, *Suicide attempt*, *Suicidal ideation*, or *Suicidal behaviour*.

3.3 PERIODIC SAFETY REPORTS

The PTs *Completed suicide*, *Suicide attempt*, *Suicidal ideation* or *Suicidal behaviour* were noted in postmarketing sources by the Applicants of dulaglutide, tirzepatide, semaglutide (subcutaneous and oral for treatment of T2DM), and exenatide (Table 9).^{17,18,19,20} None of the PTs were identified from postmarketing sources for lixisenatide.²¹ The adverse events were not considered adverse events of interest by the Applicants of the products. (The one applicable liraglutide report is discussed after Table 9)

Table 9. Interval and Cumulative Summary Tabulation of Suicidal Ideation and Behaviors from Postmarketing Sources Reported During the Most Recent Periodic Safety Report for GLP-1 RAs								
Preferred Term	Spontaneous (Including Regulatory Authority and Literature)				Total Spontaneous		Postmarketing Study	
	Serious		Non-Serious		Total		Serious	
	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
Dulaglutide								
<i>Depression Suicidal</i>	1	2	0	0	1	2	0	1
<i>Suicidal behaviour</i>	0	1	0	0	0	1	0	0
<i>Suicidal ideation</i>	5	21	0	0	5	21	1	1
<i>Suicide attempt</i>	4	13	0	0	4	13	0	0
<i>Completed Suicide</i>	0	2	0	0	0	2	0	0
Tirzepatide								
<i>Suicidal ideation</i>	2	4	0	0	2	4	0	0
Semaglutide subcutaneous for T2DM								
<i>Suicidal ideation</i>	19	38	0	0	--	38	2	4

Table 9. Interval and Cumulative Summary Tabulation of Suicidal Ideation and Behaviors from Postmarketing Sources Reported During the Most Recent Periodic Safety Report for GLP-1 RAs								
Preferred Term	Spontaneous (Including Regulatory Authority and Literature)				Total Spontaneous		Postmarketing Study	
	Serious		Non-Serious		Total		Serious	
	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
<i>Suicide attempt</i>	2	6	0	0	--	6	0	0
Semaglutide oral for T2DM								
<i>Suicidal ideation</i>	7	9	0	0	--	9	0	0
<i>Suicide attempt</i>	1	1	0	0	--	1	0	0
Exenatide								
<i>Completed suicide</i>	0	4	0	0	--	4	0	0
<i>Suicidal behaviour</i>	0	1	0	0	--	1	0	0
<i>Suicidal ideation</i>	1	37	0	9	--	46	0	1
<i>Suicidal attempt</i>	0	15	0	0	--	15	0	0
Abbreviations: GLP-1 RA= glucagon-like peptide-1 receptor agonist, T2DM=type 2 diabetes mellitus								

No causality assessments of these events were reported by the Applicants in their submissions, except for the Applicant of exenatide. The Applicant of exenatide stated, one serious report of *Suicidal ideation* was assessed as related to the drug during the interval reporting period and 37 serious reports were assessed as related to the event, cumulatively. There were no reports of *Completed suicide* or *Suicide attempt* during the reporting interval; however, cumulatively, there have been 4 serious reports of completed suicide and 15 serious reports of suicide attempt assessed by the Applicant as related to exenatide.²⁰

Among the six serious reports of misuse and abuse of liraglutide for T2DM during the reporting period, one report of suicide attempt was identified. The Applicant “inferred” a psychiatric illness based on concomitant medication of flunitrazepam and etizolam as significant risk factors for suicide. The Applicant of liraglutide stated, “The reporting pattern for misuse and abuse, including suicidal attempt, with liraglutide in T2D and liraglutide in [weight management] during the reporting period remains in line with the cumulative experience. No specific safety concerns were identified from the review of these cases.” The Applicant stated they will continue to monitor misuse and abuse, including suicidal attempt, as a safety area of interest through routine surveillance.²²

3.4 APPLICANT RESPONSES TO FDA INFORMATION REQUESTS

Postmarket information contained within the Applicant’s IR responses are summarized below.

Semaglutide and Liraglutide³⁹

The Applicant searched their safety database for relevant reports of suicidal ideation and self-injury ideation reported with Victoza, Saxenda, Xultophy, Ozempic, Rybelsus, and Wegovy from worldwide postmarketing sources through June 30, 2023. A total of 379 events in 335

reports (Victoza, n=99; Xultophy, n=10; Ozempic, n=102; Rybelsus, n=12; Wegovy, n=17; Saxenda, n=95 (according to the Applicant, a report may have contained multiple suspect products and were counted once)) were identified. According to the Applicant, most reports contained limited information (e.g., patient and family medical history of mental disorders, social history, psychosocial circumstances, concomitant medication, diagnostic evaluations, etc.) therefore precluding a complete assessment of these reports. The most frequently reported PTs were *Suicidal ideation* (56%), *Intentional overdose* (17%), and *Suicide attempt* (13%). Most were adults and female.

A history of psychiatric disorder was reported in 63 reports, most frequently depression (81%), suicidal ideation (12%), and suicide attempt (11%). Dechallenge information was available for 68 reports (58%) and of these, 63 reports were described as ‘recovered/ recovering’ after GLP-1 RA discontinuation. Five reports described a negative dechallenge.

Overall, the Applicant concluded, “there is insufficient information in the majority of cases to support a causal relationship between GLP-1 products and suicidal ideation/self-injury ideation from the available post-marketing data.” The Applicant stated, “the benefit-risk balance...remains unchanged.” The Applicant plans no updates to the product labels or risk management plans. Monitoring for reports of adverse drug reactions, including suicide and suicidal ideation, will continue through routine pharmacovigilance.

Dulaglutide⁴⁰

The Applicant performed a cumulative review of the published literature, clinical trial data, postmarketing data, and reports from studies, for all reports of depression and suicide/self-injury for Trulicity (dulaglutide). The Applicant’s search strategy included Depression (excluding suicide and self-injury) SMQ (narrow scope) and suicide/self-injury SMQ (narrow scope). There were 640 reports identified. Another search using Self-harm FDA Medical Query (FMQ) and Depression (FMQ narrow scope) resulted in 582 reports, all of which were captured in the previous search. Information written in response to a notification from the PRAC of a new signal of suicidal ideation and self-injurious ideation for GLP-1 RAs as a class received on July 7, 2023, was also included.

The 640 postmarketing reports retrieved by the Applicant’s search strategy contained 675 events. There were 581 reports (containing 594 events) the Applicant characterized as depression and 69 reports (containing 75 events) of suicide/self-injury based on their SMQ PTs, and the Applicant notes there was some overlap between the two categories.

Almost three-quarters (71%) of the evaluable reports categorized as depression were confounded (e.g., history of depression/concomitant antidepressant use, other psychiatric disorders, or chronic pain) according to the Applicant. “Five percent of the [depression] cases were serious; there was 1 fatal case.” Approximately one-third (30%) of the evaluable reports stated a time to onset and of those, 71% reported a temporal relationship within 30 days of initiation of the GLP-1 RA. The Applicant stated, 79% of the depressive events were associated with gastrointestinal events and fatigue (both are labeled events in the USPI). There were 40 reports containing information of a positive dechallenge. The Applicant stated, “Generally, these cases lacked detailed information to determine whether dulaglutide was discontinued due to the depression

event, whether the resolution of the event was a consequence of dulaglutide discontinuation, or whether the recovery was confounded by other factors such as clinical interventions or due to the cyclical nature of depression.” One positive rechallenge was reported, but the Applicant stated the report did not include the patient’s medical history or risk factors for depression, temporal relationship, rechallenge information, and the recurrence of depression.

With respect to the suicidal/self-injury reports, the Applicant stated, “The majority 83% were serious ... 78.9% reported confounding risks factors or psychosocial stressors. The time to onset in five of the seven events in evaluable cases occurred within six months of treatment initiation ... There were no positive rechallenges ... post-marketing cases did not provide sufficient evidence of a causal association between dulaglutide therapy, depression, and suicidal/self-injurious ideation.”

Tirzepatide⁴¹

The Applicant’s global safety database containing serious and nonserious adverse events reported from postmarketing experience, including spontaneous reports, literature reports, regulatory authority reports, and reports from noninterventional studies was searched cumulatively through July 24, 2023, for both postmarketing and clinical trial reports. The Applicant identified five suicidal ideation/self-injury postmarketing reports, in which five adverse events were reported. All were spontaneous reports and four of the five were reported by a non-healthcare professional. Two reports were reported in adults, one in an elderly patient, and two reports did not report the age. Three reports were of tirzepatide for the treatment of diabetes and two did not report the reason for use. The Applicant assessed two reports as probable according to WHO causality assessment. The two reports assessed as probable, were also included among the depression reports assessed as probable (Manufacturer Control #’s US202209005617 (corresponds to FAERS Case #21360692 included in DPV-I’s case series, which DPV-I assessed as possible) and US202211002493 (corresponds to FAERS Case # 21597702 included in DPV-I’s case series, which DPV-I assessed as possible)). The Applicant concluded, “the limited information provided in the cases, unpredictable nature of the underlying disease, and the limited number of cases do not provide sufficient evidence of a causal association.” The Applicant states, they will “continue to carefully monitor events of suicidal ideation, self-injurious ideation, and depression through routine surveillance.”

Lixisenatide

The Applicant searched their safety database for the SMQ “Depression and suicide/self-injury (Narrow)” through June 30, 2023, to identify reports of insulin glargine/lixisenatide (fixed ratio combination (FRC)) and lixisenatide.

There were 82 reports identified for Lixisenatide FRC. Of the 82 reports, 73 were from clinical trials and 9 were “unsolicited” from consumers and healthcare professionals. Of the 75 reports included in the Applicant’s analysis, 3 reports contained 4 SIB events (*Suicide attempt* (n=2), *Suicidal ideation* (n=1), and *Suicidal behavior* (n=1)). Two SIB reports also reported concurrent depression and one report contained a suicide attempt in a patient with a history of depression and two previous suicide attempts in a patient with “underlying stress from multiple recent socio-familial stressors and reported feeling of excessive responsibility. Lixisenatide FRC was continued, and the event resolved.” The Applicant concluded, “Overall, in the view of

underlying risk factors, confounders, and the absence of well-documented cases that provide compelling evidence for a drug-event association, the cumulative review of cases...did not provide sufficient evidence to suggest a causal association between FRC and suicidal ideation and self-injurious ideation.”⁴²

For Lixisenatide, the Applicant identified 41 reports with 43 events of interest. Of the 41 reports, 28 were solicited reports (19 from clinical trials and 9 from literature sources) and 13 were unsolicited reports (9 from consumers and 4 from healthcare professionals). Four reports were excluded from further analysis as events in these reports were not reported in the context of the event of interest. For indications other than T2DM, there were no reported events related to suicidal ideation and self-injurious ideation. Thirty-three reports had indication of T2DM/DM for lixisenatide use. Of these, 8 reports had 9 events related to suicide (Completed suicide, n=3; Intentional overdose, n=1; Suicidal ideation, n=2; Suicide attempt, n=2; Depression, n=1) and 25 reports described events related to depression. Of the eight SIB reports, the Applicant assessed the reports as “compatible chronology” (n=3), unlikely causality (n=4), and “unclassified” causality (n=1). Among the reports assessed as “compatible chronology,” two were confounded (e.g., underlying history of depression, schizophrenia, post-traumatic stress disorder) and one contained limited information. Of the three completed suicides, one was reported as a patient with multiple cardiac comorbidities enrolled in a lixisenatide clinical trial who committed rail suicide 28 days after starting the study drug (lixisenatide or placebo not specified). The other two completed suicides were classified as unlikely causality and described one patient with a history of alcoholism who recently had relapsed with subsequent diagnosis of major depression and had recently divorced his wife and a second report in a patient with metastatic pancreatic carcinoma who requested and died from “assisted suicide.”⁴³

The Applicant concluded for both lixisenatide FRC and lixisenatide, the “cumulative weighted evidence is not sufficient to support a causal association between lixisenatide and suicidal ideation and self-injurious ideation.”^{42,43}

Exenatide⁴⁴

A search of the Applicant’s Global Patient Safety Database for depression, suicidal ideation, and suicidal behavior until July 21, 2023, noted “outcome of the events of interest were reported as fatal (6), resolved (218), resolved with sequelae (6), resolving at the time of reporting (68), not resolved (266) and unknown/ not reported (486).” The most commonly reported PTs with $n \geq 20$ included *Depression* (n=553), *Depressed mood* (n=259), *Intentional overdose* (n=56), *Suicidal ideation* (n=54), and *Suicide attempt* (n=23).

In 51 of the 56 intentional overdose reports, the intentional overdose was administered by the patients to control high blood sugar and not in the context of committing suicide or as a result of suicidal ideation. Therefore, these 51 reports were excluded from further discussion. In the remaining 5 intentional overdose reports, the Applicant stated the intention was to attempt suicide, although additional details provided by the Applicant do not significantly add to our understanding of the suicide attempt.

Of 956 reports of Depression/Suicidal or Self-injury Ideation, 558 were assessed by the Applicant as reporting insufficient information for clinical evaluation. There were 198 reports

assessed by the Applicant as having an alternative explanation, concurrent illness, or social/psychological stressor as a reason for the depression or suicidal ideation events; 48 reports assessed as having a listed co-suspect/concomitant medication “that could explain the depression”; and 35 reports assessed as unlikely causality. There were 109 reports with a positive dechallenge, but that “had either insufficient information or an alternative explanation that could explain the event”; 2 reports were of a positive dechallenge and positive rechallenge for suicidal ideation; and 6 reports were of a positive dechallenge and positive rechallenge for depression not associated with suicidal ideation.

The Applicant identified 88 suicide/self-injury events among the 956 reports. Of these, there were five reports of intentional overdose with the intention of attempting suicide (see above). Of the remaining 83 reports, the majority were assessed by the Applicant as containing limited information for clinical evaluation. Ten reports were assessed by the Applicant as unlikely causality for the events of suicidal-ideation or self-injury. There was one report of a positive dechallenge and positive rechallenge with the event of suicidal ideation (Manufacturer Control #2009BM11644) and one report (Manufacturer Control #2008BM05248) had a positive dechallenge and positive rechallenge for depression (worsening) with associated event of suicidal ideation (not databased in error), and both were reported prior to the search dates of the DPV-I FAERS search. Six completed suicides were reported. Of these, 5 reports contained insufficient information for a complete assessment according to the Applicant. In the remaining one report, the patient had a history of depression that worsened 6 months after starting exenatide and the patient committed suicide 12 days after the last dose of exenatide. In all six reports, causality for exenatide was reported as not related by the reporters.

The Applicant concluded, “there is insufficient evidence to suggest a causal association between suicidal ideation and exenatide use.” The Applicant stated, “no potential amendment to the product information and/or the risk management plan is warranted at this time.” Further, “the current pharmacovigilance activities are considered adequate”, and suicidal ideation with exenatide will be “closely monitored.”

3.5 DEPI LITERATURE REVIEW^{a,b}

DEPI’s search yielded 9 articles: 1 set of guidelines, 2 review articles, 3 case reports of intentional overdose attempts, 1 randomized controlled trial focused on weight loss reporting a single case of suicide, and 2 observational studies on the association between GLP-1 RA use and

^a This literature search was conducted prior to a publication by Wang and associates entitled “Association of semaglutide with risk of suicidal ideation in a real-world cohort.” This study is a large-scale observational study of the association of GLP-1RA exposure and risk of suicidal ideation within the overweight/obese population. Please refer to DEPI’s review (uploaded March 14, 2024, DARRTS Reference ID: 5346913) for discussion on insufficiency of that study because of methodological limitations.

^b The European Medicines Agency (EMA) released a signal assessment report on suicidal ideation and self-injurious ideation with GLP-1 RA (exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide) on April 11th. Twelve additional studies were reviewed in the report. Eleven studies focused on worsening depression or psychiatric illness and did not mention suicidal ideation, attempt, or intentional self-harm. One study was an abstract from a conference whose abstract could not be found on PubMed, Embase, or google. For this reason, these studies were deemed out of scope and not added to the review. (European Medicine Agency Pharmacovigilance Risk Assessment Committee (PRAC). Signal assessment report on suicidal ideation and self-injurious ideation with GLP-1 RA (exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide). EPITT no: 19946. 11 April 2024.)

suicide or suicidal ideation. A summary of the two observational studies and their main findings pertaining to suicide and suicidal ideation can be found below:

O’Neil et al. 2016 (Pooled Analysis of 5 Randomized Clinical Trials [RCTs])⁴⁵

O’Neil et al. report on a post-hoc pooled analysis of individual-patient data (IPD) from 5 RCTs (4 phase 3 trials; 1 phase 2 trial) of liraglutide (N=3,384 patients; 72.4% female; mean age, 46.6 years) vs. placebo (N=1,941 patients; 70.8% female; mean age, 46.6 years). All but one trial was conducted between June 2011 and June 2013. The SCALE^c Maintenance trial was originally conducted between October 2008 and September 2010. A comparison of trial characteristics as reported by authors is presented in Appendix F. At baseline, 9.1% of patients in the liraglutide group and 10.6% of patients in the placebo group had a self-reported history of depression, and 7.2% vs 7.8% had a self-reported history of anxiety. None had a history of suicide attempt or self-injury. Suicidal behavior was defined as: (1) death by suicide, (2) suicidal attempts where there was intention to die, or (3) nonfatal, self-injurious acts committed without intent to die, and was measured by means of the validated C-SSRS scale^d.

Across the five trials, the rate of adverse events of suicidal ideation or behavior were higher in the liraglutide group (9/3,384, i.e., 0.3% or 2 events/1000 person-years vs. 2/1,941, i.e., 0.1% or 1 event/1000 person-years). No quantitative metrics through formal comparative analysis on the relative (risk ratio, odds ratio) or absolute (risk difference) risk scales were reported. Based on Table S2 of the O’Neil paper, all events, except for one, in either arm occurred in one trial, i.e., the SCALE Obesity and Prediabetes trial. In this trial, 2,487 patients were randomized to liraglutide, and 1,244 patients were randomized to placebo. Table 10 shows the number of events by arm in each of the five trials.

Table 10. Number of suicidality events in the 5 trials pooled by O’Neil et al.				
Trial	Liraglutide Arm		Placebo Arm	
	Patients randomized	Patients with events	Patients randomized	Patients with events
Phase 2 dose finding trial NCT00480909	93	0	98	0
SCALE Obesity and Prediabetes NCT01272219	2487	8	1244	2
SCALE Diabetes NCT01272232	423	0	212	0
SCALE Sleep Apnoea	180	1	179	0

^c SCALE, Satiety and Clinical Adiposity—Liraglutide Evidence, is the phase 3 clinical study of liraglutide.

^d C-SSRS, Columbia-Suicide Severity Rating Scale, a questionnaire popularly use for severity and immediacy assessment of suicide risk.

NCT01557166				
SCALE Maintenance NCT00781937	212	0	210	0
Total	3384	9	1941	2

Gamble et al. 2018 (Observational Study)⁴⁶

A detailed description of the observational study is provided in the Appendix Table F. Briefly, this retrospective observational study used U.K. national death register data, primary care clinical records, and hospitalization records from 2001 to 2014 to capture hospitalizations and deaths resulting from self-harm among individuals initiating incretin-based therapies (i.e., GLP-1 RAs and dipeptidyl peptidase IV inhibitors [DPP4i]) and sulfonylureas (SU). The study sample included all patients over 18 years of age with a minimum of 12 months of follow-up in the U.K.-based Clinical Practice Research Datalink (CPRD) database and that received a new diagnosis for T2DM or a new prescription for any glucose-lowering therapy. A 365-day washout period defined new T2DM diagnoses or new glucose-lowering therapy users. Patients with a history of depression, self-harm, anxiety and other serious psychiatric conditions in the year prior to a patient's cohort entry date were excluded. No definition for GLP-1 RA exposure was provided. The study used an active comparator design and employed high dimensional propensity score to improve baseline comparability. Primary outcome was a composite measure of new-onset depression or self-harm including suicide and suicidal ideation. Both outcomes were identified from diagnostic ICD-10 codes (International Classification of Diseases 10th Revision).

The study included 502 GLP-1 RA users and 16,409 SU comparators. Incident cases of depression or self-harm were identified among 10 GLP-1 RA users and 183 SU comparators. The incidence rate of depression or self-harm was not significantly higher for GLP-1 RA users compared with SU users (18.2 vs 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72 to 2.58; adjusted HR 1.25, 95% CI 0.63 to 2.50). The number of self-harm events within the composite outcome of depression and self-harm was too small to be reported.

3.6 DRUG UTILIZATION

3.6.1 Settings of Care

Based on the manufacturer sales distribution data in 2022^e, approximately 80%, 11%, and 9% of total packages^f of GLP-1 RAs were sold to U.S. outpatient retail pharmacies^g, mail-order/specialty pharmacies, and non-retail^h settings (mostly clinics), respectively. Therefore, we

^e Source: IQVIA™ National Sales Perspectives (NSP). 2022. Extracted August 2023. File: IQVIA NSP 2023-5482 GLP-1 RAs 08-21-2023 .xlsx

^f Packages include auto-injectors, pens, and bottles.

^g Retail settings include chain drug stores, independent drug stores, mass merchandisers, food stores, and mail-order services.

^h Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

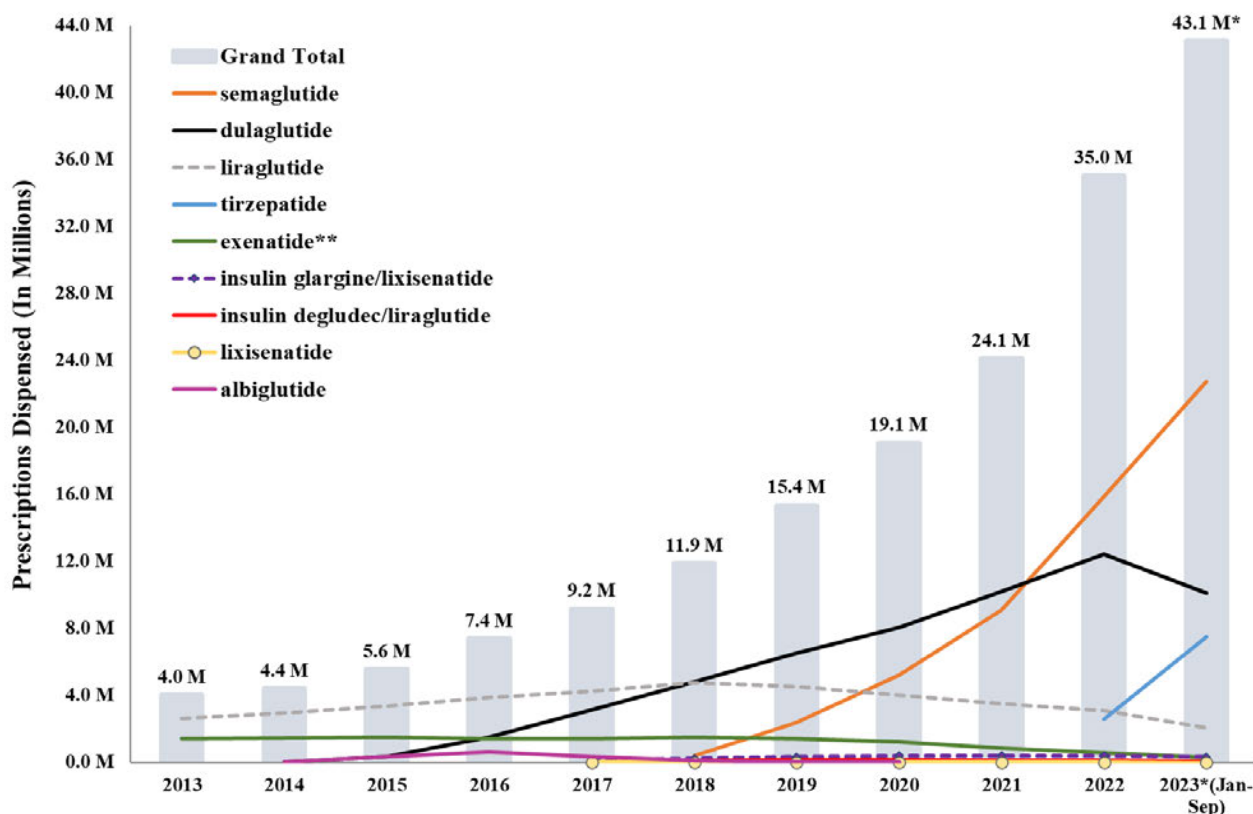
focused our analyses on utilization from U.S. outpatient retail and mail-order/specialty pharmacies.

3.6.2 U.S. Outpatient Retail and Mail-Order/Specialty Prescription Utilization

Figure 2 below and Table G1 in Appendix G provide the annual estimates of prescriptions dispensed for GLP-1 RAs from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by molecule and product, from January 2013 through September 2023, calendar year. An estimated total of 35 million GLP-1 RAs prescriptions were dispensed from U.S. outpatient retail and mail-order/specialty pharmacies in 2022. Of these total 35 million GLP-1 RAs dispensed prescriptions in 2022, semaglutide accounted for the highest proportion at approximately 45% (15.9 million prescriptions), followed by dulaglutide (35%, 12.4 million prescriptions), liraglutide (9%, 3.1 million prescriptions), tirzepatide (7%, 2.6 million prescriptions), exenatide (2%, 0.6 million prescriptions), insulin glargine/lixisenatide (1%, 0.4 million prescriptions), insulin degludec/liraglutide (<1%, 97,000 prescriptions), and lixisenatide (<1%, 1,600 prescriptions). No utilization data were captured for albiglutide (discontinued in July 2017) in 2022.⁴⁷

The estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022. Semaglutide dispensed prescriptions increased from 0.4 million prescriptions in 2018 to 15.9 million prescriptions in 2022. Similarly, dulaglutide dispensed prescriptions increased from 4,000 prescriptions in 2014 to 12.4 million prescriptions in 2022. Liraglutide dispensed prescriptions increased from 2.6 million prescriptions in 2013 to 4.8 million prescriptions in 2018, then decreased to 3.1 million prescriptions in 2022. Exenatide dispensed prescriptions remained relatively steady from 2013 through 2019 (1.4 million to 1.5 million prescriptions dispensed annually), then decreased to 0.6 million prescriptions in 2022. Insulin glargine/lixisenatide dispensed prescriptions increased from 86,000 prescriptions in 2017 to 0.4 million prescriptions in 2022. Insulin degludec/liraglutide dispensed prescriptions steadily increased from 19,000 prescriptions in 2017 to 0.1 million prescriptions in 2020, then decreased to 97,000 prescriptions in 2022. Lixisenatide dispensed prescriptions increased from 677 prescriptions in 2017 to 2,500 prescriptions in 2021, then decreased to 1,600 prescriptions in 2022. Albiglutide dispensed prescriptions increased from 20,000 prescriptions in 2014 to 0.6 million prescriptions in 2016, then decreased to 1,700 prescriptions in 2019. A negligible use of albiglutide was captured in 2020.

Figure 2. Estimated Number of Prescriptions Dispensed for GLP-1 RAs from U.S. Outpatient Retail and Mail-Order/Specialty Pharmacies, Stratified by Molecule, January 2013 through September 2023, Calendar Year



Source: Symphony Health Metys® Data years January 2013 – September 2023. Data Extracted October 2023. File: 2023-5971
GLP-1 RAs chart 10-23-2023.xlsx

*Includes January to September 2023

**Includes exenatide (immediate-release) and exenatide microsphere (extended-release) molecules

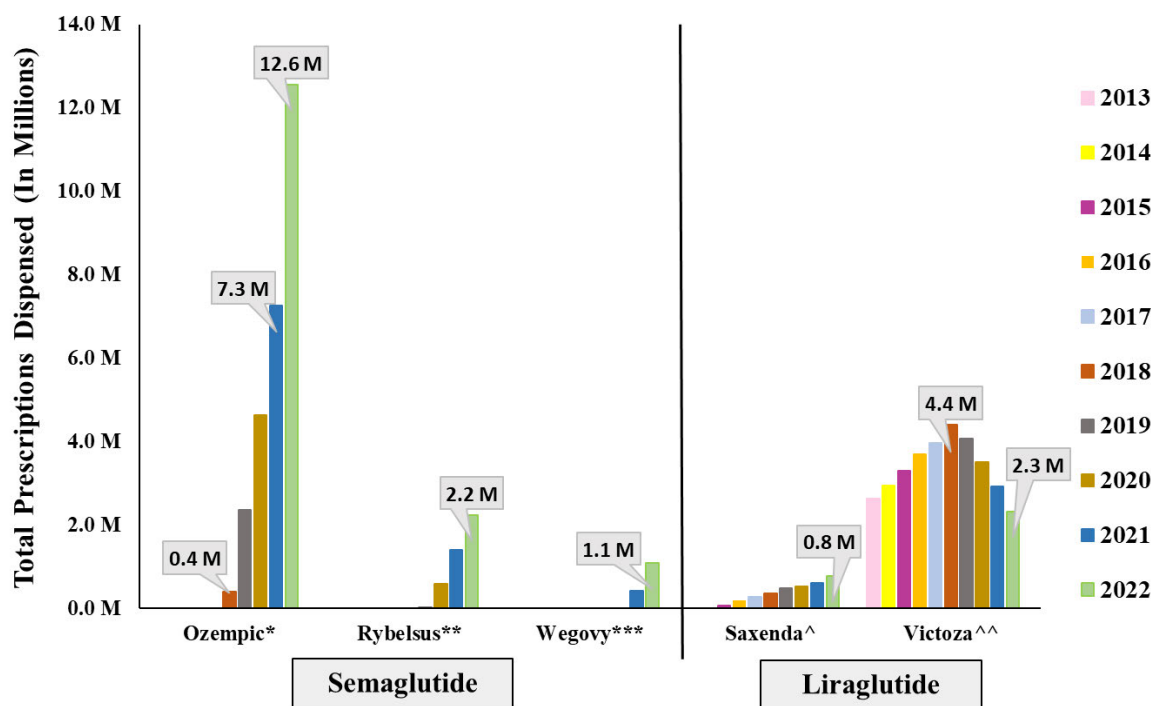
Figure 3 below shows the estimated number of prescriptions dispensed for semaglutide and liraglutide from U.S. outpatient retail and mail-order/specialty pharmacies, stratified by product, 2013 through 2022, calendar year. We are displaying the data stratified by productⁱ for semaglutide and liraglutide due to the differences in the labeled indication(s) among their products. All other GLP-1 RAs molecules and their products included in this review are currently labeled for T2DM only. Complete data for all GLP-1 RAs molecule, stratified by product, are shown in Table G2 in Appendix G.

Of the estimated total 15.9 million semaglutide prescriptions dispensed in 2022, Ozempic accounted for the highest proportion (79%, 12.6 million prescriptions), followed by Rybelsus (14%, 2.2 million prescriptions), and Wegovy (7%, 1.1 million prescriptions). We observed similar patterns for semaglutide products in 2021. Prescriptions dispensed for all semaglutide products increased during the study period examined: Ozempic increased from 0.4 million prescriptions in 2018 to 12.6 million prescriptions in 2022, Rybelsus increased from 17,000 prescriptions in 2019 to 2.2 million prescriptions in 2022, and Wegovy increased from 0.4 million prescriptions in 2021 to 1.1 million prescriptions in 2022. Of the estimated total 3.1 million liraglutide prescriptions dispensed in 2022, Victoza accounted for the highest proportion at 75% (2.3 million prescriptions), while Saxenda accounted for 25% (0.8 million prescriptions).

ⁱ Tirzepatide is not included due to its weight management indication approval in November 2023.

Victoza dispensed prescriptions steadily increased from 2.6 million prescriptions in 2013 to 4.4 million prescriptions in 2018, then decreased to 2.3 million prescriptions in 2022. Since the approval of Saxenda in December 2014, Saxenda dispensed prescriptions gradually increased from 54,000 prescriptions in 2015 to 0.8 million prescriptions in 2022.

Figure 3. Estimated Number of Prescriptions Dispensed for Semaglutide and Liraglutide from U.S. Outpatient Retail and Mail-Order/Specialty Pharmacies, Stratified by Product, 2013 through 2022, Calendar Year



Source: Symphony Health Metys™. Data years January 2013 – December 2022. Data Extracted August 2023. File: 2023-5971 GLP-1 RAs chart 10-23-2023.xlsx
 *Ozempic approved in December 2017
 **Rybelsus approved in September 2019
 ***Wegovy approved in June 2021
 ^Saxenda approved in December 2014
 ^^Victoza approved in January 2010

3.6.3 Office-Based Prescriber Survey Data

Table 11 below shows the top three diagnoses associated with the use of GLP-1 RAs, as reported by surveys from U.S. office-based health care providers, in 2022. T2DM was the top diagnosis reported for GLP-1 RAs in 2022, accounting for approximately 82% of total use mentions. This was followed by overweight and obesity, and elevated blood glucose, accounting for 11% and 6% of total use mentions, respectively.

Semaglutide (59% of use mentions), dulaglutide (28%), and liraglutide (5%) were the top mentioned GLP-1 RAs for T2DM. Semaglutide (58% of use mentions) and liraglutide (35%) were the top mentioned GLP-1 RAs for overweight and obesity. Among the semaglutide use

mentions reported for overweight and obesity, Wegovy comprised the highest proportion (44% of use mentions), followed by Ozempic (38%), and Rybelsus (18%). Among the liraglutide use mentions reported for overweight and obesity, Saxenda accounted for the vast majority (96% of use mentions), while Victoza accounted for 4%. Tirzepatide product Mounjaro accounted for 4% of use mentions and dulaglutide accounted for 3% of use mentions reported for the overweight and obesity diagnosis. Of note, the use mentions reported below 100,000 may not represent national use, given the small sample size and low precision associated with the estimates. Complete data for all GLP-1 RAs molecule, stratified by product, are shown in Table G2 in Appendix G.

Table 11. Top Three Diagnoses Associated with the Use of GLP-1 RAs, as Reported by Surveys from U.S. Office-Based Health Care Providers, in 2022

	2022		
	Uses	95% CI	%
Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%
Type 2 diabetes mellitus	10,624,000	9,831,000 - 11,416,000	82.1%
Semaglutide	6,313,000	5,702,000 - 6,924,000	59.4%
Ozempic	4,516,000	3,999,000 - 5,033,000	71.5%
Rybelsus	1,791,000	1,466,000 - 2,117,000	28.4%
Wegovy	5,000	<500 - 23,000	0.1%
Dulaglutide (Trulicity)	2,941,000	2,524,000 - 3,358,000	27.7%
Liraglutide	553,000	372,000 - 734,000	5.2%
Victoza	548,000	368,000 - 728,000	99.1%
Saxenda	5,000	<500 - 22,000	0.9%
Insulin glargine/lixisenatide (Soliqua)	388,000	237,000 - 540,000	3.7%
Exenatide	328,000	189,000 - 468,000	3.1%
Byetta	154,000	59,000 - 250,000	47.0%
Bydureon BCise	148,000	55,000 - 242,000	45.2%
Bydureon	26,000	<500 - 65,000	7.8%
Insulin degludec/liraglutide (Xultophy)	71,000	6,000 - 137,000	0.7%
Tirzepatide (Mounjaro)	30,000	<500 - 71,000	0.3%
Overweight and obesity	1,426,000	1,136,000 - 1,717,000	11.0%
Semaglutide	821,000	601,000 - 1,042,000	57.6%
Wegovy	362,000	215,000 - 508,000	44.0%
Ozempic	312,000	176,000 - 448,000	38.0%
Rybelsus	147,000	54,000 - 241,000	18.0%
Liraglutide	506,000	333,000 - 678,000	35.4%
Saxenda	485,000	315,000 - 654,000	95.9%
Victoza	21,000	<500 - 56,000	4.1%
Tirzepatide (Mounjaro)	53,000	<500 - 109,000	3.7%
Dulaglutide (Trulicity)	46,000	<500 - 99,000	3.2%
Elevated blood glucose level	716,000	510,000 - 922,000	5.5%
All other diagnoses	178,000	75,000 - 280,000	1.4%

Source: Syneos Health Research & Insights, LLC, Treatment Answers™. Year 2022. Data Extracted: October 2023. File: 2023-5971 GLP-1 RAs Syneos 2022, 10-25-2023.xls

The projected use mentions below 100,000 estimates may not be representative of providers' prescribing habits at the national level.

Abbreviations: CI=Confidence Interval

4 DISCUSSION

FAERS Cases

This review evaluated cases of completed suicide, suicide attempt, and suicidal ideation associated with GLP-1 RAs use. DPV-I identified 110 cases from FAERS of completed suicide (n=6), suicide attempt (n=6), or suicidal ideation (n=98) associated with GLP-1 RAs use. No additional cases were identified from the published medical literature. Distribution of cases in our case series is consistent with market share of respective GLP-1 RA products. The majority of cases in our case series reported semaglutide use (n=48); however, cases of interest were identified with all GLP-1 RAs indicated for the treatment of diabetes, except for lixisenatide. Diabetes was the most commonly reported reason for use (n=45), although a case may have reported more than one reason for use, and almost one-third of cases (n=31) did not report the reason for use. Although our case series included 110 cases, our FAERS search captured 285 additional reports of SIB that were excluded from our case series because they were duplicate reports, were judged as unassessable (i.e., lacked clinical details), or were assessed as unlikely causality. To enhance the quality of our case selection and causality assessment, all cases were assessed by both our DPV-I Safety Evaluator and also a Board-Certified Psychiatrist.

Using the causality criteria specified in Section 2.2, we assessed the cases included in our case series as having a possible causal relationship between SIBs and GLP-1 RAs use and cannot exclude the possibility that other conditions or drugs may have contributed to or caused the SIB events in these cases. Almost one-third (n=31) of our cases reported a pre-existing history of a psychiatric disorder and an additional 7 cases reported that a psychiatric medication had been started prior to initiation of the GLP-1 RA, despite the case not otherwise specifying an accompanying psychiatric disorder. Psychiatric disorders, particularly mood and psychotic disorders, are associated with increased risk for completed suicide and suicide attempts. Two cases that specified trade name Ozempic reported a positive rechallenge; however, both cases reported subjective suicidal ideation symptoms, and not suicidal behavior. Of the 57 cases with sufficient information to calculate a time to onset, 48 reported SIB occurred within 3 months of GLP-1 RA initiation, and 35 of these were within 1 month of GLP-1 RA initiation. Nonetheless, consensus is lacking on the expected timeline for development of drug-related SIB events.

Notably, there were multiple mainstream media news reports in 2023 regarding GLP-1 RA use and suicidality following EMA's July 11, 2023, announcement. The four cases directly submitted to the FDA after July 11, 2023, may have represented stimulated reporting, with one of these cases confirming that media generated awareness prompted submission of the MedWatch report. Stimulated reporting refers to the increase in reporting of cases to FDA as the result of greater awareness of the risk associated with a drug or drug class. A 2008 analysis found that the extent of reporting to the FDA Adverse Event Reporting System (AERS, a predecessor to FAERS) to be between 5 and 30% for hospitalized statin-associated rhabdomyolysis; however, in the absence of stimulated reporting, the extent of reporting ranged from 5 to 15% demonstrating the effect awareness of an adverse event may have.⁴⁸ Additionally, the 40 SIB cases reported in 2023 represents a marked increase in yearly reporting. There was an almost 3-fold increase in reporting from 2022 to 2023, although some of this increase may have represented increased market utilization of GLP-1 RAs, in addition to the potential for stimulated reporting in 2023.

Assessing potential mechanistic effects of GLP-1 RAs on SIB is challenging given limited understanding of the pathophysiology of suicidal behaviors and mechanisms by which drugs affect suicidality. In addition, preclinical data have significant limitations in the study of complex suicidal phenomena. GLP-1 receptors are distributed throughout the central nervous system, and GLP-1 signaling appears to be involved in complex systems associated with appetite regulation, including reward processing and stress response.^{49,50} GLP-1 RAs have shown varying ability to cross the blood-brain barrier (BBB), and penetrance across the BBB is generally low, although there is evidence that GLP-1 RAs exert central nervous system effects via areas with incomplete BBB (e.g., circumventricular organs).^{51,52,53}

There is little mechanistic data examining GLP-1 RAs and SIB specifically, although one recent small study examining resting state functional connectivity after semaglutide intervention found no significant changes in regions of interest (ROI) previously linked to SIB.⁵⁴ However, this study was limited by lack of comparative details on ROI between treatment groups and lack of assessment of suicidal thoughts, major depressive disorder, or other psychiatric disorders. Preclinical data suggest that GLP-1 RAs have neuroprotective effects, and although some preclinical studies have shown anxiogenic effects with acute administration, chronic GLP-1 RA administration has generally shown either neutral or anxiolytic/anti-depressive effects.^{55,56,57} Preclinical studies have shown that GLP-1 RAs can stimulate the Hypothalamic-Pituitary-Adrenal (HPA) axis, but the limited human data on GLP-1 RAs and HPA axis activation is mixed.^{58,59,60,61} In summary, although it is difficult to exclude the possibility that GLP-1 RAs could have negative impacts on SIB, the degree of brain penetrance, neuroprotective profile, and preclinical and limited clinical data do not suggest this is likely.⁶² On the other hand, the balance of available information suggests potential benefits from GLP-1 RAs in some neuropsychiatric domains, but further clinical study and articulation of specific mechanisms is needed in these areas.^{50,55,56}

Overall, our analysis of the FAERS cases was subject to significant limitations, and we were unable to draw substantive conclusions about a potential causal association of GLP-1 RAs and SIB events. SIBs are complex phenomena involving a dynamic interplay of biological, psychological, and social factors, and FAERS cases often lacked data pertinent to SIB risk, including psychiatric, medical, and family history; prior history of SIB or impulsive behaviors; concurrent medications; and psychological and social factors. When reported, pre-existing psychiatric conditions complicated assessment of the cases. Alternatively, the absence of pre-existing psychiatric history in other cases does not exclude non-GLP-1 RA etiologies, as SIB may occur in patients without pre-existing diagnosed psychiatric conditions, irrespective of GLP-1 RA use. Furthermore, although completed suicide is a relatively infrequent event, suicidal ideation and suicidal attempts are more frequent, and as noted, diabetic patients are at increased risk for depression and suicide leading to potential confounding by indication.^{1,63} Finally, it is difficult to interpret dechallenge information in postmarketing reports, especially as related to subjectively reported suicidal ideation and symptomatology that may be affected by non-pharmacologic factors, limited detail on treatment interventions, and the fluctuating nature of suicidal ideation in particular.

Literature Reviewⁱ

Published observational or pooled studies on the relationship between GLP-1 RAs and suicide or suicidal ideation are inconclusive. DEPI-I identified one observational and one pooled analysis for review. The results from this pooled analysis are reported in the label for Saxenda. Both studies found a higher incidence of either SIB or depression and self-harm in GLP-1 RA users compared to placebo or SUs. However, methodological limitation could account for the small differences in incidence identified. As well, neither study had the sufficient sample size for SIB or self-harm for meaningful inference with reasonable statistical power.

Primary findings and methodological limitations by study are described below.

O'Neil et al. 2016 (Pooled Analysis of 5 RCTs)⁴⁵

Across all 5 RCTs included in the pooled analysis, rates of suicide or suicidal ideation were double in the liraglutide group compared to the placebo arm (0.3% or 9/3,384 vs. 0.1% or 2/1,941). Strengths of the pooled analysis are inclusion of RCTs and use of a validated scale to capture suicide and suicidal ideation.

- Results are driven by cases identified in the SCALE Prediabetes and Obesity trial. In this trial, 8 patients out of 2,487 in the liraglutide arm and 2 patients out of 1,244 in the placebo arm had a suicidal behavior or suicide event. The respective incidences are 0.32% and 0.16%. Given the rarity of the outcome, the remaining trials did not have sufficient power to detect an imbalance between arms. Including trials without events increases the denominators of rates and relative risks. Thus, the pooled analysis reflects a slightly lower ratio of adverse events in both the liraglutide arm ($9/3384=0.27\%$) and the control arm ($2/1941=0.1\%$) compared to the SCALE Prediabetes and Obesity trial. However, these numbers do not reflect clinically meaningful differences, especially since the imbalance in adverse events between arms remains practically the same (difference in risks is 0.16% in the pooled analysis and 0.17% in the SCALE Prediabetes and Obesity trial).
- The study pooled individual RCTs with slightly different eligibility criteria, which may complicate the interpretability of its finding. Of the five RCTs, one included patients with diabetes, whereas four RCTs were conducted among patients without diabetes. The sparsity of event data precludes a data-driven evaluation of the heterogeneity of the treatment effect by diabetes status.
- Findings from the O'Neil study are consistent with current labelings for Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide). Current USPIs for these agents include the same rates of suicide or suicidal ideation (i.e., 0.3% among liraglutide-treated patients and 0.1% among placebo-treated patients) in the warnings and precautions section as reported in the O'Neil study.^{12-13,14}

^j In January of 2024 (five months after the literature search for this integrated review), Nature Medicine published a retrospective cohort study on semaglutide and suicidal ideation and attempts. Due to significant methodological concerns, DEPI-I found the internal and external validity of this study to be limited. Please refer to DEPI-I's review of the study by Wang and associates for a full discussion on the limitations and findings from that study.

Gamble et al. 2018 (Observational Study)⁴⁶

This retrospective observational study found the incidence rate of depression or self-harm was not statistically significantly higher for GLP-1 RA users compared with SU users (18.2 vs 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72 to 2.58; adjusted HR 1.25, 95% CI 0.63 to 2.50). Strengths of the retrospective observational study included a new user active comparator design and accounted for treatment switching during follow-up, high dimensional propensity scores to balance the baseline comparability, and the incorporation of death data to capture self-harm events that resulted in death outside of the hospital. Major methodological limitations are described below.

- Lack of statistically significant difference could be due to insufficient power.
This study cannot rule out small or modest difference in risk of depression or self-harm between incretin-based therapy users and other glucose-lowering agent users due to study power limitations.
- Misclassification of exposure is possible.
The CPRD database consists of only primary care clinical records; specialty practice clinician records and subsequently their prescriptions are not captured. It is likely that given the novelty of incretin-based agents during the study period, more prescriptions were dispensed by specialty clinicians. Differential misclassification of these GLP-1 RA users could bias results toward the null.
- Misclassification of outcome is also a concern.
The sensitivity of ICD-10 CM codes for identifying depression is low.⁶⁴ While the low sensitivity of ICD-10 codes to detect depression is non-differential, random differential variation by non-differential processes could still bias results away or towards the null especially when outcomes are rare and numerators are small.^{65,66,67}
- External validity is also a concern.
The study included diabetic patients from the U.K. Finding may have limited generalizability to the obese/overweight U.S. population. As well, generalizability of findings to users of specific products within the GLP-1 RA class are unclear. There was no description of which GLP-1 RAs were captured, therefore, it is possible that predominant exposure to a single product were driving results.
- Study outcome has unclear implications for suicidal ideation and attempt.
The outcome of this study was a composite outcome of depression and self-harm with the number of self-harm events being too small to report (CPRD masks numbers 4 and lower). As well, self-harm if not necessarily associated with an individual's desire to end their life. Thus, the implications of this study on self-harm risks and on SIB is unclear.

Drug Utilization

DEPI-II's utilization analyses from U.S. outpatient retail and mail-order/specialty pharmacies showed that the estimated total prescriptions dispensed for GLP-1 RAs increased from 4 million prescriptions in 2013 to 35 million prescriptions in 2022. Semaglutide accounted for 45% of the total GLP-1 RAs prescriptions dispensed in 2022. Ozempic accounted for the majority of

semaglutide dispensed prescriptions in 2022. Of note, we observed a sharp increase in Ozempic dispensed prescriptions from 2021 to 2022. This may be attributed to factors such as the ongoing shortage (started in March 2022) of Wegovy (another injectable semaglutide product) and new clinical data suggesting the use of injectable semaglutide over liraglutide for weight loss in patients without diabetes.^{68,69} However, we did not examine the reasons behind the utilization patterns observed in our analyses. Office-based prescriber survey data showed that T2DM (82% of use mentions), overweight and obesity (11%), and elevated blood glucose (6%) were the top 3 diagnoses for GLP-1 RAs in 2022. Results from the survey data showed use of semaglutide products Ozempic and Rybelsus, liraglutide product Victoza, tirzepatide product Mounjaro, and dulaglutide for overweight and obesity, suggesting off-label use of these products. However, the use mentions reported for liraglutide product Victoza, tirzepatide product Mounjaro, and dulaglutide for the overweight and obesity diagnosis were too low (<100,000) and therefore, may not represent national use, given the small sample size and low precision associated with the estimates.

Drug Safety Communication⁷⁰

On January 11, 2024, FDA posted a Drug Safety Communication (DSC) to inform patients and health professionals of FDA's ongoing evaluation of reports of suicidal thoughts or actions associated with GLP-1 RAs, and noted additional evaluations include a meta-analysis of clinical trials across all GLP-1 RA products and an analysis of postmarketing data in the Sentinel System. The DSC noted that FDA's preliminary evaluation has not found evidence that use of these medicines causes suicidal thoughts or actions.

5 CONCLUSION

In conclusion, we identified FAERS cases of patients who were taking GLP-1 RAs and had completed suicide, suicide attempt, and/or suicidal ideation. Implications of observational studies related to GLP-1 RAs and SIB are unclear at this time. Given the limitations of FAERS data and available observational studies, the information contained in this analysis should be taken in context of other evidence, including, but not limited to, clinical trial data, ongoing meta-analysis, and Sentinel System evaluations.

6 REFERENCES

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7 APPENDICES

APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

APPENDIX B. LITERATURE SEARCH STRATEGY

Table B1. Literature Search Strategy		
Date of search	September 7, 2023	
Database	PubMed	Embase
Search terms	Suicidal ideation ((((suicidal ideation OR suicidal ideations OR 'suicidal thought' OR 'suicidal thoughts' OR 'suicide ideation' OR 'suicide ideations' OR 'suicide thought' OR 'suicide thoughts') AND (exendin 4 OR bydureon OR bydureon bcise OR bydureon pen OR byetta OR exenatide OR exenatide synthetic OR lixisenatide OR adlyxin OR liraglutide OR liraglutide recombinant OR saxenda OR English OR dulaglutide OR English OR semaglutide OR English OR rybelsus OR semaglutide OR wegovy OR tirzepatide OR mounjaro OR albiglutide OR syncria OR tanzeum)) NOT ((animals[mh] NOT (human [mh] AND animals[mh])))) AND (English[Language])) ('suicidal ideation'/exp OR 'suicidal ideations':ti,ab,kw OR 'suicidal thought'/exp OR 'suicidal thoughts'/exp OR 'suicide ideation'/exp OR 'suicide ideations':ti,ab,kw OR 'suicide thought'/exp OR 'suicide thoughts'/exp) AND ('exendin 4'/exp OR 'bydureon'/exp OR 'bydureon bcise'/exp OR 'bydureon pen'/exp OR 'byetta'/exp OR 'exenatide'/exp OR 'exenatide synthetic'/exp OR 'lixisenatide'/exp OR 'adlyxin'/exp OR 'liraglutide'/exp OR 'liraglutide recombinant'/exp OR 'saxenda'/exp OR 'victoza'/exp OR 'dulaglutide'/exp OR 'trulicity'/exp OR 'ozempic'/exp OR 'rybelsus'/exp OR 'semaglutide'/exp OR 'wegovy'/exp OR 'tirzepatide'/exp OR 'mounjaro'/exp OR 'albiglutide'/exp OR 'syncria'/exp OR 'tanzeum'/exp) AND ('case reports' OR 'case study'/exp OR 'case studies'/exp OR 'case histories'/exp OR 'case reports as topic'/exp OR 'single-case studies as topic'/exp OR 'single case studies as topic'/exp OR 'n-of-1 trials as topic' OR 'n of 1 trials as topic' OR 'n-of-1 trial'/exp OR 'n of 1 trial'/exp OR 'n-of-1 clinical trial'/exp OR 'n of 1 clinical trial'/exp OR 'single-subject trial'/exp OR 'single subject trial'/exp OR 'single-subject trials' OR 'single subject trials' OR 'single case trials' OR 'single-case trial'/exp OR 'single case trial'/exp OR 'single-case trials' OR 'clinical trials, observational study' OR 'observational stud*' OR 'non experimental studies'/exp OR 'non experimental study'/exp OR 'nonexperimental studies'/exp OR 'nonexperimental study'/exp OR 'review'/exp OR 'review of reported cases' OR 'review literature'/exp OR 'multicase review' OR 'academic review' OR 'meta-analysis'/exp OR 'meta-analyses' OR 'meta analysis'/exp OR 'meta analyses' OR 'systematic review'/exp) AND [46nglish]/lim NOT ([animals]/lim NOT [humans]/lim) Suicide attempt	

Table B1. Literature Search Strategy		
	((attempted suicide OR attempted suicides OR suicide attempt OR suicide attempts OR suicidal attempt) AND (exendin 4 OR bydureon OR bydureon bcise OR bydureon pen OR byetta OR exenatide OR exenatide synthetic OR English OR adlyxin OR liraglutide OR liraglutide recombinant OR saxenda OR English OR dulaglutide OR English OR semaglutide OR English OR rybelsus OR semaglutide OR wegovy OR tirzepatide OR mounjaro OR albiglutide OR syncria OR tanzeum)) NOT ((animals[mh] NOT (human [mh] AND animals[mh]))) AND (English[Language])	('attempted suicide'/exp OR 'attempted suicide*':ti,ab,kw OR 'suicide attempt'/exp OR 'suicide attempt*':ti,ab,kw OR 'suicidal attempt'/exp OR 'suicidal attempt*':ti,ab,kw) AND ('exendin 4'/exp OR 'bydureon'/exp OR 'bydureon bcise'/exp OR 'bydureon pen'/exp OR 'byetta'/exp OR 'exenatide'/exp OR 'exenatide synthetic'/exp OR 'lixisenatide'/exp OR 'adlyxin'/exp OR 'liraglutide'/exp OR 'liraglutide recombinant'/exp OR 'saxenda'/exp OR 'victoza'/exp OR 'dulaglutide'/exp OR 'trulicity'/exp OR 'ozempic'/exp OR 'rybelsus'/exp OR 'semaglutide'/exp OR 'wegovy'/exp OR 'tirzepatide'/exp OR 'mounjaro'/exp OR 'albiglutide'/exp OR 'syncria'/exp OR 'tanzeum'/exp) AND ('case reports' OR 'case study'/exp OR 'case studies'/exp OR 'case histories'/exp OR 'case reports as topic'/exp OR 'single-case studies as topic'/exp OR 'single case studies as topic'/exp OR 'n-of-1 trials as topic' OR 'n of 1 trials as topic' OR 'n-of-1 trial'/exp OR 'n of 1 clinical trial'/exp OR 'n of 1 clinical trial'/exp OR 'single-subject trial'/exp OR 'single subject trial'/exp OR 'single-subject trials' OR 'single subject trials' OR 'single case trials' OR 'single-case trial'/exp OR 'single case trial'/exp OR 'single-case trials' OR 'clinical trials, observational study' OR 'observational stud*' OR 'non experimental studies'/exp OR 'non experimental study'/exp OR 'nonexperimental studies'/exp OR 'nonexperimental study'/exp OR 'review'/exp OR 'review of reported cases' OR 'review literature'/exp OR 'multicase review' OR 'academic review' OR 'meta-analysis'/exp OR 'meta-analyses' OR 'meta analysis'/exp OR 'meta analyses' OR 'systematic review'/exp) AND [47nglish]/lim NOT ([animals]/lim NOT [humans]/lim)
	Completed Suicide	

Table B1. Literature Search Strategy		
	(((suicide OR suicides OR 'suicidal completion' OR completed suicide OR completed suicides OR fatal attempt OR fatal attempts OR fatal suicide OR fatal suicides) AND (exendin 4 OR bydureon OR bydureon bcise OR bydureon pen OR byetta OR exenatide OR exenatide synthetic OR English OR adlyxin OR liraglutide OR liraglutide recombinant OR saxenda OR English OR dulaglutide OR English OR semaglutide OR English OR rybelsus OR semaglutide OR wegovy OR tirzepatide OR mounjaro OR albiglutide OR syncria OR tanzeum)) NOT ((animals[mh] NOT (human [mh] AND animals[mh]))) AND (English[Language]))	('suicide'/exp OR suicide\$:ti,kw OR 'suicidal completion'/exp OR 'completed suicide'/exp OR 'completed suicide\$:ti,kw OR 'fatal attempt':ti,kw OR 'fatal attempts':ti,kw OR 'fatal suicide':ti,kw OR 'fatal suicides':ti,kw) AND ('exendin 4'/exp OR 'bydureon'/exp OR 'bydureon bcise'/exp OR 'bydureon pen'/exp OR 'byetta'/exp OR 'exenatide'/exp OR 'exenatide synthetic'/exp OR 'lixisenatide'/exp OR 'adlyxin'/exp OR 'liraglutide'/exp OR 'liraglutide recombinant'/exp OR 'saxenda'/exp OR 'victoza'/exp OR 'dulaglutide'/exp OR 'trulicity'/exp OR 'ozempic'/exp OR 'rybelsus'/exp OR 'semaglutide'/exp OR 'wegovy'/exp OR 'tirzepatide'/exp OR 'mounjaro'/exp OR 'albiglutide'/exp OR 'syncria'/exp OR 'tanzeum'/exp) AND ('case reports' OR 'case study'/exp OR 'case studies'/exp OR 'case histories'/exp OR 'case reports as topic'/exp OR 'single-case studies as topic'/exp OR 'single case studies as topic'/exp OR 'n-of-1 trials as topic' OR 'n of 1 trials as topic' OR 'n-of-1 trial'/exp OR 'n of 1 trial'/exp OR 'n-of-1 clinical trial'/exp OR 'n of 1 clinical trial'/exp OR 'single-subject trial'/exp OR 'single subject trial'/exp OR 'single-subject trials' OR 'single subject trials' OR 'single case trials' OR 'single-case trial'/exp OR 'single case trial'/exp OR 'single-case trials' OR 'clinical trials, observational study' OR 'observational stud*' OR 'non experimental studies'/exp OR 'non experimental study'/exp OR 'nonexperimental studies'/exp OR 'nonexperimental study'/exp OR 'review'/exp OR 'review of reported cases' OR 'review literature'/exp OR 'multicase review' OR 'academic review' OR 'meta-analysis'/exp OR 'meta-analyses' OR 'meta analysis'/exp OR 'meta analyses' OR 'systematic review'/exp) AND [48nglish]/lim NOT ([animals]/lim NOT [humans]/lim)
	Suicidality	

Table B1. Literature Search Strategy		
	((self-injurious behavior OR self-injurious behaviors OR self injurious behavior OR self injurious behaviors OR intentional self injury OR intentional self injuries OR intentional self harm OR deliberate self-harm OR deliberate self harm OR suicidal behavior OR suicidal behaviors OR suicidality) AND (exendin 4 OR bydureon OR bydureon bcise OR bydureon pen OR byetta OR exenatide OR exenatide synthetic OR English OR adlyxin OR liraglutide OR liraglutide recombinant OR saxenda OR English OR dulaglutide OR English OR semaglutide OR English OR rybelsus OR semaglutide OR wegovy OR tirzepatide OR mounjaro OR albiglutide OR syncria OR tanzeum)) NOT ((human [mh] AND animals[mh])) AND (English[Language])	(‘self-injurious behavior’/exp OR ‘self-injurious behavior*’:ti,ab,kw OR ‘self injurious behavior’/exp OR ‘self injurious behavior*’:ti,ab,kw OR ‘intentional self injury’:ti,ab,kw OR ‘intentional self injuries’:ti,ab,kw OR ‘intentional self-harm*’:ti,ab,kw OR ‘intentional self harm*’:ti,ab,kw OR ‘deliberate self-harm’/exp OR ‘deliberate self harm’/exp OR ‘suicidal behavior’/exp OR ‘suicidal behavior*’:ti,ab,kw OR ‘suicidality’/exp OR ‘suicidality’:ti,ab,kw) AND (‘exendin 4’/exp OR ‘bydureon’/exp OR ‘bydureon bcise’/exp OR ‘bydureon pen’/exp OR ‘byetta’/exp OR ‘exenatide’/exp OR ‘exenatide synthetic’/exp OR ‘lixisenatide’/exp OR ‘adlyxin’/exp OR ‘liraglutide’/exp OR ‘liraglutide recombinant’/exp OR ‘saxenda’/exp OR ‘victoza’/exp OR ‘dulaglutide’/exp OR ‘trulicity’/exp OR ‘ozempic’/exp OR ‘rybelsus’/exp OR ‘semaglutide’/exp OR ‘wegovy’/exp OR ‘tirzepatide’/exp OR ‘mounjaro’/exp OR ‘albiglutide’/exp OR ‘syncria’/exp OR ‘tanzeum’/exp) AND (‘case reports’ OR ‘case study’/exp OR ‘case studies’/exp OR ‘case histories’/exp OR ‘case reports as topic’/exp OR ‘single-case studies as topic’/exp OR ‘single case studies as topic’/exp OR ‘n-of-1 trials as topic’ OR ‘n of 1 trials as topic’ OR ‘n-of-1 trial’/exp OR ‘n of 1 trial’/exp OR ‘n-of-1 clinical trial’/exp OR ‘n of 1 clinical trial’/exp OR ‘single-subject trial’/exp OR ‘single subject trial’/exp OR ‘single-subject trials’ OR ‘single subject trials’ OR ‘single case trials’ OR ‘single-case trial’/exp OR ‘single case trial’/exp OR ‘single-case trials’ OR ‘clinical trials, observational study’ OR ‘observational stud*’ OR ‘non experimental studies’/exp OR ‘non experimental study’/exp OR ‘nonexperimental studies’/exp OR ‘nonexperimental study’/exp OR ‘review’/exp OR ‘review of reported cases’ OR ‘review literature’/exp OR ‘multicase review’ OR ‘academic review’ OR ‘meta-analysis’/exp OR ‘meta-analyses’ OR ‘meta analysis’/exp OR ‘meta analyses’ OR ‘systematic review’/exp) AND [49english]/lim NOT ([animals]/lim NOT [humans]/lim)
Years included in search	All	
Limits	English, Human studies, Study types: case reports, case studies, case series, clinical trials, observational studies, reviews, systematic reviews and meta analysis	

APPENDIX C. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IQVIA National Sales Perspectives™

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~90% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys®

Powered by IDV®, Metys® is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys® accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 74% of all U.S. mail order prescriptions, 73% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys® Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level

Syneos Health Research & Insights Llc., Treatmentanswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,500 office-based physicians, physician assistants and nurse practitioners representing 32 specialties across the United States that report on all patient activity

during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists' physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. In August 2019, the nurse practitioner and physician assistant specialties were added to the panel. This enhancement provides a more precise view of prescribing habits since nurse practitioners and physician assistants are increasingly playing an important role in patient care. All data collected, is projected nationally by physician specialty and region to reflect national prescribing patterns.

Drug Utilization Databases Limitations

The drug utilization findings from this review should be interpreted in the context of the known limitations of the databases used. Dispensed prescriptions are nationally projected based on a sample of prescription claims from U.S. outpatient retail and mail-order/specialty pharmacies. Summation of these projected estimates across time periods may lead to differences in prescription due to rounding attributable to the projection methodology utilized. Moreover, GLP-1 RAs utilization patterns in the outpatient settings might not represent GLP-1 RAs utilization patterns in other settings of care such, as clinics and hospitals, where these products may be used. Of note, the prescription data provided in this review are regardless of indication. Drug use mentions and diagnoses data were generated from surveys conducted for one day out a month for outpatient office visits from a sample of 3,500 office-based providers and are not directly linked to dispensed prescriptions. Drug use mentions with diagnoses data did not necessarily result in dispensed prescriptions; rather they were the number of outpatient visits with a drug and diagnosis recorded. Use mentions below 100,000 do not represent sufficient portion of the population and are not representative of actual providers prescribing habits at a national level.

APPENDIX D. FAERS LINE LISTING OF SUICIDAL IDEATION AND BEHAVIOR ASSOCIATED WITH GLP-1 RA USE CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Dulaglutide(n=9)									
1	04-OCT-2022	21407026	1	US-ELI_LILLY_AND_COMPANY-US202209014140	Expedited (15-Day)		Male	U.S.	DE
2	08-AUG-2022	21186438	1	US-ELI_LILLY_AND_COMPANY-US202208000005	Expedited (15-Day)	80	Male	U.S.	OT
3	27-AUG-2020	18205925	1	FR-ELI_LILLY_AND_COMPANY-FR202008010230	Expedited (15-Day)	73	Male	FRA	DE, OT
4	07-JUL-2020	17991824	1	US-ELI_LILLY_AND_COMPANY-US202007001487	Expedited (15-Day)	71.89596	Male	U.S.	LT, HO
5	25-AUG-2020	18192761	1	GB-ELI_LILLY_AND_COMPANY-GB202004006694	Expedited (15-Day)	64.92539 Year	Female	GBR	OT
6	09-AUG-2022	21191910	1	GB-ELI_LILLY_AND_COMPANY-GB202208002548	Expedited (15-Day)	52		GBR	LT
7	16-FEB-2016	12081744	2	US-ELI_LILLY_AND_COMPANY-US201602002097	Expedited (15-Day)		Female	U.S.	OT
8	14-NOV-2018	15616321	1	US-ELI_LILLY_AND_COMPANY-US201811002335	Expedited (15-Day)		Female	U.S.	OT
9	31-JAN-2019	15896761	1	US-ELI_LILLY_AND_COMPANY-US201901010471	Expedited (15-Day)		Female	U.S.	OT
Exenatide (n=7)									
10	05-AUG-2019	16669284	2	US-ASTRAZENECA-2019SF08793	Expedited (15-Day)	67	Female	U.S.	OT
11	15-MAY-2015	11118883	1	596851	Direct	55	Female	U.S.	LT
12	24-AUG-2017	13901006	1	US-AMGEN-U.S.SP2017124848	Expedited (15-Day)	53	Male	U.S.	OT
13	21-MAR-2013	9179784	1	AU-ELI_LILLY_AND_COMPANY-AU201302002936	Expedited (15-Day)	53	Female	AUS	OT
14	01-JUL-2013	9376349	2	US-BRISTOL-MYERS SQUIBB COMPANY-19048412	Expedited (15-Day)	45	Male	U.S.	OT

15†	15-MAR-2019	16078992	2	TR-AstraZeneca-2019SE39425	Expedited (15-Day)	14	Male	TUR	HO
15†	08-DEC-2022	21697840	1	TR-SUN PHARMACEUTICAL INDUSTRIES LTD-2022RR-366641	Expedited (15-Day)	14	Male	TUR	Hospitalization, Other
15†	12-DEC-2022	21716700	2	TR-TEVA-2022-TR-2835115	Expedited (15-Day)	14	Male	TUR	Hospitalization
16	12-SEP-2018	15375311	2	US-ASTRAZENECA-2018SF13228	Expedited (15-Day)		Female	U.S.	OT
Liraglutide, other than Saxenda (n=19)									
17	17-OCT-2016	12854779	1	FR-NOVOPROD-513834	Expedited (15-Day)	74	Female	FRA	OT
17†	22-DEC-2016	13054750	1	FR-NOVOPROD-523849	Expedited (15-Day)	74	Female	FRA	OT
18	03-OCT-2018	15487925	1	FDA-CDER-CTU-2018-92792	Direct	70	Male	U.S.	LT
19	14-JUL-2020	18024116	1	FR-NOVOPROD-739404	Expedited (15-Day)	70	Male	FRA	HO, LT
20	20-MAY-2016	12388977	2	US-NOVOPROD-492192	Expedited (15-Day)	69	Male	U.S.	OT
21	20-MAY-2015	11124684	1	US-NOVOPROD-449339	Expedited (15-Day)	64	Male	U.S.	OT
22	17-DEC-2019	17162618 *	1	FR-EMD SERONO-E2B_90061040	Expedited (15-Day)	63	Male	FRA	HO
22†	18-DEC-2019	17169650	1	FR-EMD SERONO-E2B_90061040	Expedited (15-Day)	63	Male	FRA	Hospitalization
22†	20-DEC-2019	17185693	1	FR-NOVOPROD-625743	Expedited (15-Day)	63	Male	FRA	Hospitalization
22†	23-DEC-2019	17189701	1	FR-ZYDUS-029036	Expedited (15-Day)	63	Male	FRA	Hospitalization, Other
22†	03-JAN-2020	17233023	1	FR-AUROBINDO-AUR-APL-2018-050044	Expedited (15-Day)	63	Male	FRA	Other, Hospitalization
22†	07-JAN-2020	17241309	1	FR-TEVA-2018-FR-966059	Expedited (15-Day)	63	Male	FRA	Hospitalization
22†	10-FEB-2020	17397227	1	FR-SUN PHARMACEUTICAL INDUSTRIES LTD-2018RR-188442	Expedited (15-Day)	63	Male	FRA	Hospitalization
22†	02-MAR-2020	17482041	1	FR-MYLANLABS-2019M1032901	Expedited (15-Day)	63	Male	FRA	Hospitalization, Other
22†	06-SEP-2018	15357437	1	FR-NOVOPROD-619134	Expedited (15-Day)	62	Male	FRA	Hospitalization, Other

23	27-JAN-2016	11966823	2	US-NOVOPROD-478000	Expedited (15-Day)	60	Female	U.S.	HO
24	02-APR-2015	10977965	3	JP-NOVOPROD-442478	Expedited (15-Day)	55	Male	JPN	DE
25	04-FEB-2015	10763268	1	JP-NOVOPROD-420804	Expedited (15-Day)	53	Female	JPN	OT, HO
26	08-JUN-2020	17871757	1	FDA-CDER-CTU-2020-53817	Direct	52	Female	U.S.	LT
27	13-DEC-2018	15720502	1	US-NOVOPROD-636964	Expedited (15-Day)	51	Female	U.S.	OT
28	24-MAR-2016	12207630	1	CA-NOVOPROD-484619	Expedited (15-Day)	50	Male	CAN	OT
29	27-MAR-2014	10041556	2	PL-NOVOPROD-403888	Expedited (15-Day)	42	Male	POL	LT
30	10-JAN-2017	13100998	3	JP-PFIZER INC-2017005113	Expedited (15-Day)	42	Female	JPN	HO, LT
31	26-DEC-2018	15761398	1	FDA-CDER-CTU-2018-118460	Direct	42	Male	U.S.	LT
32	11-DEC-2017	14268262	2	US-NOVOPROD-575863	Expedited (15-Day)	28	Male	U.S.	OT
33	17-OCT-2014	10524325	1	US-NOVOPROD-425694	Expedited (15-Day)		Male	U.S.	OT
34	05-MAY-2015	11090106	1	GB-NOVOPROD-447358	Expedited (15-Day)		Female	GBR	OT
35‡	21-JUL-2023	22734986	2	GB-NOVOPROD-1092780	Expedited (15-Day)	59	Female	GBR	DS, OT
Semaglutide, other than Wegovy (n=41)									
36	27-JUN-2022	21008159	1	ES-NOVOPROD-929108	Expedited (15-Day)	56	Female	ESP	OT, LT
37	02-OCT-2020	18340030	3	JP-NOVOPROD-754978	Expedited (15-Day)	54	Male	JPN	DE, OT
38	11-OCT-2021	19937917	1	SE-NOVOPROD-851902	Expedited (15-Day)	52	Female	SWE	DS
39	16-DEC-2022	21737344	2	US-NOVOPROD-1002043	Expedited (15-Day)	52	Male	U.S.	OT
40	25-AUG-2022	21251594	1	US-NOVOPROD-950873	Expedited (15-Day)	50	Female	U.S.	OT
41	13-DEC-2020	18608700	1	US-NOVOPROD-772669	Expedited (15-Day)	47	Male	U.S.	OT
42	07-OCT-2021	19932827	1	FDA-CDER-CTU-2021-74585	Direct	39	Male	ISR	DS, OT, LT, RI

43	28-JAN-2019	15880466	2	US-NOVOPROD-643097	Expedited (15-Day)	36	Male	U.S.	OT
44	02-DEC-2019	17101755	1	US-NOVOPROD-698699	Expedited (15-Day)	35	Female	U.S.	OT
45	01-JUL-2022	21043767	1	FDA-CDER-CTU-2022-52286	Direct	28	Female	U.S.	LT
46	05-SEP-2018	15351842	1	US-NOVOPROD-619034	Expedited (15-Day)		Male	U.S.	OT
47	30-MAR-2021	19073132	1	BR-NOVOPROD-798434	Expedited (15-Day)		Female	BRA	OT
48	22-OCT-2021	19982528	2	US-NOVOPROD-858420	Expedited (15-Day)		Female	U.S.	OT
49	02-AUG-2022	21159058	1	CA-NOVOPROD-943524	Expedited (15-Day)		Female	CAN	OT
50	25-OCT-2022	21501458	1	AU-NOVOPROD-970983	Expedited (15-Day)		Female	AUS	OT
51	13-FEB-2023	21982301	1	US-NOVOPROD-1003792	Expedited (15-Day)	61	Male	U.S.	OT
52	21-MAR-2023	22118110	1	US-NOVOPROD-1037279	Expedited (15-Day)			U.S.	OT
53	21-Mar-23	22118076	2	IS-NOVOPROD-1035846	Expedited (15-Day)	36	Female	ISL	OT
54	06-APR-2023	22179046	1	US-NOVOPROD-1045491	Expedited (15-Day)		Male	U.S.	OT
55	26-APR-2023	22255819	1	FDA-CDER-CTU-2023-31081	Direct	26	Female	U.S.	RI
56	05-MAY-2023	22291720	1	FDA-CDER-CTU-2023-33638	Direct	40	Female	U.S.	RI
57	07-MAY-2023	22295577	1	FDA-CDER-CTU-2023-34040	Direct	37	Female	U.S.	LT
58	17-MAY-2023	22329031	1	GB-NOVOPROD-1062947	Expedited (15-Day)		Female	GBR	OT, LT
59	23-MAY-2023	22359564	1	FDA-CDER-CTU-2023-38607	Direct	65	Male	U.S.	RI, LT
60	25-MAY-2023	22363722	1	GB-NOVOPROD-1065719	Expedited (15-Day)		Female	GBR	LT
61	02-JUN-2023	22518701	1	FDA-CDER-CTU-2023-41147	Direct		Male	U.S.	DE
62	20-JUN-2023	22625748	1	FDA-CDER-CTU-2023-45611	Direct	73	Female	U.S.	RI, LT, DS
62‡	24-JUL-2023	22743336	1	US-ELI_LILLY_AND_COMPANY-US202307008619	Periodic	--	Female	U.S.	OT
63	03-JUL-2023	22663558	1	US-NOVOPROD-1083637	Expedited (15-Day)		Male	U.S.	OT
64‡	21-JUL-2023	22734960	2	GB-NOVOPROD-1091197	Expedited (15-Day)	44	Male	GBR	LT, OT

65‡	21-JUL-2023	22734973	2	GB-NOVOPROD-1091052	Expedited (15-Day)	43	Female	GBR	OT, DS
66‡	21-JUL-2023	22734978	2	GB-NOVOPROD-1091135	Expedited (15-Day)	37	Female	GBR	OT
67‡	24-JUL-2023	22740956	1	GB-NOVOPROD-1093498	Expedited (15-Day)	52	Female	GBR	LT
68‡	25-JUL-2023	22745167	1	DE-NOVOPROD-1091823	Expedited (15-Day)	42	Female	DEU	OT
69‡	27-JUL-2023	22754312	2	GB-NOVOPROD-1094285	Expedited (15-Day)		Female	GBR	OT
70‡	27-JUL-2023	22754336	1	NL-NOVOPROD-1093740	Expedited (15-Day)	64	Male	NLD	DE
71‡	31-JUL-2023	22764565	2	PL-NOVOPROD-1095344	Expedited (15-Day)	27	Male	POL	OT, LT
72‡	01-AUG-2023	22770370	2	GB-NOVOPROD-1096432	Expedited (15-Day)		Male	GBR	OT, LT, DS
73‡	08-AUG-2023	22803675	1	FDA-CDER-CTU-2023-57558	Direct	48	Female	U.S.	LT, DS, RI, HO, OT
74‡	13-AUG-2023	22821276	1	FDA-CDER-CTU-2023-58809	Direct	59	Male	U.S.	OT
75‡	18-AUG-2023	22839340	1	DK-NOVOPROD-1101273	Expedited (15-Day)	49	Male	DNK	OT
76‡	22-AUG-2023	22846811	1	NO-NOVOPROD-1102733	Expedited (15-Day)	59	Male	NOR	OT
Tirzepatide (n=4)									
77	08-FEB-2023	21974341	1	FDA-CDER-CTU-2023-10933	Direct	54	Male	U.S.	LT
78	09-FEB-2023	21979556	1	FDA-CDER-CTU-2023-11602	Direct	42	Female	U.S.	OT
79	15-NOV-2022	21597702	2	US-ELI_LILLY_AND_COMPANY-US202211002493	Expedited (15-Day)	--	Female	U.S.	OT
80	21-SEP-2022	21360692	2	US-ELI_LILLY_AND_COMPANY-US202209005617	Expedited (15-Day)	--	Male	U.S.	OT
Albiglutide (n=1)									
81	06-APR-2016	12243550	1	US-GLAXOSMITHKLINE-US2016045660	Expedited (15-Day)	--	Female	U.S.	OT
Saxenda (N=22)									
82	22-FEB-2022	20502265	1	US-NOVOPROD-817380	Periodic	--	Female	U.S.	OT
83	22-FEB-2022	20502267	1	US-NOVOPROD-816177	Periodic	--	Female	U.S.	OT
84	22-FEB-2022	20502322	1	US-NOVOPROD-833662	Periodic	--	Female	U.S.	OT
85	13-OCT-2015	11625182	1	US-NOVOPROD-464885	Periodic	--	Female	U.S.	OT
86	15-APR-2016	12271797	1	US-NOVOPROD-482732	Periodic	--	Female	U.S.	OT

87	11-JUL-2017	13742948	1	US-NOVOPROD-546316	Periodic	--	Female	U.S.	HO
88	17-JAN-2018	14402770	1	US-NOVOPROD-577580	Periodic	--	Female	U.S.	OT
89	01-JUL-2020	17971467	2	SE-NOVOPROD-736179	Expedited (15-Day)	44	Male	SWE	OT
90	16-MAR-2021	19014613	2	CA-NOVOPROD-781457	Expedited (15-Day)	43	Female	CAN	OT
91	17-JUL-2015	11279923	2	US-NOVOPROD-452756	Periodic	40	Female	U.S.	OT
92	02-MAR-2021	18960812	1	US-NOVOPROD-739659	Periodic	38	Female	U.S.	OT
93	13-OCT-2015	11624991	1	US-NOVOPROD-459926	Periodic	48	Male	U.S.	OT
94	08-JUN-2018	14988618	1	CA-NOVOPROD-603445	Expedited (15-Day)	47	Female	CAN	OT
95	11-JUL-2017	13742984	1	US-NOVOPROD-548062	Periodic	46	Female	U.S.	OT
96	18-JUN-2018	15023503	3	US-NOVOPROD-605585	Expedited (15-Day)	69	Female	U.S.	OT
97	27-FEB-2019	16013385	1	US-NOVOPROD-617240	Expedited (15-Day)	64	Male	U.S.	OT
98‡	18-AUG-2023	22839342	1	GB-NOVOPROD-1091041	Expedited (15-Day)	46	Female	GBR	OT
99‡	18-AUG-2023	22839343	1	IS-NOVOPROD-1100586	Expedited (15-Day)	36	Female	ISL	OT
100‡	23-AUG-2023	22852498	1	GB-NOVOPROD-1097448	Expedited (15-Day)	49	Female	GBR	OT, LT
101	18-APR-2023	22220847	1	GB-NOVOPROD-1043057	Expedited (15-Day)	16	Female	GBR	OT
102	02-MAR-2023	22054115	1	US-NOVOPROD-942724	Periodic		Female	U.S.	OT
103	02-MAR-2023	22054156	1	US-NOVOPROD-919560	Periodic	26	Female	U.S.	OT
Wegovy (N=7)									
104	26-MAY-2023	22370050	2	DK-NOVOPROD-1064502	Expedited (15-Day)	44	Female	DNK	OT
105‡	17-JUL-2023	22709858	1	DK-NOVOPROD-1087688	Expedited (15-Day)	53	Male	DNK	LT
106‡	21-JUL-2023	22738712	1	US-NOVOPROD-1024060	Periodic		Female	U.S.	OT
107‡	21-JUL-2023	22739003	1	US-NOVOPROD-1056614	Periodic	23	Female	U.S.	OT
108‡	26-JUL-2023	22756238	1	FDA-CDER-CTU-2023-54709	Direct	50	Female	U.S.	OT
109	22-OCT-2021	19982084	3	US-NOVOPROD-858578	Periodic	55	Female	U.S.	OT
110	29-SEP-2021	19893595	3	US-NOVOPROD-851090	Periodic	--	Female	U.S.	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant

disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.

† Duplicate report

‡ Report received by FDA on or after July 11, 2023

Abbreviations: AUS=Australia, BRA=Brazil, CAN=Canada, DE=death, DNK=Denmark, DS= disability, ESP=Spain, FDA=France, GBR=United Kingdom of Great Britain and Northern Ireland, HO=hospitalization, ISL=Iceland, ISR=Israel, JPN=Japan, LT= life-threatening, NLD=Netherlands, NOR=Norway, OT=other medically significant, POL=Poland, RI=required intervention, SWE=Sweden, TUR=Turkey, U.S.=United States

APPENDIX E. NARRATIVE CASE SUMMARIES OF COMPLETED SUICIDES (N=18)

Narrative Case Summaries of Completed Suicides in Patient's Taking a GLP-1 RAs (N=18)			
FAERS Case #	Manufacturer Control #	Narrative Summary	Reviewer Comments
Included (n=6)			
21407026	#US-ELI_LILLY_AND_COMPANYUS 202209014140	A 52-year-old male initiated dulaglutide 0.75 mg for an unknown indication. Medical history and concomitant medications other than insulin were not reported. Four and a half months after initiation, the dulaglutide dose was increased to 1.5 mg and approximately 2 months later, the dose was increased again to 3 mg. Four months after the second dose titration, while on dulaglutide and insulin, the patient committed suicide. Additional details were not reported.	The patient's medical history and concomitant medications were not reported. Based upon the limited clinical details, a GLP-1 RA-related causality cannot be excluded.
18340030	JP-NOVOPROD-754978	A 54-year-old male with a history of diabetes, end stage renal disease (ESRD) and obesity initiated Ozempic (semaglutide) 0.25 mg weekly. Three weeks after initiation of semaglutide, the patient deliberately overdosed with insulin degludec for suicide attempt. Semaglutide was being administered by a nurse after dialysis at the hospital. The patient developed hypoglycemia and died.	A number of factors may contribute to distress and poor mental health in ESRD patients receiving dialysis. These include loss of freedom and disruption of family and social life; the awareness of physical vulnerability and psychological dependence on the dialysis; feelings of stigma and rejection; and depression that is underdiagnosed and undertreated. Studies have reported an 84% increase in suicide risk in patients with ESRD compared to the general population (Chen IM, Lin PH, Wu VC, Wu CS, Shan JC, Chang SS, Liao SC. Suicide deaths among patients with end-stage renal disease receiving dialysis: A population-based retrospective cohort study of 64,000 patients in Taiwan. J Affect Disord. 2018 Feb;227:7-10. Doi: 10.1016/j.jad.2017.10.020. Epub 2017 Oct 9. PMID: 29045916.). Based upon the limited clinical details regarding the patient's mental health leading up to the event and the short time to onset between the initiation of semaglutide and the event, a GLP-1 RA-related causality cannot be excluded.

10977965	JP-NOVOPROD-442478	A 55-year-old male patient was treated with Victoza (liraglutide) 0.3 mg daily for type 2 diabetes mellitus. Medical history included type 2 diabetes mellitus, proliferative diabetic retinopathy, hypertension, and dyslipidemia. Concomitant medications included metformin, valsartan, amlodipine, eicosapentaenoic acid ethyl ester, and insulin glargine. Fifteen days after initiation, Victoza was increased to 0.6mg daily. Approximately 8 months later, “the patient disappeared from his house” The reporter “heard that the patient completed suicide.” Additional details were not reported.	Although a history of depression was not reported, the presence of diabetic retinopathy could have affected the patient’s psychosocial well-being. Increased severity of diabetic retinopathy has been shown to be associated with negative impact on quality of life and depression (Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol. 2016 May;44(4):260-77. doi: 10.1111/ceo.12696. Epub 2016 Feb 17. PMID: 26716602). The length of time between GLP-1 RA initiation and occurrence of the event would typically make a casual association less likely, but there is no consensus on expected timeline for drug-related SIB, and therefore GLP-1 RA-related causality cannot be ruled out.
18205925	FR-ELI_LILLY_AND_COMPANYFR 202008010230	A 73-year-old male patient with a history of depression, T2DM and basal cell carcinoma experienced “worsening” depression approximately 2.5 months after initiating dulaglutide 1.5 mg weekly for the treatment of diabetes. Two months later, the patient committed suicide. Additional details were not reported.	This case is complicated by a history of depression. The absence of information regarding the prior course, severity, and treatment history of the patient’s depression coupled with higher risk demographic factors makes it difficult to determine whether or not his worsening depression (and subsequent suicide) were GLP-1 RA-related or reflect fluctuating or episodic symptoms occurring in the course of his depressive illness.
22754336	Novo Nordisk NL-NOVOPROD-1093740	A 64-year-old male was treated with Rybelsus (semaglutide) 14 mg for the treatment of diabetes. The patient had an approximately 5-year history of depression. Concomitant medications included metformin, insulin degludec, clomipramine, omeprazole, and simvastatin. Two months after initiation, the patient committed suicide. Additional details were not reported.	This case is also complicated by a history of depression. In addition, clomipramine contains a boxed warning for increased risk of suicidality, although the referenced short-term studies in the boxed warning did not show an increase in risk in adults beyond age 24. However, this does not preclude the possibility that an older individual might experience adverse psychiatric effects, including suicidal ideation or behaviors, related to clomipramine as noted elsewhere in the clomipramine USPI. Based

			on the time to onset, a GLP-1RA-related causality cannot be excluded; however limited information is provided in the case.
22518701	Direct Report	The patient's sister reported her brother was diagnosed with new onset clinical depression 13 months prior to committing suicide. He "was doing very well" after unspecified treatment. Approximately 9-10 months later, he was prescribed Ozempic (semaglutide) for T2DM by his family medicine physician. The patient was told to titrate upward at an unreported schedule to 1 mg weekly. The patient "had extreme weight-loss of 60lbs in a matter of months on Ozempic and no monitoring." Three or four months after Ozempic initiation, "he got up early, made coffee, while his fiancé was in nearby bedroom, and preceded at some point to go outside to their patio pavilion and kill himself by gunshot wound to the head." The patient's sister reported, "He was on medications he had been on for years. He was not on anything new until Ozempic was prescribed. There were no outward reasons or any warning for this to happen. It seemingly was a spur of the moment decision he made. His life was very good. He was getting married in the fall – he said he was the happiest he had ever been. He had a great job, he was financially secure and had 4 beautiful children, and his second grandchild on the way. He had a very loving and close immediately and extended family. My family and I feel this could have caused the suicide or significantly contributed."	This patient had a history of "clinical depression," complicating assessment. The patient's sister reported the patient was doing well after unspecified mental health treatment; however, the sister's recall may have been biased in assigning causality to semaglutide in the wake of the patient's death. Also, depression is often a chronic condition with fluctuating symptom severity and episodic course, including periods of recovery, remission, and relapse, and it is possible the patient did not report ongoing or intermittent psychiatric symptoms to his sister. Although a complete listing of concurrent medications was not provided, we do note that there were no new medications other than semaglutide reported and thus cannot exclude a GLP-1 RA-related contribution in this case.
Excluded (n=12)			
10072436	US-NOVOPROD-405498	A 67-year-old male patient initiated Victoza (liraglutide) on an unknown date for the treatment of type 2 diabetes mellitus. About 1.5 years later, the patient was diagnosed with pancreatic cancer. The pancreatic cancer was terminal. The patient received unspecified chemotherapy. On an unknown date, the patient no longer wanted to receive treatment and committed suicide.	This case was assessed as unlikely as the terminal cancer diagnosis along with the patient's decision to discontinue treatment was considered a more plausible explanation for his completed suicide. The diagnosis of a severe physical illness, such as cancer, is associated with an increased risk of suicide.
10945415	JP-NOVOPROD-442338	A 61-year-old male patient was treated with Victoza (liraglutide) for type 2	This case was assessed as unlikely due to the presence of

		diabetes mellitus. Medical history included hypertension, dyslipidemia, and diabetic nephropathy (stage 2). Concomitant medications included multiple antihypertensive, oral hypoglycemic agents, and ursodeoxycholic acid. Five months after initiating liraglutide, “the patient visited the hospital and complained about his busy work (occupation unknown)”. One and a half months after the hospital visit, the patient hanged himself in his house and was found by his family who called emergency medical services. Cardiopulmonary resuscitation was initiated but was not effective. The patient was declared dead the following day. The report stated, “the patient's wife heard that he complained about his busy work.” Additional clinical details were not reported.	occupational stress which provided a plausible alternative explanation for his completed suicide, although there is a lack of detail regarding the hospital visit, and the relationship of this to implied occupational stress and the patient’s mental health. In addition, the patient had multiple comorbidities which may have contributed to the event.
19323626 (duplicate of case #'s 19899171, 19938264, 20030735, and 20937969)	CA-NOVOPROD-814263	A 57-year-old male was treated with Victoza (liraglutide) from unknown start date for an unknown indication. Medical history was not reported. Concomitant medications included metformin and perindopril. On an unknown date, the patient died from suicide.	This case cannot be judged and is unassessable because information is insufficient to assess causality. Medical history and clinical details (i.e., time to onset and a detailed description of the events leading up to the suicide) were not reported.
15431750	US-ASTRAZENECA-2018SF20420	A 53-year-old male patient initiated exenatide 2 mg once a week via subcutaneous injection for diabetes. The patient's past and current medical history included type 2 diabetes mellitus, hypertension, depression (“ongoing”), benign prostatic hyperplasia, erectile dysfunction, and dyslipidemia. Concomitant medications included acetylsalicylic acid and unspecified angiotensin converting enzyme inhibitor. The sender also reported the patient had experienced a recent job loss. The patient committed suicide by firearm approximately 22 months after initiating exenatide.	This case was assessed as unlikely due to the long time to onset between initiation of the GLP-1 RA and the event of suicide which makes a causal relationship improbable. Additionally, the patient had an underlying history of depression (past and current treatment was not reported) accompanied by report of recent loss of employment that may have contributed to the patient’s suicide.
17269117 (duplicate of case #'s 17277168, 17319427, 17335307, 17358395, 17367994,	US-PFIZER INC-2020013775	The 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report described a 23-year-old female who died of suspected suicide following a possible multi-drug overdose. Alprazolam was the primary toxic	This case was judged as unassessable. The role of liraglutide in the patient’s suicide cannot be assessed. In addition, a temporal relationship was not reported and the presence of other drugs such as antidepressants suggests a possible mental health

17449263, and 18004461)		substance, but other drugs may have included insulin, liraglutide, metformin, extended-release bupropion, fluoxetine, and cyclobenzaprine.	disorder than may have contributed to the patient's death.
14722111	US-ELI_LILLY_AND_COMPANYUS 201804001415	An elderly male received dulaglutide injections via a pre-filled pen for an unknown indication. Medical history and concomitant medications were not provided. Dosage regimen, indication for use, and start date were not reported. On unknown date, while on dulaglutide, the patient committed suicide.	This case was judged as unassessable due the lack of reported information such as temporal relationship, medical history, concomitant medications, and clinical details leading to the patient's suicide.
20412875	FR-ALLERGAN-2203855US	A 73-year-old female who experienced road traffic accident, intentional overdose following the administration of milnacipran (co-suspect drugs include zopiclone, metformin, and bromazepam, ethanol, and liraglutide). The patient's medical history included sleep apnea, and "Gross obesity". Concomitant disease included ongoing depression and ovarian cancer. The patient died following a "road traffic accident," intentional overdose and thermal burns.	This case was judged as unassessable because the information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide.
22593148	US-NOVOPROD-1075387	A 58-year-old male was treated with Ozempic (semaglutide) 2 mg weekly for type 2 diabetes mellitus. Medical history and concomitant medications were not reported. The patient "experienced anxiety depression and had suicidal thoughts" 3.5 months after initiation. The patient committed suicide. Additional details were not reported.	This case was judged as unassessable because the information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide.
22632639	US-NOVOPROD-1079624	A female of unknown age was treated with Ozempic (semaglutide) from unknown start date for an unknown indication. Medical history included bipolar disease. Concomitant medications were not reported. On an unspecified date, the patient committed suicide while taking the medication. Additional details were not reported.	This case was judged as unassessable because the information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide.
22638742	IL-NOVOPROD-1078441	A male of unreported age was treated with Ozempic (semaglutide) from unknown start date for an unknown indication. Medical history and concomitant medications were not reported. On an unknown date, the patient "was in depression" and committed suicide. Additional details were not reported	This case was judged as unassessable because the information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide.
22796612 (duplicate)	NL-SANDOZ-SDZ2023NL009965	A 55-year-old female presented to the emergency department (ED) after	This case was judged as unassessable because the

of case #'s 22800701, 22802744, 22802873, 22806229, 22813239, 22818499, 22818977, 22821857, 22824212, 22844011, 22844498, and 22856052)		ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency medical services herself and presented within 1 hour of ingestion. In the ED, she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She developed severe vasoplegic shock due to metformin overdose for which high dose noradrenalin and vasopressin were considered insufficient, and the decision was made to treat the patient with methylene blue. The patient stabilized for the next 24-hour following methylene blue administration. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase of 10518 U/L and aspartate aminotransferase of 4171 U/L, and developed progressive shock again. A computed tomography scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and the patient died.	information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide.
22852516	US-NOVOPROD-1104167	A male patient of unknown age was treated with Ozempic (semaglutide) from unknown start date for an unknown indication. Medical history was not provided. On an unknown date patient committed suicide.	This case was judged as unassessable because the information reported is insufficient to assess the causal relationship of the GLP-1 RA to the patient's suicide. Information regarding event and therapy dates,

			indication for use of the suspect product, complete medical history (psychological disorder), social habits, past history of attempt to suicide, family history, and socioeconomic conditions limits the medical assessment of the case.
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APPENDIX F: TABULAR SUMMARY OF OBSERVATIONAL STUDY AND META-ANALYSIS ON ASSOCIATION OF DEPRESSION AND SELF-HARM AND GLP-1 RA EXPOSURE.

Table F1. Tabular Summary of Observational Study

	Study (Gamble et al.)
Objectives/ Aims/ Scope	To compare population-based incidence rates of new-onset depression or self-harm in patients initiating incretin-based therapies with that of sulfonylureas (SU) and other glucose-lowering agents.
Design	Observational study
Type	Cohort
Data Source	UK-based Clinical Practice Research Datalink (CPRD). Hospital Episode Statistics (HES—follow-up until 31 March 2014), Office for National Statistics (ONS— follow-up until 30 April 2014), and Index of Multiple Deprivation (IMD (2010)) data to capture hospital records, causes of death and socioeconomic status information, respectively.
Time Period	1 January 2001 through February 2016 Patients were followed starting on the day of their 1 st prescription or date of diagnosis until the patient discontinued the drug, left the CPRD practice, died or the final day of follow-up. 50% of the prescription duration was added to the period of exposure to account for non-adherence.
Criterion (Selection) Standards	Inclusion criteria: all patients over 18 years of age with a minimum of 12 months of up-to-standard medical history in the CPRD database that received a new diagnosis for type 2 diabetes or a new prescription for any glucose-lowering therapy Exclusion criteria: Women with polycystic ovarian syndrome, gestational diabetes or whom were pregnant during the study period were excluded. Patients with a study entry date prior to 1 January 2007 were also excluded (the first incretin-based therapies became available in the UK in early 2007). Patients with a history of depression, self-harm, anxiety and other serious psychiatric conditions in the year prior to a patient's cohort entry date.
Setting	The CPRD contains nationally representative de-identified individual- level longitudinal data collected from a subset of primary care practices (~700) in the UK.

Exposure/ Intervention	Person-time exposure to all classes of glucose-lowering therapy including (1) DPP-4 inhibitors, (2) GLP-1 receptor agonists, (3) sulfonylureas, (4) metformin, (5) thiazolidinediones (TZDs), (6) sodium glucose cotransporter- 2 inhibitors, (7) meglitinides, (8) acarbose, (9) insulin and (10) no glucose-lowering drug therapy (ie, diet/lifestyle). Patient's contributed person-time to each of the aforementioned categories on the day of their first prescription or date of diagnosis (defined as the patient's index date) until a patient discontinued the drug, left a CPRD practice, died or on the final date of follow-up, whichever occurred first. A gap equal to 50% of the prescription duration was included to account for non-adherence.
Outcome(s)	Primary outcome was a composite measure of new-onset depression or self-harm including suicide and suicidal ideation. Both outcomes were identified from diagnostic codes.
Covariates	Covariates were adjusted for using high dimensional propensity score algorithm consisting of up to 40 covariates. Propensity score matched covariates included age, sex, measure of deprivation, BMI, number of hospitalizations in the prior year, number of drugs in the prior year, Hb1ac, eGFR, heart failure, hypertension, dyslipidemia, ischemic heart disease, peripheral vascular disease and prescriptions for metformin, acarbose, SGLT2 inhibitors, meglitinide, thiazolidinedione, insulin, hypnotic, mood, anticonvulsant and antipsychotics.
Sample Size	501 GLP-1 RA new users 16,409 sulfonylurea user comparators
Statistical Analyses	New-user active comparator design with High-Dimensional Propensity Scores to control for confounding. Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm.
Results The incidence rate of depression or self-harm was non-significantly higher for GLP-1 receptor users compared with sulfonylurea users (18.2 vs 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72 to 2.58; adjusted HR 1.25, 95% CI 0.63 to 2.50). “There were a limited number of self-harm events and our study was not powered to detect clinically relevant differences across exposure groups for this component of our composite outcome.”	

Table F2. Summary of randomized, placebo-controlled trials included in the pooled analysis as presented by O'Neil et al.

Trial	Phase 2 dose-finding^a [1,2]	SCALE Obesity and Prediabetes^b [3]	SCALE Diabetes [4]	SCALE Sleep Apnoea [5]	SCALE Maintenance^c [6]
ClinicalTrials.gov ID	NCT00480909	NCT01272219	NCT01272232	NCT01557166	NCT00781937
Population and treatments					
BMI / comorbidity	30–40 kg/m ²	≥30 or ≥27 kg/m ² with dyslipidaemia and/or hypertension	≥27 kg/m ²	≥30.0 kg/m ² with moderate or severe OSA	≥30 or ≥27 kg/m ² with dyslipidaemia and/or hypertension
Type 2 diabetes	No	No	Yes	No	No
Obstructive sleep apnoea	No	No	No	Yes	No
Treatment	Liraglutide 1.2, 1.8, 2.4 and 3.0 mg, placebo and orlistat	Liraglutide 3.0 mg, placebo	Liraglutide 3.0 mg, 1.8 mg and placebo	Liraglutide 3.0 mg, placebo	Liraglutide 3.0 mg, placebo
Allocation ratio	1:1:1:1:1:1	2:1	2:1:1	1:1	1:1
N randomised to liraglutide 3.0 mg / placebo	93 / 98	2487 / 1244	423 / 212	180 / 179	212 / 210
Treatment duration (weeks)	104	160	56	32	56
MHQs included	No	Yes	Yes	Yes	Yes
Primary endpoint(s)	Mean weight loss	1. Mean weight loss; 2. Proportion with ≥5% weight loss; 3. Proportion with >10% weight loss 4. Time to T2DM onset	1. Mean weight loss; 2. Proportion with ≥5% weight loss; 3. Proportion with >10% weight loss	Change in the apnoea-hypopnea index (AHI)	1. Mean weight loss after LCD; 2. Proportion maintaining ≥5% weight loss; 3. Proportion with ≥5% weight loss
% Weight loss at end of treatment (liraglutide 3.0 mg vs. placebo)	9.2 vs. 2.1 (at 52 weeks)	8.0 vs. 2.6 (at 56 weeks) 6.2 vs. 1.8 (at 160 weeks)	5.9 vs. 2.0 (at 56 weeks)	5.7 vs. 1.6 (at 32 weeks)	6.3 vs. 0.2 (at 56 weeks)
Trial location	8 countries in Europe	27 countries in Europe, North and South America, Asia, Africa and Australia	7 countries in Europe; South Africa and United States	United States and Canada	United States and Canada

Data in the pooled analysis are included for liraglutide 3.0 mg and placebo only. Weight data are estimated means for the full analysis set using LOCF imputation.

BMI, body mass index; ID, identifier; LCD, low-calorie diet; LOCF, last observation carried forward; MHQ, mental health questionnaire; N, number of participants; OSA, obstructive sleep apnoea; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence; T2DM, type 2 diabetes mellitus.

^aThe phase 2 trial was a 20-week trial with an extension of up to 2 years of treatment and an interim analysis after 52 weeks.

^bSCALE Obesity and Prediabetes had two parts: a 56-week period for individuals with and without prediabetes, after which endpoints 1-3 were evaluated. Individuals with prediabetes at screening continued in the second part of the trial for up to 160 weeks of treatment, after which endpoint 4 was evaluated.

^cSCALE Maintenance had a 4–12 week run-in period prior to randomization, during which participants had to lose a minimum 5% of their body weight using a low-calorie diet. Mean weight loss during the run-in period was 6.0%.

APPENDIX G. DRUG UTILIZATION TABLES

Table G1. Estimated Number of Prescriptions Dispensed for GLP-1 RAs from U.S. Outpatient Retail and Mail-Order/Specialty Pharmacies, Stratified by Molecule and Product, January 2013 through September 2023, Calendar Year

	2013		2014		2015		2016		2017		2018	
	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%
Grand Total	4,030,772	100.0%	4,428,689	100.0%	5,590,028	100.0%	7,394,460	100.0%	9,171,831	100.0%	11,879,037	100.0%
Semaglutide	-	-	-	-	-	-	-	-	-	-	387,504	3.3%
Ozempic ^a	-	-	-	-	-	-	-	-	-	-	387,504	100.0%
Dulaglutide (Trulicity^b)	-	-	4,292	0.1%	364,239	6.5%	1,488,583	20.1%	3,116,132	34.0%	4,788,089	40.3%
Liraglutide	2,626,207	65.2%	2,939,001	66.4%	3,353,403	60.0%	3,881,716	52.5%	4,224,620	46.1%	4,769,306	40.1%
Victoza [*]	2,626,207	100.0%	2,939,001	100.0%	3,299,208	98.4%	3,695,981	95.2%	3,957,592	93.7%	4,405,921	92.4%
Saxenda ^c	-	-	-	-	54,195	1.6%	185,735	4.8%	267,028	6.3%	363,385	7.6%
Exenatide**	1,404,565	34.8%	1,465,342	33.1%	1,516,796	27.1%	1,409,224	19.1%	1,388,560	15.1%	1,505,202	12.7%
Bydureon BCise ^d	-	-	-	-	-	-	-	-	456	<0.1%	376,336	25.0%
Byetta	756,600	53.9%	568,893	38.8%	428,377	28.2%	320,589	22.7%	255,894	18.4%	189,391	12.6%
Bydureon***	647,965	46.1%	896,449	61.2%	1,088,419	71.8%	1,088,635	77.3%	1,132,210	81.5%	939,475	62.4%
Insulin glargine/Lixisenatide (Soliqua 100-33^e)	-	-	-	-	-	-	-	-	85,912	0.9%	234,507	2.0%
Insulin degludec/Liraglutide (Xultrophy 100-3.6^f)	-	-	-	-	-	-	-	-	19,167	0.2%	101,128	0.9%
Lixisenatide (Adlyxin^g)	-	-	-	-	-	-	-	-	677	<0.1%	1,551	<0.1%
Albiglutide (Tanzeum^h)	-	-	20,054	0.5%	355,590	6.4%	614,937	8.3%	336,763	3.7%	91,750	0.8%

	2019		2020		2021		2022		2023 (Jan - Sep)	
	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%	TRx	Share%
Grand Total	15,355,658	100.0%	19,075,801	100.0%	24,135,468	100.0%	35,043,907	100.0%	43,095,732	100.0%
Semaglutide	2,377,781	15.5%	5,201,674	27.3%	9,062,532	37.5%	15,882,972	45.3%	22,738,333	52.8%
Ozempic ^a	2,360,999	99.3%	4,621,618	88.8%	7,250,119	80.0%	12,564,246	79.1%	16,534,172	72.7%
Rybelsus ⁱ	16,782	0.7%	580,056	11.2%	1,395,306	15.4%	2,240,269	14.1%	2,257,835	9.9%
Wegovy ^j	-	-	-	-	417,107	4.6%	1,078,457	6.8%	3,946,326	17.4%
Dulaglutide (Trulicity^b)	6,521,055	42.5%	8,039,261	42.1%	10,209,347	42.3%	12,439,669	35.5%	10,109,411	23.5%
Liraglutide	4,545,045	29.6%	4,033,504	21.1%	3,522,176	14.6%	3,094,823	8.8%	2,049,713	4.8%
Victoza [*]	4,066,394	89.5%	3,511,830	87.1%	2,922,237	83.0%	2,319,731	75.0%	1,437,419	70.1%
Saxenda ^c	478,651	10.5%	521,674	12.9%	599,939	17.0%	775,092	25.0%	612,294	29.9%
Tirzepatide (Mounjaro^k)	-	-	-	-	-	-	2,563,076	7.3%	7,499,720	17.4%
Exenatide**	1,420,457	9.3%	1,246,180	6.5%	830,040	3.4%	557,401	1.6%	306,650	0.7%
Bydureon BCise ^d	590,817	41.6%	599,978	48.1%	641,292	77.3%	513,660	92.2%	283,120	92.3%
Byetta	133,516	9.4%	96,461	7.7%	64,385	7.8%	41,729	7.5%	23,283	7.6%
Bydureon***	696,124	49.0%	549,741	44.1%	124,363	15.0%	2,012	0.4%	247	0.1%
Insulin glargine/Lixisenatide (Soliqua 100-33^e)	337,200	2.2%	398,879	2.1%	389,231	1.6%	407,238	1.2%	326,793	0.8%
Insulin degludec/Liraglutide (Xultrophy 100-3.6^f)	150,372	1.0%	154,454	0.8%	119,669	0.5%	97,132	0.3%	65,075	0.2%
Lixisenatide (Adlyxin^g)	2,046	<0.1%	1,842	<0.1%	2,473	<0.1%	1,596	<0.1%	36	<0.1%
Albiglutide (Tanzeum^h)	1,702	<0.1%	7	<0.1%	-	-	-	-	1	<0.1%

Source: Symphony Health Metys™. Data years Jan 2013 – Sep 2023. Data Extracted October 2023. File: Symphony Health Metys 2023-5482 GLP-1 RAs 10-23-2023.xlsx

*includes Victoza 2-Pack and Victoza 3-Pack products

***includes Bydureon and Bydureon pen products

**includes exenatide and exenatide microsphere molecules

^dOzempic approved in December 2017

^dBydureon BCise approved in October 2017

^gAdlyxin approved in July 2016

^jWegovy approved in June 2021

^bTrulicity approved in September 2014

^eSoliqua 100/33 approved in November 2016

^hTanzeum approved in April 2014

^kMounjaro approved in May 2022

^cSaxenda approved in December 2014

^fXultrophy 100/3.6 approved in November 2016

ⁱRybelsus approved in September 2019

Table G2. Diagnoses Associated with the Use of GLP-1 RAs, as Reported by Surveys from U.S. Office-Based Health Care Providers, Stratified by Molecule and Product, in 2022

	2022				2022		
	Uses	95% CI	%		Uses	95% CI	%
Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%	Total GLP-1 RAs	12,944,000	12,069,000 - 13,819,000	100.0%
E11 Type 2 diabetes mellitus	10,624,000	9,831,000 - 11,416,000	82.1%	R73 Elevated blood glucose level	716,000	510,000 - 922,000	5.5%
Semaglutide	6,313,000	5,702,000 - 6,924,000	59.4%	Semaglutide	648,000	452,000 - 844,000	90.6%
Ozempic	4,516,000	3,999,000 - 5,033,000	71.5%	Ozempic	422,000	264,000 - 580,000	65.1%
Rybelsus	1,791,000	1,466,000 - 2,117,000	28.4%	Wegovy	226,000	111,000 - 342,000	34.9%
Wegovy	5,000	<500 - 23,000	0.1%	Dulaglutide (Trulicity)	68,000	4,000 - 131,000	9.4%
Dulaglutide (Trulicity)	2,941,000	2,524,000 - 3,358,000	27.7%	N18 Chronic kidney disease (CKD)	68,000	4,000 - 131,000	0.5%
Liraglutide	553,000	372,000 - 734,000	5.2%	Semaglutide (Ozempic)	68,000	4,000 - 131,000	100.0%
Victoza	548,000	368,000 - 728,000	99.1%	E10 Type 1 diabetes mellitus	50,000	<500 - 105,000	0.4%
Saxenda	5,000	<500 - 22,000	0.9%	Dulaglutide (Trulicity)	38,000	<500 - 86,000	75.8%
Insulin glargine/lixisenatide (Soliqua)	388,000	237,000 - 540,000	3.7%	Semaglutide (Ozempic)	7,000	<500 - 28,000	14.4%
Exenatide	328,000	189,000 - 468,000	3.1%	Exenatide (Byetta)	5,000	<500 - 22,000	9.8%
Byetta	154,000	59,000 - 250,000	47.0%	R63 Signs and symptoms concerning food and fluid intake	22,000	<500 - 58,000	0.2%
Bydureon BCise	148,000	55,000 - 242,000	45.2%	Liraglutide (Saxenda)	22,000	<500 - 58,000	100.0%
Bydureon	26,000	<500 - 65,000	7.8%	E88 Other metabolic disorders	21,000	<500 - 56,000	0.2%
Insulin degludec/liraglutide (Xultophy)	71,000	6,000 - 137,000	0.7%	Semaglutide (Ozempic)	21,000	<500 - 56,000	100.0%
Tirzepatide (Mounjaro)	30,000	<500 - 71,000	0.3%	Z79 Long term (current) drug therapy	17,000	<500 - 49,000	0.1%
E66 Overweight and obesity	1,426,000	1,136,000 - 1,717,000	11.0%	Insulin glargine/lixisenatide (Soliqua)	17,000	<500 - 49,000	100.0%
Semaglutide	821,000	601,000 - 1,042,000	57.6%				
Wegovy	362,000	215,000 - 508,000	44.0%				
Ozempic	312,000	176,000 - 448,000	38.0%				
Rybelsus	147,000	54,000 - 241,000	18.0%				
Liraglutide	506,000	333,000 - 678,000	35.4%				
Saxenda	485,000	315,000 - 654,000	95.9%				
Victoza	21,000	<500 - 56,000	4.1%				
Tirzepatide (Mounjaro)	53,000	<500 - 109,000	3.7%				
Dulaglutide (Trulicity)	46,000	<500 - 99,000	3.2%				

Source: Syneos Health Research & Insights, LLC, Treatment Answers™. Year 2022. Data Extracted: September 2023. File: 2023-5971 GLP-1 RAs Syneos 2022, 10-23-2023.xls
The projected use mentions below 100,000 estimates may not be representative of providers' prescribing habits at the national level.
Abbreviations: CI=Confidence Interval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY M SUGGS
05/08/2024 09:34:02 AM

ZOYA RAMZAN
05/08/2024 09:40:38 AM

FREDERICK Y WU
05/08/2024 09:50:54 AM

AIDA E KUZUCAN
05/08/2024 10:56:36 AM

DANIEL I WORONOW
05/08/2024 11:47:23 AM

SHEHERYAR MUHAMMAD
05/08/2024 12:02:15 PM

YANDONG QIANG
05/08/2024 01:23:47 PM

WEI HUA
05/08/2024 02:58:20 PM

RAJDEEP K GILL
05/09/2024 01:21:35 PM

LISA M WOLF
05/09/2024 01:48:38 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Published Study

Date: 2/20/2024

Reviewer(s): Aida Kuzucan, PhD
Andrew D. Mosholder, MD, MPH
Division of Epidemiology 1

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Deputy Division Director: Wei Hua, MD, PhD, MSc, MHS
Division of Epidemiology 1

Subject: Review of a published observational study of the
association of semaglutide with suicidal ideation

NISS#: 1005164

Drug Names:

Product Names, Applicant Type/Number, Applicant:

Product Name	Active Ingredient(s)	NDA/BLA	Applicant
Byetta	Exenatide synthetic	021773	AstraZeneca AB
Byetta	Exenatide synthetic	021919	Amylin
Bydureon	Exenatide synthetic, extended release	022200	AstraZeneca AB
Bydureon BCise	Exenatide synthetic, extended release	209210	AstraZeneca AB
Victoza	Liraglutide recombinant	022341	Novo Nordisk Inc.
Saxenda	Liraglutide recombinant	206321	Novo Nordisk Inc.
Xultophy 100/3.6	Insulin degludec, liraglutide	208583	Novo Nordisk Inc.
Tanzeum	Albiglutide	125431	GlaxoSmithKline
Trulicity	Dulaglutide	125469	Eli Lilly and Co.
Adlyxin	Lixisenatide	208471	Sanofi-Aventis US
Soliqua 100/33	Insulin glargine, lixisenatide	208673	Sanofi-Aventis US
Ozempic	Semaglutide	209637	Novo Nordisk Inc.
Rybelsus	Semaglutide	213051	Novo Nordisk Inc.
Rybelsus	Semaglutide	213182	Novo Nordisk Inc.
Wegovy	Semaglutide	215256	Novo Nordisk Inc.
Mounjaro	Tirzepatide	215866	Eli Lilly and Co.
Zepbound	Tirzepatide	217806	Eli Lilly and Co.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	2
1 INTRODUCTION.....	4
1.1 Background.....	4
1.2 Regulatory history.....	4
2 REVIEW METHODS AND MATERIALS.....	5
3 REVIEW RESULTS	5
3.1 Study Overview.....	5
3.2 Study Objectives/Specific Aims/Scope.....	6
3.3 Study Methods	6
3.3.1 Design & Setting	6
3.3.2 Outcome & Exposure	7
3.3.3 Covariates	8
3.3.4 Sample Size/Power	8
3.3.5 Statistical Analyses.....	8
3.4 Study Results	9
3.4.1 Overweight/Obese cohort	9
3.4.2 T2DM cohort	10
3.5 Study Conclusions.....	12
4 DISCUSSION	12
5 CONCLUSION	16
6 REFERENCES	18
APPENDICES	20

EXECUTIVE SUMMARY

This Division of Epidemiology I (DEPI-I) review assesses a newly published retrospective cohort study evaluating the association of semaglutide with suicidal ideation in the overweight/obese population. This study by Wang and associates[1] was published on January 5th 2024.

On July 11th, 2023, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) issued a statement, describing an ongoing review of suicidal thoughts and thoughts of self-harm with glucagon-like peptide 1 receptor agonists (GLP-1 RAs), including Ozempic (semaglutide), Saxenda (liraglutide), and Wegovy (semaglutide). On July 12th, 2023, the U.S. Food and Drug Administration (FDA) opened a Newly Identified Safety Signal (NISS, SS ID #1005164) for all GLP-1 RAs and suicidal ideation which was moved to the evaluation phase on July 14, 2023. The current FDA evaluation includes (1) a Division of Pharmacovigilance I (DPV-I)/DEPI I integrated review of published observational studies, pooled randomized controlled trial analyses, and applicant-provided postmarketing case reports, (2) an Office of New Drugs (OND)-led meta-analysis of suicidality-related events in clinical trials, (3) a DEPI-I-lead retrospective cohort study using FDA's Sentinel system, and (4) this DEPI-I review of a published retrospective cohort study of semaglutide and suicidal ideation in overweight/obese and type 2 diabetes mellitus (T2DM) populations.

Wang and associates' retrospective cohort study uses electronic health records (EHR) data from the TriNetX Analytics Network to compare the incidence of new and recurrent events of suicidal ideation and suicidal attempts among patients who were prescribed semaglutide therapy and those who were prescribed alternative treatments during June 2021 and December 2022. The study consists of two cohorts, a cohort treated for overweight/obese cohort and a cohort treated for T2DM and compared individuals prescribed semaglutide to those prescribed non-GLP-1 RA chronic weight management treatments or anti-diabetic agents, respectively. The primary analysis used a single International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnosis code for suicidal ideation or attempt to capture events within 6-months following the first identified prescription of prevalent users of semaglutide or comparative treatments. Propensity scores for semaglutide versus non-GLP-1 RA treatments in the overweight/obese cohort, and for semaglutide versus non-GLP-1 RA treatments for T2DM, were used to balance a broad set of baseline patient characteristics including demographic, socioeconomic, mental health history, and other potentially confounding factors.

After propensity score matching, 52,783 users remained in each overweight/obese exposure group (68% of comparator users and 22% of semaglutide users were not matched). In the T2DM cohort, 27,276 patients in either group were matched (98% of comparator users and 0.02% of semaglutide users were not matched). The study reported a lower risk of suicidal ideation with semaglutide in both the T2DM cohort and the overweight/obese cohort. Compared to users of non-GLP-1 RA antidiabetics the HR of suicidal ideation among semaglutide-treated T2DM patients was 0.36 (95% Confidence Interval [CI] 0.25-0.53). Compared to non-GLP-1 RA chronic weight management medications, the HR of suicidal ideation among semaglutide-treated overweight/obese

patients was 0.27 (95% CI 0.20-0.36). Relative to the non-GLP-1 RA users, semaglutide users had a lower risk of recurrent suicidal ideation among the overweight/obese population and among T2DM patients with longer follow-up periods.

DEPI-I identified several methodological concerns with this study. The very low sensitivity of the codes used to capture suicidal ideation, selection of the non-GLP-1 RA comparator groups with a possibly higher baseline risk of suicidality compared to semaglutide users, inclusion of potentially unexposed time among semaglutide or non-GLP-1 RA comparator users, and residual and unmeasured confounding by psychiatric medication use and disease severity severely weaken the internal validity of this study. The large unmatched population in comparator groups in both analyses also hinder the external validity of findings. The findings regarding the association of semaglutide with suicidal ideation and suicide attempt in this study should be interpreted with caution. Continuation of ongoing efforts to evaluate this signal remain warranted.

1 INTRODUCTION

1.1 BACKGROUND

On July 11, 2023, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) safety committee issued a statement describing an ongoing review on the risk of suicidal thoughts and thoughts of self-harm following GLP-1 RA use, including Ozempic (semaglutide), Saxenda (liraglutide) and Wegovy (semaglutide).[2] The statement was triggered by the Icelandic Medicines Agency following spontaneous reports of suicidal thoughts and self-injury in people using liraglutide and semaglutide.¹

On July 12, 2023, FDA opened a Newly Identified Safety Signal (NISS, SS ID #1005164) for all GLP-1 RAs and suicidal ideation, which was moved to the evaluation phase on July 14, 2023. Several concurrent analyses are in progress to address this NISS, including 1) The Division of Pharmacovigilance I (DPV-I) and DEPI-I in Office of Surveillance and Epidemiology (OSE) are conducting a joint review of the spontaneous cases reported to the FDA Adverse Event Reporting System (FAERS), medical literature including published case reports, case series, observational studies, and pooled analyses, and applicant-provided postmarketing case reports as of August 2023; 2) The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) in Office of New Drugs (OND) has requested data from applicants on trial experiences with self-harm (IR sent in July and applicants' responses received in December 2023) and is conducting a meta-analysis of events in clinical trials; and 3) DEPI-I is conducting a retrospective cohort study to describe the risk of intentional self-harm following GLP-1 RA products and assess the association between GLP-1 RA and intentional self-harm patients through hypothesis testing using FDA's Sentinel System.²

In January of 2024, Nature Medicine published a retrospective cohort study by Wang, et al. on semaglutide and suicidal ideation and attempts in both overweight/obese and Type 2 Diabetes Mellitus (T2DM) populations. DEPI-I review of this study is conducted as part of NISS evaluation.

1.2 REGULATORY HISTORY

Following the first GLP-1 RA product approval on April 28, 2005, Byetta (exenatide synthetic, NDA 021773), the U.S. Food and Drug Administration (FDA) has approved several GLP-1 RA products. All GLP-1 RA products except Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) are indicated as adjunct therapy to diet and exercise to improve glycemic control in patients with T2DM. This indication is extended to pediatric patients with T2DM aged 10 years and older for Bydureon BCise (exenatide synthetic, extended release), Victoza (liraglutide), and Trulicity (dulaglutide). Victoza (liraglutide), Trulicity (dulaglutide), and Ozempic (semaglutide) are also

¹ Zepbound (tirzepatide) gained approval in the United States for chronic weight management after EMA's issued statement.

² An inferential analysis with an active comparator will be conducted only in the T2DM population. A subset analysis will also be conducted in a comorbid T2DM and obese population.

indicated to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease. Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) are indicated for chronic weight management in adults and pediatric patients aged 12 years and older.

In alignment with other chronic weight management products, the U.S. Prescribing Information (USPI) for Saxenda (liraglutide), Wegovy (semaglutide), and Zepbound (tirzepatide) contains WARNINGS and PRECAUTION subsection relative to suicidal ideation and behaviors.

An excerpt of Wegovy labeling is provided below:[3]

WARNINGS AND PRECAUTIONS

Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue WEGOVY if symptoms develop (5.9).

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with WEGOVY for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue WEGOVY in patients who experience suicidal thoughts or behaviors. Avoid WEGOVY in patients with a history of suicidal attempts or active suicidal ideation.

Currently, GLP-1 RAs indicated for T2DM do not have statements regarding suicidality in labeling.

2 REVIEW METHODS AND MATERIALS

This review is of the following publication,

Wang, W., Volkow, N.D., Berger, N.A. et al. Association of semaglutide with risk of suicidal ideation in a real-world cohort. Nat Med (2024).
<https://doi.org/10.1038/s41591-023-02672-2>

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

Wang and associates conducted a retrospective cohort study using electronic health records (EHR) data from the TriNetX Analytics Network, to assess the potential association between suicidal ideation and attempt and semaglutide therapy.

The study consists of two populations, an overweight/obese and T2DM cohort, where individuals prescribed semaglutide were compared separately to those who received non-GLP-1 RA chronic weight management treatments or diabetic treatments. The primary analysis used a single International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) diagnosis code for suicidal ideation (R45.851) and suicide attempt (T14.91) to capture these events within 6-months following the first visible prescription among prevalent users of semaglutide or comparative treatments. The two comparative treatments included a broad list of other antidiabetic medications (metformin,

sulfonylureas, alpha glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporter 2 inhibitors) and chronic weight management products (orlistat, setmelanotide, phentermine, topiramate, bupropion, and naltrexone). Propensity scores for semaglutide versus non-GLP-1 RA treatments in the overweight/obese cohort, and for semaglutide versus non-GLP-1 RA treatments for T2DM, were used to balance a broad set of baseline patient characteristics including demographic, socioeconomic, mental health history, and other potentially confounding factors.

The study reported lower risks of suicide ideation following semaglutide use in both the T2DM cohort and the overweight/obese cohort. Compared to users of non-GLP-1 RA antidiabetics, the hazard ratio (HR) of suicidal ideation among semaglutide T2DM patients was 0.36 (95% CI 0.25-0.53). Compared to non-GLP-1 RA chronic weight management medications, the HR of suicidal ideation among semaglutide chronic weight management patients was 0.27 (95% CI 0.20-0.36). This observed relationship was also identified for recurrent suicidal ideation among T2DM and the overweight/obese cohort and among T2DM patients with longer follow-up periods.

See Appendix 1 for a tabular summary of the study.

3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The aim of this study was to assess the risk of new and recurrent events of suicidal ideation and suicidal attempts among overweight/obese and T2DM patients who use semaglutide. Specifically, the primary objectives are:

- To compare the incidence of new onset suicidal ideation and suicidal attempt among overweight or obese patients who initiate semaglutide to non-GLP-1 RA chronic weight management medications.
- To compare the incidence of new onset suicidal ideation and suicidal attempt among T2DM patients who initiate semaglutide to non-GLP-1 RA antidiabetic medications.

Secondary objectives were to compare incidences of recurrent suicidal ideation in both the T2DM and overweight/obese cohorts.

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type & Setting

This study is a retrospective cohort study using EHR data from TriNetX Analytics Network (TriNetX). TriNetX provides Web-based and secure access to patient EHR data from hospitals, primary care, and specialty treatment providers, covering diverse geographical locations, age groups, ethnic groups, income levels and insurance types, including several commercial insurances, governmental insurance (Medicare and Medicaid), self-pay and uninsured, worker compensation insurance, and military and Veterans Affairs insurance, among others. Most data come from large academic medical institutions with both inpatient and outpatient facilities.[4] The TriNetX platform

includes aggregated de-identified EHRs of 100.8 million patients from 59 healthcare organizations in the United States, per the study investigators.

3.3.1.2 Population & Time Period

The study consists of two populations, an overweight/obese cohort and a T2DM cohort, where individuals who received semaglutide were separately compared to those who received non-GLP-1 RA because of chronic weight management or antidiabetic treatments.[5] The overweight/obese cohort contained individuals with a BMI-related diagnostic code ($\text{BMI} \geq 25 \text{ kg/m}^2$) within one month prior to the index semaglutide prescription. The T2DM cohort contained individuals with a diabetes diagnostic code within one month prior to the index semaglutide prescription.

For the overweight/obese cohort, the study period spanned from June 2021 (U.S. FDA approval date of Wegovy for chronic weight management) through December 2022.

For the T2DM, the study period spanned from December 2017 (U.S. FDA approval date of Ozempic for T2DM)[6] through May 2021. Patient follow-up began after an index semaglutide or non-GLPRA T2DM medication prescription that was within 1 month of a medical encounter with a T2DM diagnosis.

3.3.1.3 Selection, Inclusion and Exclusion Criteria

The overweight/obese cohort includes individuals who received semaglutide or non-GLP-1 RA chronic weight management medications within one month following a medical encounter with an overweight or obesity diagnosis. Overweight or obesity diagnosis were defined as ICD-10 codes indicating a body mass index greater or equal to 25 kg/m^2 .

The T2DM cohort included individuals who received a semaglutide or non-GLP-1 RA antidiabetic medications within one month of a medical encounter with a T2DM diagnosis during the study period.

Individuals with evidence of use of other GLP-1 RA (lixisenatide, albiglutide, liraglutide, exenatide, or tirzepatide) or with a medical encounter indicating a history of suicidal ideation or suicidal attempt were excluded from both cohorts.

3.3.1.4 Protected Health Information (PHI) Requirements

This study's analysis of de-identified patient data from TriNetX Analytics was exempted from review by the MetroHealth System Institutional Review Board.

3.3.2 Outcome & Exposure

3.3.2.1 Outcome

The primary analysis identified suicidal ideation or attempt within 6-months following the cohort index prescription. Suicidal ideation was defined as the presence of ICD-10 code R45.851 "Suicidal ideations" in the patient record. Suicide attempt was defined as the presence of ICD-10 code T14.91 "Suicide attempt."

3.3.2.2 Exposure

In the overweight/obese cohort, exposure to semaglutide and other non-GLP-1 RA chronic weight management agents were identified using Rxnorm codes from patient medical records. Non-GLP-1 RA chronic weight management agents included orlistat, setmelanotide, phentermine, topiramate, bupropion, and naltrexone.

In the T2DM cohort, exposure to semaglutide and other non-GLP-1 RA antidiabetic agents were identified using Anatomical Therapeutic Chemical (ATC) codes. Non-GLP-1 RA antidiabetic agents included metformin, sulfonylureas, alpha glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporter 2 inhibitors.

To avoid mixing the T2DM cohort with users of semaglutide for chronic weight management, the investigators required an index date prior to May 31, 2021, in the T2DM cohort, before FDA's approval of Wegovy (semaglutide) for chronic weight management.

No censoring criteria to account for treatment switching or discontinuation in either cohort were described. No washout period was used to create either cohort; this was a prevalent user design.

3.3.3 Covariates

Covariates included in the propensity score included demographic variables (age, sex, race, and marital status), socioeconomic factors (ICD-10 codes for socioeconomic determinants of health, personal history of psychological trauma, family history of behavioral disorders, and problems related to lifestyle), comorbidities, and prior medications or procedures. Definitions and codes used to identify covariates are shown in Appendix table 2. No literature or justification of covariate operationalization was provided in publication. The period where covariate information was captured was any time prior to the day before the patient's index date (per footnotes to Tables 1 and 2 in the publication).

3.3.4 Sample Size/Power

In the overweight/obese cohort, there were 67,804 semaglutide users and 164,967 users of non GLP-1 RA weight management products without history of suicidal ideation before propensity matching. After 1:1 propensity score matching, the sample included 52,783 patients in each exposure group.

In the T2DM cohort, there were 27,282 semaglutide users and 1,545,603 users of other antidiabetic products before propensity matching. After 1:1 propensity score matching, 27,276 patients remained in each exposure group.

3.3.5 Statistical Analyses

The investigators reported that all statistical analyses were conducted using the built-in functions of the TriNetX platform. Propensity scores for semaglutide versus non-GLP-1 RAs in the overweight/obese cohort, and for semaglutide versus non-GLP-1 RA antidiabetic agents for T2DM, were calculated using a broad set of baseline patient characteristics as described above in Section 3.3.3. Within the overweight/obese cohort

and the T2DM cohort, patients were 1:1 matched by propensity score to yield the analytic samples, with nearest neighbor greedy matching and a caliber of 0.25 standard deviations. Covariate balance was assessed by standardized mean differences (SMDs) with an SMD > 0.1 taken to represent imbalance between groups in that characteristic.

The investigators state they used the Kaplan-Meier method to analyze the daily probability of the outcome, with censoring of a patient on the day after the “last fact” appeared in their record. Accordingly, the investigators adopted what could be termed an “intent-to-treat” approach with follow-up of all patients continuing after their index date regardless of treatment discontinuation, add-on, or switching, until the last “fact.” A “fact” was defined as an outcome or other medical encounter (no further details were provided). The follow-up time window for the main analysis was 6 months after the index date, with additional time windows of 1, 2, and 3 years after the index date in the T2DM cohort. HRs and 95% CIs were calculated although the publication does not describe the analytic model or whether proportionality was assessed. Kaplan-Meier survival plots were not provided. To protect patient privacy, outcome counts of suicide attempts with numbers of cases between 1 and 9 were rounded up and reported as 10 cases.

3.4 STUDY RESULTS

3.4.1 Overweight/Obese cohort

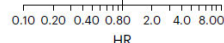
Before propensity score matching, 67,804 semaglutide users and 164,967 users of comparator drugs were identified having a first prescription from June 1, 2021, through December 31, 2022. The sample was predominantly female (68% semaglutide, 75% non-GLP-1 RA comparators) and the mean age was 52 (SD 13.5) years for semaglutide and 48 (SD 15) years for comparators. Before matching, with respect to the comparison group, semaglutide users were less likely to have had depression (27% versus 41%), anxiety (37% versus 49%), alcohol use disorder (2% versus 5%), and less likely to have used bupropion (15% versus 31%), antidepressants in general (44% versus 60%), and topiramate (10% versus 18%). Semaglutide users were also more likely to have used other antidiabetic products. Adverse socioeconomic factors were infrequent (4% for semaglutide and 6% for comparator users). Characteristic tables for the overweight/obese cohort as presented in the publication are presented in Appendix table 3.

After 1:1 propensity score matching, there were 52,783 users remaining in each exposure group, representing a loss of 68% of comparator users and 22% of semaglutide users. All baseline covariates after matching showed SMDs < 0.1 indicating acceptable balance in the analytic sample.

Mean follow-up duration was 161 days (standard deviation [SD] 18 days) for semaglutide users and 150 days (SD 27 days) for comparator-drug users. A total of 0.11% of semaglutide users had a diagnostic code for suicidal ideation during follow-up, compared to 0.43% of comparator drug users, yielding a HR of 0.27 (95% CI 0.20-0.36). The lower risk in semaglutide users was also reported across subgroups by age, sex, and race, as shown in the figure below, reproduced from the publication.

Figure 1. Hazard ratios for suicidal ideation in weight control cohort (reproduced from publication)

Population	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	HR (95% CI)
Overall (n = 52,783 per group)	0.11% (60)	0.43% (226)	0.27 (0.20–0.36)
Females (n = 39,004 per group)	0.11% (43)	0.35% (136)	0.32 (0.23–0.45)
Males (n = 13,191 per group)	0.13% (17)	0.64% (85)	0.20 (0.12–0.34)
Age ≤45 years (n = 19,650 per group)	0.17% (33)	0.51% (100)	0.34 (0.23–0.50)
Age 46–64 years (n = 24,508 per group)	0.09% (22)	0.34% (84)	0.26 (0.16–0.42)
Age ≥65 years (n = 8,106 per group)	0.12% (10)	0.31% (25)	0.28 (0.12–0.64)
Black (n = 8,288 per group)	0.12% (10)	0.42% (35)	0.20 (0.09–0.45)
White (n = 37,133 per group)	0.14% (50)	0.39% (145)	0.35 (0.25–0.48)
Hispanic ethnicity (n = 3,666 per group)	0.27% (10)	0.49% (18)	0.40 (0.17–0.95)



With respect to suicide attempts, in the matched sample there were no attempts among semaglutide users during the 6-month follow-up period and there were 14 attempts among users of comparator drugs (p-value <0.001). Assuming one-half person year per subject, 14 suicide attempt events represent a rate of approximately 0.53 events per 1000 person-years.

In a matched cohort of 865 semaglutide users and 865 comparator drug users with a history of suicidal ideation and diagnoses of overweight or obesity, 6.5% of semaglutide users and 14.1% of comparator drug users had recurrence of suicidal ideation diagnoses during follow-up (HR 0.44, 95% CI 0.32–0.60).

3.4.2 T2DM cohort

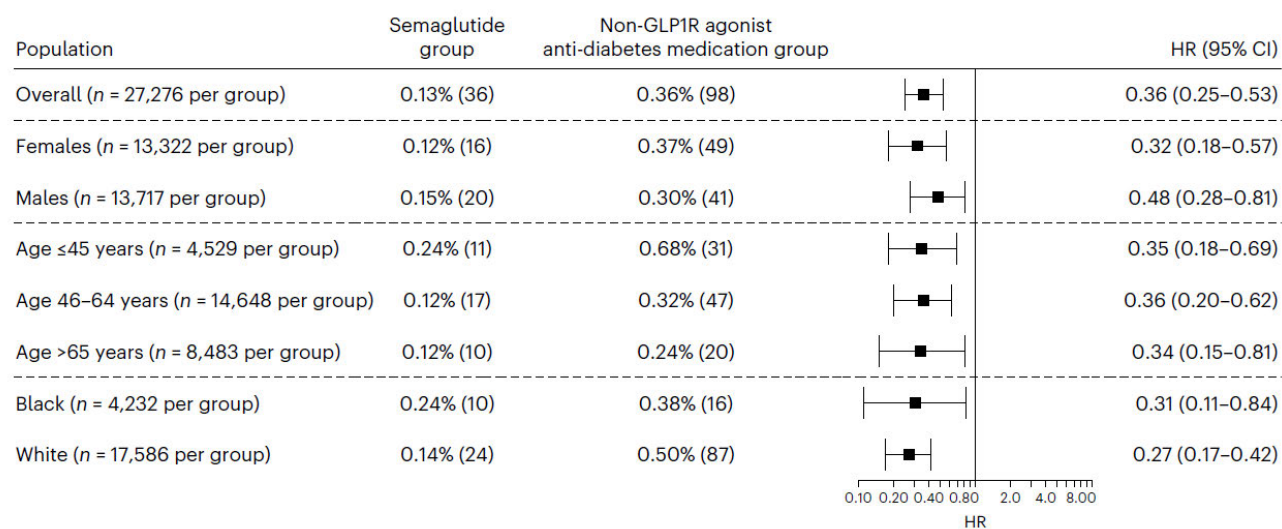
Before propensity score matching, the cohort included 27,282 semaglutide users and 1,545,603 users of non-GLP-1 RA antidiabetic products with initial prescriptions from December 1, 2017, through May 31, 2021. Prior to matching, semaglutide users (versus comparator drug users) were slightly younger on average (mean age 58 years versus 62 years), included slightly less Hispanic, and had more baseline mood disorders (21% versus 15%), anxiety disorders (22% versus 14%), sleep disorders (29% versus 17%), and chronic pain (17% versus 11%). They were also more likely to have had a baseline diagnosis of overweight/obesity (47% versus 24%) and more likely to have used antidepressants (30% versus 21%). The pattern of prior use of antidiabetic medications also differed, with the semaglutide group more likely to have used all other types of antidiabetic products. Adverse socioeconomic factors were infrequent (~approximately 2%) in both exposure groups.

After 1:1 propensity score matching, there were 27,276 patients in either group, representing a much greater loss of patients from the comparator treatment group (98%) than the semaglutide group (0.02%). After propensity score matching, all baseline covariates were balanced, as evidenced by SMDs < 0.1. Characteristic tables for the overweight/obese cohort as presented in the publication are presented in Appendix table 4.

Mean follow-up time was 173 days (SD 7.8 days) with semaglutide and 167 days (SD 13 days) with comparator drugs. The proportion of patients with a suicidal ideation diagnostic code during follow-up was 0.13% for semaglutide and 0.36% for comparator

uses, yielding a HR of 0.36 (95% CI 0.25-0.53). Similar magnitudes were observed in subgroups by age, sex, and race (see Figure 3 in the published article, reproduced below). With respect to suicide attempts, less than 10 patients in each group had a suicide attempt during follow-up so this outcome was not analyzed.

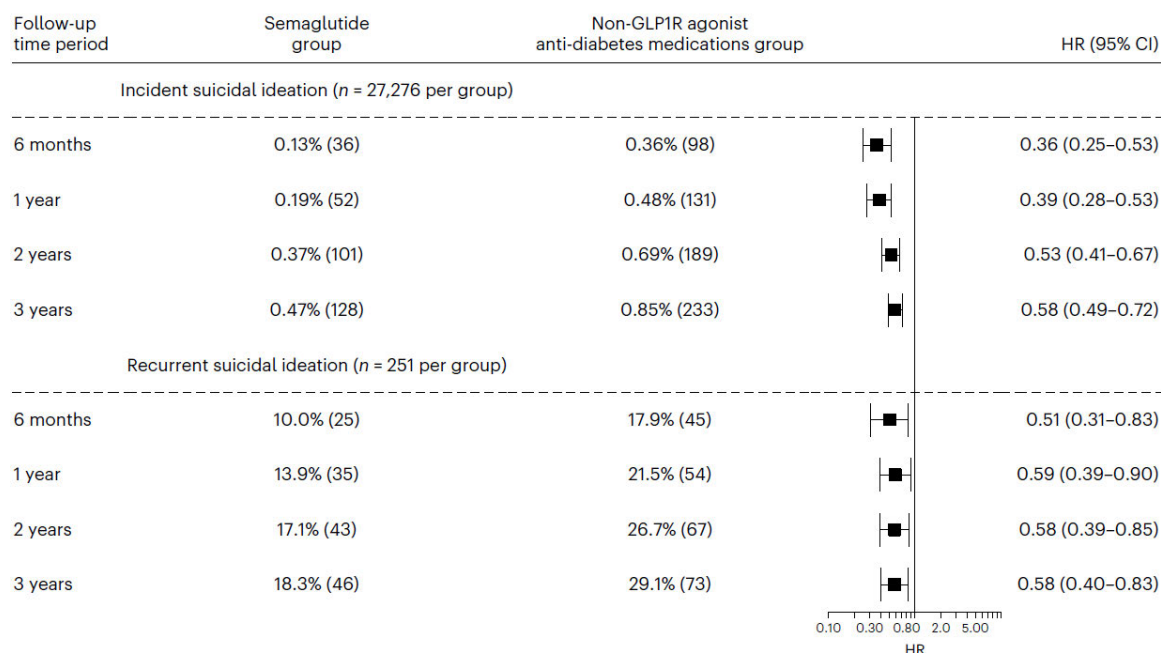
Figure 2. Hazard ratios for suicidal ideation in T2DM cohort (reproduced from publication).



A secondary analysis included only T2DM patients who had a prior history of a suicidal ideation diagnostic code. After propensity score matching, there were 251 patients in each treatment group for this analysis of recurrent suicidal ideation. The HR for recurrent suicidal ideation in this sample was 0.51 (95% CI 0.31-0.83).

The investigators analyzed suicidal ideation at other follow-up times, of 1, 2, and 3 years, finding similar risks in both new onset and recurrent suicidal ideation among semaglutide users. Note that an intent-to-treat approach was adopted for these analyses regardless of treatment discontinuation, add-on, or treatment switching. These data are presented in the figure below, reproduced from the publication.

Figure 3. Hazard ratios for suicidal ideation at various follow-up times (reproduced from article).



3.5 STUDY CONCLUSIONS

The authors concluded that use of semaglutide is associated with a lower risk of incident or recurrent suicidal ideation compared to use of non-GLP-1 RA products indicated for chronic weight management or treatment of diabetes.

4 DISCUSSION

The study by Wang and associates used a large database with EHR to compare incidence of suicidal ideation among overweight/obese and T2DM adults who received semaglutide or other chronic weight management and antidiabetic medications. The study reported a potential protective effect with semaglutide use that is considerably higher than that seen with antidepressants in randomized placebo-controlled trials. Compared to users of non-GLP-1 RA antidiabetics, the HR of suicidal ideation with semaglutide in T2DM patients was 0.36 (95% CI 0.25–0.53). Compared to non-GLP-1 RA chronic weight management medications, the HR of suicidal ideation among semaglutide exposed obesity/overweight patients was 0.27 (95% CI 0.20–0.36). In the Stone et al. BMJ meta-analysis of 372 randomized controlled placebo trials, the OR for suicidal ideation among adults aged 25 to 64 in trials for antidepressants versus placebo was 0.72 (0.56 to 0.92).[7] In other words, taken at face value, this study would indicate that semaglutide reduced suicidal ideation in a nonpsychiatric population to a greater extent than antidepressants did in placebo-controlled trials of psychiatric disorders. Although theoretically possible, a more plausible explanation would be that this result with semaglutide reflects residual confounding or other biases.

Significant sources of bias from the operationalization of the outcome, selection of the comparator groups, operationalization of the exposure, and operationalization of covariates decrease confidence in findings. These limitations are discussed below.

- Under capture of outcome using single diagnostic codes could negate or reverse findings.

Capture of suicidal ideation using ICD-10 diagnostic codes R45.851 is apt to have low sensitivity. One retrospective study in EHR data found that only 3% of individuals with suicidal ideation noted in the notes field of their medical record also had a corresponding ICD-9 diagnosis code³ for suicidal ideation[8]. This poor capture of suicidal ideation in health administrative data is one of the major rationales for most observational studies' use of self-harm events as the outcome of interest.[9] Validated well performing algorithms capturing self-harm events resulting in medical encounters have been developed for ICD-10.[9, 10] A recent study by Simon and associates reported that about 90% of self-harm events described in medical records were captured as intentional in ICD-10 CM claims suggesting improved sensitivity.[11] These algorithms contain multiple codes (not only the single code for suicide attempt used by Wang et al., [T14.91], but also codes for intentional injuries (ICD 10 codes beginning with X71-X83 and T71) and intentional poisonings (ICD10 CM codes beginning with T36-T65)) and have acceptable positive predictive values (to nearly 90% in one study).[10] We expect that had Wang and colleagues used a more complete set of ICD-10 diagnostic codes for suicide attempt, additional events would have been ascertained, and perhaps suicide attempt could have been analyzed as an additional study outcome.

Incomplete outcome capture is likely non-differential. However, given the small event count capture, a study using a more appropriate algorithm with higher event capture could negate or reverse findings. Bias could be away from or towards the null.

- TriNetX does not capture events outside of included health systems.

Use of the TriNetX data and a single ICD10 CM code for suicidal ideation (R45.851) and attempt (T14.91) likely led to under capture of the outcome. TriNetX is comprised of select contributing health care systems. Suicidal ideation or attempt-related medical encounters outside of health care systems included in the TriNetX dataset would not be captured.

Incomplete outcomes capture due to medical encounters outside of the medical system is likely non-differential. Still, given the small event count capture, other sources/databases that capture medical encounters across multiple medical systems could yield different results.

- Selection bias and confounding is a major concern in the overweight/obese population.

A prescription for a non GLP-1 RA chronic weight management agent was required for inclusion in the comparison group in the overweight/obese cohort. The combination products Contrave (bupropion and naltrexone) and Qsymia (phentermine and topiramate) are indicated for weight loss in the United States. The generic medications included in these products do not individually hold indications for weight loss and have indications

³ This study evaluated the presence of ICD9CM codes in electronic health records. Specifically, V62.84 was used to identify suicidal ideation diagnoses. The equivalent ICD10CM code for V62.84 is R45.851.

or are used off label for mental health disorders. While bupropion and naltrexone are marketed as a fixed dose combination product for weight loss (Contrave),[12] the comparator exposure was not limited to this combination product and so could have included single-entity bupropion or single-entity naltrexone, which are indicated for smoking cessation (bupropion), depression (bupropion), treatment of alcohol dependence (naltrexone), and prevention of relapse to opioid dependence (naltrexone). Similarly, Qsymia, a combination product of topiramate and phentermine, is approved for chronic weight management,[13] but the comparator exposure could have included single-entity topiramate, marketed as an anti-epileptic drug. Allowing these individual treatments to define the non-GLP-1 RA chronic weight management drug use group likely created a comparator with a higher baseline risk of suicidal ideation. Also, given the single-entity drug indications for mental health conditions, it is likely that individuals using these agents are being monitored for suicidal ideation more closely compared to GLP-1 RA chronic weight management products. Propensity score methods would likely not be able to overcome this confounding or selection bias.[14] This could explain the lower risk of suicide ideation observed with semaglutide use in the overweight/obese population.

- The intent-to-treat approach includes unexposed time or periods with exposure to both semaglutide and non-GLP-1 RA comparators.

Treatment discontinuation, switching, or add on therapy was not accounted for in this analysis. Particularly in T2DM patients where modifications in treatment in one year are estimated to occur in 63.6% with 38.6% discontinuing treatment[15], follow-up periods that assume persistent use of a single agent likely misclassify unexposed periods as exposed to either semaglutide or non-GLP-1 RA comparators. Patients with an index semaglutide (or comparator) prescription might immediately switch, receive a prescription in combination with other antidiabetic treatment, or discontinue the treatment. The rate and length of switching, add on treatments, and discontinuation in each group are unclear. Depending on the occurrence of event after treatment switching, add-on, or discontinuation, the risk of outcome in each group could be overestimated or underestimated; therefore, bias could be away from or towards the null.

- A prevalent user approach to selecting the analytic cohorts may have introduced bias.

This analysis was not limited to new users of semaglutide or non-GLP-1 RAs comparator treatments. It is unclear how many prevalent users were included in the semaglutide and comparator groups. Adverse events could lead to early discontinuation of medications among those individuals most susceptible to the suicidal ideation or attempt event and in follow up of low-risk individuals with better tolerance to drugs.[16] Individuals who discontinued semaglutide, for example, prior to appearing in TriNetX might be less likely to restart treatment based on their prior experience. Thus, studies including prevalent users might artificially deflate risks in one or both exposure groups.

- Identification of the diabetic and obese cohort may lack sensitivity.

The requirement of a diagnostic code within one month prior to a prescription might have excluded or led to misclassification of diabetic or overweight/obese patients. It is unclear how many individuals with or without semaglutide use and without relevant diagnoses were excluded. Given the small number of cases, the addition of these individuals could have negated or reversed findings.

- Insufficient assessment period of covariates could introduce residual confounding.

The analysis did not require a minimum period of baseline observation prior to the index date for determination of covariates, which were determined at any time up to the day before the index date. Patients who entered the TriNetX data shortly before their index dates may have had incomplete capture and thus misclassification of their baseline covariates. Propensity score matching on these covariates would be incomplete and residual confounding is likely. FDA’s Draft Guidance for Industry on Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision Making for Drug and Biological Products denotes the importance of allowing sufficient time before the exposure of interest to determine baseline characteristics.[17]

- Residual confounding by measured covariates is a major concern.

The study provides no justification for covariate definitions. The validity of covariate capture is unclear and an evaluation of the success of the propensity score match to reduce confounding by those covariates is limited. Specifically, codes listed by authors to capture socioeconomic status and traumatic brain injury are either not reliable or not consistent with current validated ICD-10 diagnosis algorithms.

Given semaglutide’s high cost and the likely association between socioeconomic status and semaglutide use, we applaud Wang and associate’s attempt to capture socioeconomic status. However, the authors’ captured socioeconomic ICD10 codes have low sensitivity.[18] Low socioeconomic status is associated with suicidality.[19] Further to this point, socioeconomic diagnostic codes were more prevalent among patients with recurrent suicidal ideation versus incident suicidal ideation (Extended Data Tables 1 and 2 in the publication). Residual confounding by socioeconomic status could, therefore, explain to an extent, more events in the comparator group and less events in the semaglutide exposed group.

Table 1 below provides a comparison of definition used by Wang and associates to an example of a validated algorithm for capture of traumatic brain injury (TBI). Incomplete codes listings likely resulted in misclassification of these covariates in the analysis.

Table 1. Comparison of validated algorithms for traumatic brain injury and chronic pain used with definitions used in Wang and associates.

Covariate	Definition used in Wang study	Validated definition identified in literature
Traumatic brain injury	ICD 10 CM: S06	ICD 10 CM: S02.0, S02.1; S02.8, S02.91, S04.02, S04.03, S04.04, S06, S07.1, and T74.4 [20]

- Consistency in results over a 3-year period suggests differences in population risks rather than effects of the drug.

In the T2DM cohort, an additional subset analysis was conducted to identify suicidal ideation risks at 1-year, 2-years, and 3-years after the first captured eligible semaglutide prescription. HRs do not appear to change with different follow-up periods, particularly for the outcome of recurrent suicidal ideation (HR= 0.59 at 1 year, 0.58 at 2-years, and 0.58 at 3- years). There was some attenuation of the HRs for incident suicidal ideation although the reduced risk with semaglutide remained at 3 years (HR 0.58). With some discontinuation of treatments expected over the three-year period, one would expect a diminishing of the association over time. Stability in risk estimates suggest baseline differences, such as differences in mental health, in the population rather than a drug effect persisting for 3 years after the index date.

- Unmeasured confounding from psychiatric medication use is a concern.

Mental health disorders were identified with only diagnostic codes in the primary analysis of new-onset suicidal ideation. This likely led to misclassification of individuals with a history of mental health disorders. In the subset analysis assessing recurrent suicidal ideation, previous exposure to psychiatric medication was also included in the propensity score. Interestingly, the analysis of recurrent suicidal ideation events in semaglutide vs. non-GLP-1 RA antidiabetics yielded a diminished association compared to that identified in the new-onset suicidal ideation analysis (0.51 vs. 0.36 in the T2DM group). This could indicate better control for confounding by including use of these agents as a covariate.

- Unmeasured confounding by disease severity in the T2DM and overweight/obese cohort could have been accounted for with validated composite scores.

Validated algorithms for capture of diabetes severity (such as the adapted Diabetes Complications Severity Index), duration of diabetes, and general health severity (such as the Charlson Comorbidity Index) were not used[21, 22], which may have contributed to residual confounding by these factors.

- A substantial proportion of comparators and semaglutide users were excluded from the propensity matched analysis potentially limiting generalizability.

Prior to propensity score matching, the study sample included 67,804 semaglutide users and 164,967 non-GLP-1 RA comparators in the overweight/obese cohort and 27,282 semaglutide users and 1,545,603 non-GLP-1 RA comparators in the T2DM cohort. After propensity score matching, 68% of comparator users and 22% of semaglutide users in the overweight/obese cohort, and 98% of comparators and 0.02% of semaglutide users in the T2DM cohort, were not matched and thus were excluded from the inferential analysis. The unmatched individuals in either cohort were not described, so it is difficult to assess the impact of their removal on the analysis. Generalization of findings to all U.S. adults who receive semaglutide for chronic weight management or treatment of T2DM is unclear.

5 CONCLUSION

Due to significant methodological concerns, DEPI-I finds the internal and external validity of this study to be limited. Significant sources of uncertainty or bias from the operationalization of the outcome, selection of the comparator groups, operationalization of the exposure, and operationalization of covariates could negate or even reverse findings. Continuation of ongoing efforts to evaluate this signal remain warranted.

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APPENDICES

Table 2: Design Summary

	Study
1.1 Objectives/ Aims /Scope	To compare the incidence of new onset suicidal ideation and suicidal attempt among overweight or obese patients who initiate semaglutide to non-GLP-1 RA chronic weight management medications. To compare the incidence of new onset suicidal ideation and suicidal attempt among T2DM patients who initiate semaglutide to non-GLP-1 RA antidiabetic medications.
1.2.1 Design	
1.2.1.1 Type	Retrospective cohort
1.2.1.2 Data Source	TriNetX Analytics platform based on the Research US Collaborative Network. The dataset consists of aggregated, de-identified EHRs from 59 healthcare organizations across the 50 states. Most included healthcare institutions are large academic medical institutions. EHR data comes from hospitals, inpatient, and outpatient settings are included.
1.2.1.3 Time Period	Two look back periods were used for each cohort. In the obesity cohort: June 2021 through December 2022 (study start date is semaglutide chronic weight management approval date) In the diabetic population: December 2017 through May 2021 (study start date is approval date of semaglutide for type 2 diabetes)
1.2.1.4 Criterion (Selection) Standards	<u>Type 2 diabetes</u> Inclusion: had medical encounter for T2DM within one-month semaglutide or another antidiabetic medication. Exclusion: history of suicidal ideation and use of any other GLP-1 RA <u>Obesity cohort</u> Inclusion: had a medical encounter for overweight or obesity (BMI>25) within one month of semaglutide or another chronic weight management medications. Exclusion: history of suicidal ideation and use of any other GLP-1 RA
1.2.1.5 Protected Health Information	The dataset consists of aggregated, de-identified EHRs.

1.2.2 Setting	Electronic Healthcare Records
1.2.3 Exposure/ Intervention	In the obesity cohort, exposure was determined by RxNorm code. Semaglutide exposure was determined from and RxNorm code 1991302. Non-GLP-1 RA chronic weight management agents included orlistat, setmelanotide, phentermine, topiramate, bupropion and naltrexone. In the T2DM cohort, exposure to semaglutide and other non-GLPRA antidiabetic agents were identified using Anatomical Therapeutic Chemical (ATC) codes. Non-GLPRA antidiabetic agents included metformin, sulfonylureas, alpha glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporter 2 inhibitors
1.2.4 Outcome(s)	The primary outcome assessed suicidal ideation and attempt within 6-months after the index event (prescription of GLP-1 RA or comparator agent). Suicidal ideation was defined as ICD-10 code R45.851 in the electronic health record. Suicidal attempt was defined as ICD-10 code T14.91.
1.2.5 Covariates	No minimum baseline period for covariate capture was described. Covariates in propensity-score matched analysis included demographics (age, sex, ethnic grouping/ethnicity, marriage status); adverse socioeconomic determinants of health (ICD10-CM Z55-Z65 persons with potential health hazards related to socioeconomic and psychosocial circumstances); lifestyle problems (ICD10-CM Z72 problems related to lifestyle); substance use disorders (for example, alcohol, tobacco or other nicotine products, cannabis, cocaine, stimulants); psychiatric comorbidities (for example, mood disorders, anxiety disorders, psychotic disorders); behavior disorders (for example, eating or sleep disorders); chronic pain, cancers, traumatic brain injury and bariatric surgery; previous medication prescriptions for obesity and T2DM for all groups. Included in the analysis of recurrent suicide attempt and intentional self-harm was the additional covariate of pharmacotherapies for suicidal ideation. This included esketamine, ketamine, lithium, antidepressants, antipsychotics, antiepileptics, benzodiazepines and hypnotics.
1.2.6 Sample Size	In the overweight/obese cohort, there were 67,804 semaglutide users and 164,967 users of other chronic weight management products without history of suicidal ideation. After 1:1 propensity score matching, the sample included 52,783 patients in each exposure group. In the T2DM cohort, there were 27,282 semaglutide users and 1,545,603 users of other antidiabetic products. After 1:1 propensity score matching, 27,726 patients remaining in each exposure group.

1.2.7 Statistical Analyses	All statistical analyses were conducted using the built-in functions of the TriNetX platform. Propensity scores for semaglutide versus non-GLP-1 RAs in the overweight/obese cohort, and for semaglutide versus non-GLP-1 RAs for T2DM, were calculated using a broad set of baseline patient characteristics as described above. Patients were 1:1 matched by propensity score to yield the analytic sample, with nearest neighbor greedy matching and a caliber of 0.25 standard deviations. Covariate balance was assessed by standardized mean differences (SMDs) with an SMD > 0.1 taken to represent imbalance between groups in that characteristic. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated although the publication does not describe the analytic model or whether proportionality was assessed. Kaplan-Meier survival plots were not provided.
1.2.8 Study Results (if relevant)	With respect to suicide attempts, less than 10 patients in each group had a suicide attempt during follow-up so this outcome was not analyzed. <u>Overweight/obese cohort:</u> Before propensity score matching, 67,804 semaglutide users and 164,967 users of comparator drugs were identified having a first prescription from June 1, 2021, to December 31, 2022. After 1:1 propensity score matching, there were 52,783 users remaining in each exposure group, representing a greater loss of comparator users (-68%) than semaglutide users (-22%). All baseline covariates after matching showed SMDs < 0.1 indicating acceptable balance. A total of 0.11% of semaglutide users had a diagnostic code for suicidal ideation during follow-up, compared to 0.43% of comparator drug users, yielding a HR of 0.27 (95% CI 0.20-0.36). <u>TDM2 cohort:</u> Before propensity score matching the cohort included 27,282 semaglutide users and 1,545,603 users of non-GLP-1 RA antidiabetic products with initial prescriptions December 1, 2017, through May 31, 2021. After 1:1 propensity score matching, there were 27,276 patients in either group, representing a much greater loss of patients from the comparator treatment group (98%) than the semaglutide group (0.02%). After propensity score matching all baseline covariates were balanced, as evidenced by SMDs < 0.1. The proportion of patients with a suicidal ideation diagnostic code during follow-up was 0.13% for semaglutide and 0.36% for comparator drugs, yielding a hazard ratio (HR) of 0.36 (95% CI 0.25-0.53)

Table 3 – Clinical diagnosis, medications, procedure, and other covariate definitions as presented in the article by Wang and associated.

Suicidal ideations	Suicidal ideations (ICD-10 code: R45.851)
Overweight or obesity	Overweight and obesity (ICD-10 code: E66) Body mass index [BMI] 40 or greater, adult (ICD-10 code: Z68.4) Body mass index [BMI] 30-39, adult (ICD-10 code: Z68.3) Body mass index [BMI] 25.0-25.9, adult (ICD-10 code: Z68.25) Body mass index [BMI] 26.0-26.9, adult (ICD-10 code: Z68.26) Body mass index [BMI] 27.0-27.9, adult (ICD-10 code: Z68.27) Body mass index [BMI] 28.0-28.9, adult (ICD-10 code: Z68.28) Body mass index [BMI] 29.0-29.9, adult (ICD-10 code: Z68.29)
T2DM	Type 2 diabetes mellitus (ICD-10 code: E11)
Other GLP1R agonists medications	lixisenatide (RxNorm code: 1440051), albiglutide (RxNorm code: 1534763), dulaglutide (RxNorm code: 1551291) liraglutide (RxNorm code: 475968), exenatide (RxNorm code: 60548), tirzepatide (RxNorm code: 2601723)
Semaglutide	Semaglutide (RxNorm code: 1991302)
non-GLP1R agonists anti-obesity medications	Orlistat (RxNorm code: 37925), Phentermine (RxNorm code 8152), Topiramate (RxNorm code 38404), bupropion (RxNorm code 42347), naltrexone (RxNorm code 7243)
Non- GLP1R agonists anti-diabetes medications	Drugs used in diabetes (ATC code: A10) with GLP1R agonists excluded
Suicidal ideations	Suicidal ideations (ICD-10 code: R45.851)
Medications related to suicidal ideation pharmacotherapy	Antidepressants (ATC code: N06A), Antipsychotics (ATC code: N05A), Antiepileptics (ATC code: N03), Benzodiazepine derivative sedatives/hypnotics (VA code: CN302), Esketamine (RxNorm code: 2119365), Ketamine (RxNorm code: 6130), Lithium (RxNorm code:6448)
Age at the index event	Age
Female	F
Male	M
Asian	Asian (Demographics: 2028-9)
Black or African American	Black or African American (Demographics: 2054-5)
white	white (Demographics: 2106-3)
Hispanic/Latino	Hispanic or Latino (Demographics: 2135-2)
Not Hispanic or Latino	Not Hispanic or Latino (Demographics: 2186-5)
Unknown race	Unknown Race (Demographics: 2131-1)
Unknown ethnicity	Unknown Ethnicity (Demographics: UN)
Divorced	Divorced (Demographics: D)
Widowed	Widowed (Demographics: W)
Never married	Never Married (Demographics: S)
Adverse socioeconomic and psychosocial circumstances	Persons with potential health hazards related to socioeconomic and psychosocial circumstances (ICD-10 code: Z55-Z65), including Problems related to education (Z55), employment/unemployment (Z56), housing and economic circumstances (Z59), social environment (Z60), upbringing (Z62), family circumstances (Z63), psychosocial circumstances (Z64, Z65)
Personal history of psychological trauma	Personal history of psychological trauma, not elsewhere classified (ICD-10 code: Z91.4)
Family history of mental disorders	Family history of mental and behavioral disorders (ICD-10 code: Z81)
Problems related to lifestyle	Problems related to lifestyle (ICD-10 code: Z72)
Depression	Depressive episode (ICD-10 code: F32)
Mood disorders	Mood [affective] disorders (ICD-10 code: F30-F39)
Anxiety	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (ICD-10 code: F40-F48)
Psychotic disorders	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10 code: F20-F29)
Behavioral disorders	Behavioral syndromes associated with physiological disturbances and physical factors (ICD-10 code: F50-F59)
Disorders of adult personality and behavior	Disorders of adult personality and behavior (ICD-10 code: F60-F69)
Sleeping disorders including insomnia	Sleeping disorders (ICD-10 code: G47)
Suicide attempt	Suicide attempt (ICD-10 code: T14.91)
Intentional self-harm	Intentional self-harm (ICD-10 code: X71-X83)
Personal history of self-harm	Personal history of self-harm (ICD-10 code: Z91.5)
Chronic pain	Chronic pain, not elsewhere classified (ICD-10 code: G89.2)
Alcohol use disorder	Alcohol use disorders (ICD-10 code: F10)
Tobacco use disorder	Nicotine dependence (ICD-10 code: F17)
Opioid use disorder	Opioid use disorders (ICD-10 code: F11)
Cannabis use disorder	Cannabis use disorders (ICD-10 code: F12)
Cocaine use disorder	Cocaine use disorders (ICD-10 code: F14)
Other stimulant disorders	Other stimulant disorders (ICD-10 code: F15)
Other psychoactive substance use disorders	Other psychoactive substance related disorders (ICD-10 code: F19)
Cancer	Neoplasms (ICD-10 code: C00-D49)
Traumatic brain injury	Intracranial injury (ICD-10 code: S06)
Bariatric surgery	Bariatric surgery (ICD-10 code: Z98.84)
Insulins	Insulins and analogues (ATC code: A10A)
Metformin	Metformin (RxNorm code: 6809)
Sulfonylureas	Sulfonylureas (ATC code: A10BB)
Alpha glucosidase inhibitors	Alpha glucosidase inhibitors (ATC code: A10BF)
Thiazolidinedione	Thiazolidinediones (ATC code: A10BG)
Dipeptidyl peptidase 4 (dpp-4) inhibitors	Dipeptidyl peptidase 4 (dpp-4) inhibitors (ATC code: A10BH)
SGLT2 inhibitors	Sodium-glucose co-transporter 2 (sglt2) inhibitors (ATC code: A10BK)

Table 3. Characteristics of overweight/obese cohort before and after propensity score matching as presented in Wang and associates.

Table 1 | Characteristics of the semaglutide and non-GLP1R agonist anti-obesity medication groups for the study population with overweight or obesity and no history of suicidal ideation before the index event (first prescription of semaglutide or non-GLP1R agonist anti-obesity medications from 1 June 2021 through to 31 December 2022), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	SMD	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	SMD
Total number	67,804	164,967		52,783	52,783	
Age at the index event, years, mean±s.d.	51.6±13.5	47.5±15.3	0.29 ^a	50.0±13.4	50.3±15.1	0.03
Sex (%)						
Female	67.7	75.2	0.17 ^a	72.6	72.5	0.002
Male	31.8	24.3	0.17 ^a	26.9	27.0	0.002
Ethnicity (%)						
Hispanic/Latino	7.5	7.9	0.01	7.6	7.3	0.008
Non-Hispanic/Latino	69.9	76.9	0.16 ^a	70.9	71.4	0.01
Unknown	22.6	15.3	0.19 ^a	21.6	21.3	0.008
Ethnic group (%)						
Asian	2.6	0.9	0.13 ^a	1.6	1.7	0.004
Black	16.0	14.9	0.03	15.9	16.1	0.007
White	68.1	71.7	0.08	69.6	69.5	0.002
Unknown	12.0	11.9	0.003	12.0	11.7	0.008
Marital status (%)						
Never married	12.5	17.3	0.14 ^a	13.4	13.1	0.009
Divorced	5.5	6.0	0.02	5.6	5.6	<0.001
Widowed	3.6	3.6	0.003	3.4	3.5	0.006
Adverse socioeconomic determinants of health (%)	4.1	6.2	0.10 ^a	4.4	4.6	0.01
Personal history of psychological trauma (%)	0.2	0.4	0.05	0.2	0.2	0.005
Family history of mental and behavioral disorders (%)	0.6	1.1	0.06	0.7	0.7	0.005
Lifestyle-related problems (%)	7.9	10.7	0.09	8.2	8.5	0.01
Pre-existing medical conditions (%)						
Depression	26.9	40.7	0.30 ^a	30.2	31.9	0.04
Mood disorders, including bipolar disorder	32.0	48.0	0.33 ^a	35.9	37.6	0.04
Anxiety, dissociative, somatoform and other nonpsychotic mental disorders, including posttraumatic stress disorder	37.2	48.7	0.23 ^a	40.3	41.4	0.02
Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders	1.0	2.0	0.08	1.2	1.2	0.004
Behavioral disorders, including sleep disorders	9.2	10.9	0.06	9.7	10.0	0.009
Disorders of adult personality and behavior, including impulse and gender identity disorders	1.1	2.3	0.09	1.2	1.4	0.01
Symptoms and signs involving an emotional state	4.0	5.4	0.07	4.2	4.5	0.01
Sleeping disorders including insomnia	39.5	37.0	0.05	38.0	38.8	0.02
Chronic pain	25.3	26.9	0.04	25.2	26.0	0.02
Alcohol use disorder	2.4	5.2	0.15 ^a	2.7	3.0	0.02
Tobacco use disorder	11.7	17.9	0.18 ^a	12.4	13.0	0.02
Opioid use disorder	1.5	3.0	0.10 ^a	1.7	1.9	0.01
Cannabis use disorder	1.1	2.4	0.10 ^a	1.2	1.4	0.02
Cocaine use disorder	0.4	1.1	0.08	0.5	0.6	0.01
Other stimulant-related disorders	0.4	1.0	0.06	0.5	0.6	0.01
Other psychoactive substance-related disorders	1.0	2.4	0.11 ^a	1.1	1.3	0.02

Table 3 continued. Characteristics of overweight/obese cohort before and after propensity score matching as presented in Wang and associates.

Table 1 (continued) | Characteristics of the semaglutide and non-GLP1R agonist anti-obesity medication groups for the study population with overweight or obesity and no history of suicidal ideation before the index event (first prescription of semaglutide or non-GLP1R agonist anti-obesity medications from 1 June 2021 through to 31 December 2022), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	SMD	Semaglutide group	Non-GLP1R agonist anti-obesity medication group	SMD
T2DM	44.8	15.6	0.67 ^a	30.6	31.7	0.02
Cancer	32.6	29.5	0.07	30.7	31.1	0.008
Traumatic brain injury	2.1	3.1	0.06	2.3	2.4	0.009
Previous medication prescription or procedures (%)						
Bariatric surgery	4.4	5.4	0.05	4.9	5.1	0.007
Antidepressants	44.0	60.4	0.33 ^a	48.1	49.7	0.03
Antipsychotics	16.2	22.7	0.17 ^a	17.4	18.0	0.02
Antiepileptics	32.1	40.8	0.18 ^a	33.4	34.7	0.03
Benzodiazepine-derivative sedatives or hypnotics	44.0	47.0	0.06	43.5	44.2	0.01
Esketamine	0.1	0.2	0.03	0.1	0.1	0.006
Ketamine	5.2	6.4	0.05	5.5	5.6	0.004
Lithium	0.1	0.2	0.03	0.1	0.1	0.005
Bupropion	15.2	30.5	0.37 ^a	18.6	20.8	0.05
Naltrexone	3.6	3.7	0.006	4.1	4.1	<0.001
Phentermine	10.4	13.3	0.09	12.2	12.6	0.01
Orlistat	0.6	0.5	0.02	0.6	0.6	0.006
Topiramate	9.5	17.7	0.24 ^a	11.6	12.4	0.03
Insulin	21.5	9.8	0.33 ^a	15.0	15.8	0.02
Metformin	39.1	13.0	0.62 ^a	25.6	27.3	0.04
Alpha glucosidase inhibitors	0.2	0.1	0.03	0.1	0.1	0.005
DPP-4 inhibitors	8.2	1.5	0.32 ^a	3.4	3.8	0.02
SGLT2 inhibitors	10.3	1.5	0.38 ^a	3.5	4.0	0.03
Sulfonylureas	11.6	2.6	0.36 ^a	5.5	6.2	0.03
Thiazolidinediones	2.7	0.7	0.16 ^a	1.4	1.6	0.01

The status of variables was based on the presence of related clinical codes any time to 1 day before the index event. ^aSMD greater than 0.1, a threshold indicating group imbalance. SMD, standardized mean difference.

Table 4. Characteristics of T2DM cohort before and after propensity score matching as presented in Wang and associates.

Table 2 | Characteristics of the semaglutide group and non-GLP1R agonist anti-diabetes medication group for the study population with T2DM and no history of suicidal ideation before the index event (first prescription of semaglutide or other non-GLP1R agonist anti-diabetes medications from 1 December 2017 to 31 May 2021), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	Non-GLP1R agonist anti-diabetes medication group	SMD	Semaglutide group	Non-GLP1R agonist anti-diabetes medication group	SMD
Total number	27,282	1,545,603		27,276	27,726	
Age at the index event, years, mean $\pm$ s.d.	57.5 $\pm$ 12.5	62.0 $\pm$ 15.2	0.32 ^a	57.5 $\pm$ 12.5	57.4 $\pm$ 14.4	0.006
Sex (%)						
Female	48.8	47.6	0.02	48.8	49.5	0.006
Male	50.3	52.1	0.04	50.3	49.7	0.01
Ethnicity (%)						
Hispanic/Latino	5.8	9.6	0.14 ^a	5.8	5.8	0.001
Non-Hispanic/Latino	66.1	62.6	0.08	66.1	68.0	0.04
Unknown	28.1	27.9	0.005	28.1	26.2	0.04
Ethnic grouping (%)						
Asian	4.6	4.5	0.003	4.6	4.0	0.03
Black	15.5	17.8	0.06	15.5	15.3	0.007
White	64.5	61.6	0.06	64.5	66.0	0.03
Unknown	13.7	15.0	0.04	13.7	13.1	0.02
Marital status (%)						
Never married	9.4	10.1	0.03	9.4	9.5	0.005
Divorced	4.8	4.4	0.02	4.8	5.1	0.02
Widowed	5.0	6.5	0.07	5.0	5.8	0.04
Adverse socioeconomic determinants of health, personal and family history, lifestyle factors (%)	2.4	2.1	0.02	2.4	2.3	0.009
Personal history of psychological trauma	0.1	0.1	0.01	0.1	0.1	0.002
Family history of mental and behavioral disorders	0.3	0.2	0.01	0.3	0.3	0.001
Lifestyle-related problems	5.8	4.4	0.06	5.8	5.4	0.01
Pre-existing medical conditions (%)						
Depression	17.9	12.8	0.14 ^a	17.9	17.9	<0.001
Mood disorders, including bipolar disorders	21.1	15.1	0.16 ^a	21.1	21.0	0.001
Anxiety, dissociative, somatoform and other nonpsychotic mental disorders, including posttraumatic stress disorder	21.9	14.4	0.19 ^a	21.9	21.6	0.007
Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders	1.1	1.8	0.06	1.1	0.9	0.02
Behavioral disorders, including sleep disorders	4.7	2.5	0.12 ^a	4.7	4.6	0.007
Disorders of adult personality and behavior, including impulse and gender identity disorders	0.7	0.7	0.003	0.7	0.7	0.002
Symptoms and signs involving an emotional state	2.4	2.1	0.02	2.4	2.3	0.007
Sleeping disorders including insomnia	29.4	16.8	0.30 ^a	29.4	29.1	0.006
Chronic pain	17.1	11.2	0.17 ^a	17.1	16.9	0.007
Alcohol use disorder	2.2	3.1	0.06	2.2	2.0	0.009
Tobacco use disorder	12.1	11.4	0.02	12.1	11.4	0.02
Opioid use disorder	1.2	1.2	0.005	1.2	1.0	0.01
Cannabis use disorder	0.8	1.1	0.03	0.8	0.7	0.01
Cocaine use disorder	0.5	0.8	0.03	0.5	0.4	0.02
Other stimulant-related disorders	0.4	0.4	0.004	0.4	0.3	0.003
Other psychoactive substance-related disorders	0.9	1.0	0.02	0.9	0.8	0.01
Overweight and obesity	46.3	23.5	0.49 ^a	46.3	47.0	0.01

Table 4 continued. Characteristics of T2DM cohort before and after propensity score matching as presented in Wang and associates.

Table 2 (continued) | Characteristics of the semaglutide group and non-GLP1R agonist anti-diabetes medication group for the study population with T2DM and no history of suicidal ideation before the index event (first prescription of semaglutide or other non-GLP1R agonist anti-diabetes medications from 1 December 2017 to 31 May 2021), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	Non-GLP1R agonist anti-diabetes medication group	SMD	Semaglutide group	Non-GLP1R agonist anti-diabetes medication group	SMD
Cancer	28.4	23.5	0.11*	28.4	28.0	0.007
Traumatic brain injury	1.5	1.6	0.01	1.5	1.4	0.008
Previous medication prescription or procedures (%)						
Bariatric surgery	1.6	0.7	0.09	1.6	1.5	0.002
Antidepressants	29.8	20.7	0.21*	29.8	29.6	0.005
Antipsychotics	10.8	9.1	0.06	10.8	10.1	0.02
Antiepileptics	26.6	19.5	0.17*	25.7	25.6	0.001
Benzodiazepine-derivative sedatives or hypnotics	36.2	28.5	0.17*	36.2	35.4	0.02
Esketamine	0.2	0.2	0.01	0.2	0.2	0.002
Ketamine	2.8	2.1	0.05	2.8	2.7	0.007
Lithium	0.1	0.1	0.005	0.1	0.1	0.01
Bupropion	6.3	3.1	0.15*	6.3	6.4	0.001
Naltrexone	0.7	0.2	0.08	0.7	0.7	0.002
Phentermine	2.0	0.4	0.15*	2.0	2.0	0.004
Orlistat	0.3	0.1	0.04	0.3	0.2	0.009
Topiramate	3.2	1.3	0.12*	3.0	3.2	0.009
Insulin	43.0	22.1	0.46*	43.0	43.6	0.01
Metformin	60.0	27.3	0.70*	60.0	61.5	0.03
Alpha glucosidase inhibitors	0.4	0.2	0.04	0.4	0.4	0.005
DPP-4 inhibitors	21.6	6.4	0.45*	21.6	21.6	<0.001
SGLT2 inhibitors	17.9	1.5	0.56*	17.9	16.6	0.04
Sulfonylureas	28.0	13.1	0.38	27.9	28.3	0.008
Thiazolidinediones	6.6	2.9	0.17*	6.6	6.7	0.003

The status of variables was based on the presence of related clinical codes any time to 1 day before the index event. *SMD greater than 0.1, a threshold indicating group imbalance.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AIDA E KUZUCAN
03/14/2024 10:46:45 AM

ANDREW D MOSHOLDER
03/14/2024 11:27:08 AM

YANDONG QIANG
03/14/2024 12:43:01 PM

WEI HUA
03/14/2024 06:20:42 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	11/1/2023		
To:	Oriola Temitope temitope.oriola@fda.hhs.gov		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	N/A-OPQ/OSE led
From	Farzaneh Akhavanik, updates to Robert Nakielny's previous memo are made in OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Subject	ANDA 215503 Liraglutide ICC# (b) (4) Case (b) (4)		
Recommendation	Filing Recommendation Date: N/A ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 6/6/2022 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies Reviewer Comment: CDER is planning to CR this file for other review areas, and we are therefore wrapping up our review with all remaining deficiencies identified in red below. Updated Reviewer Comments: The sponsor has provided a response to the remaining deficiencies. Please see Appendix A for the sponsor's response and reviewer's notes. The sponsor's response is (b) (4). There are no remaining deficiencies identified.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
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ICC# 2300588
ANDA 215503 ,Liraglutide
Hikma Pharmaceuticals USA INC.

Farzaneh S. Akhavannik -S	Digitally signed by Farzaneh S. Akhavannik -S Date: 2023.11.01 13:00:22 -04'00'	Courtney Evans -S	Digitally signed by Courtney Evans -S Date: 2023.11.01 21:39:32 -04'00'	
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1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	ANDA 215503
Sponsor	HIKMA PHARMACEUTICALS USA INC
Drug/Biologic	Liraglutide
Indications for Use	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Device Constituent	Pen-Injector
Related Files	(b) (4)

Review Team	
Lead Device Reviewer	<i>Rob Nakielny</i>
Lead Device Reviewer	<i>Farzaneh Akhavannik</i>

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
 - ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Clinical Validation			X	The clinical review is deferred to CDER/OSE/DMEPA.
Human Factors Validation			X	The human factors review is deferred to CDER/OSE/DMEPA. Per FDA response CC#10691: Additional comparative HF testing is not warranted.
Facilities & Quality Systems	X			(b) (4) A final deficiency related to (b) (4) is presented for the final CR letter- (b) (4) - Please refer to Appendix A, IR#7 for the sponsor's response and reviewer's comments.

2.1. Comments to the Review Team

- ☐ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

Comment #:1

Note: (b) (4)

Comment:

1. (b) (4)
2. (b) (4)
3. (b) (4)

b.

(b) (4)

c.

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

(b) (4)

Reviewer's notes:

The sponsor has provided an acceptable response to IR#7. Please refer to Appendix A, IR#7 for the sponsor's response and reviewer's comments.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW.....	3
2. EXECUTIVE SUMMARY AND RECOMMENDATION	4
2.1. Comments to the Review Team	4
2.2. Complete Response Deficiencies	5
2.3. Recommended Post-Market Commitments/Requirements	5
3. PURPOSE/BACKGROUND	8
3.1. Scope	8
3.2. Prior Interactions	8
3.2.1. Related Files.....	8
3.3. Indications for Use	9
3.4. Materials Reviewed.....	9
4. DEVICE DESCRIPTION.....	9
4.1. Device Description (per 3.2.P.7 Container Closure System).....	9
4.2. Steps for Using the Device.....	11
4.3. Device Description Conclusion.....	13
5. FILING REVIEW.....	13
5.1. Filing Review Checklist.....	13
5.2. Facilities Information	15
5.3. Quality System Documentation Triage Checklist.....	15
5.4. Filing Review Conclusion.....	16
6. LABELING	17
6.1. General Labeling Review	17
6.2. Labeling Review Conclusion	19
7. DESIGN CONTROL SUMMARY.....	19
7.1. Summary of Design Control Activities.....	19
(b) (4)	
7.3. Applicable Standards and Guidance Documents	21
7.4. Design Control Review Conclusion.....	21
8. RISK ANALYSIS	21
(b) (4)	
9. DESIGN VERIFICATION REVIEW	25
9.1. Performance/Engineering Verification	25
(b) (4)	
10. CLINICAL VALIDATION REVIEW	37
10.1. Review of Clinical Studies	37
11. HUMAN FACTORS VALIDATION REVIEW	37
12. FACILITIES & QUALITY SYSTEMS	38
12.1. Facility Inspection Report Review	38
12.2. Quality Systems Documentation Review	38
(b) (4)	

	(b) (4)
12.3. Control Strategy Review	44
12.4. Facilities & Quality Systems Review Conclusion.....	45
13. APPENDIX A (INFORMATION REQUESTS)	47
	(b) (4)

3. PURPOSE/BACKGROUND

3.1.Scope

HIKMA PHARMACEUTICALS USA INC. is requesting approval of Liraglutide through an ANDA submission. The device constituent of the combination product is a Pen-Injector.

Choose an item. has requested the following [consult](#) for review of the device constituent of the combination product:

Facilities inspection consult and Technical Consult

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device Description, Labeling, Design Controls, Risk Analysis, Design Verification, Facilities & Quality Systems

This review will not cover the following review areas:

- Clinical - the review of this information is deferred to CDER/OSE/DMEPA
- Components that are part of primary packaging
- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors -the review of this information is deferred to CDER/OSE/DMEPA
- The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

- 1) FDA response of CC#01606 for Q1/Q2 confirmation;
- 2) FDA response of CC#10691 for Human Factor Study Waiver;
- 3) FDA response of CC#12118 for packaging requirement;
- 4) FDA response of CC#12332 for Q1Q2 confirmation;
- 5) ANDA-215503-PSUB-Meeting-17677

Device related details (for reviewer reference) were identified in the above related files and provided below as written in the corresponding response memos:

#2. CC#10691:

“identified differences are minor design differences in that they would not be expected to impact an external critical design attribute involving the administration of the drug product, and therefore we agree that **additional comparative human factors testing would not be warranted**”.

(b) (4)

“We acknowledge that you have submitted the performance comparison of your test device and the RLD device, (b) (4). Assessment of this data will be determined during the scientific review of the ANDA and is out of scope of the current controlled correspondence”.

“OGD recommends that you provide data on device robustness of the proposed test pen injector device up to 30 days’ use, as indicated in the RLD labeling, within the ANDA submission”.

#3. CC#12118:



3.3.Indications for Use

Combination Product	Indications for Use
Liraglutide	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Pen-Injector	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	3.2.P.7 Container Closure System
0001	3.2.P.3.1 Manufacturer(s)
0001	3.2.P.8 Stability
0001	3.2.R Regional Information
0010	1.2 Responses to Discipline Review Letter (DRL) 4/14/22 (pg 83-90)
	(b) (4)

4. DEVICE DESCRIPTION

4.1.Device Description (per 3.2.P.7 Container Closure System)

Liraglutide injection is a clear, almost colorless solution. The device constituent (b) (4) of the combination product is a pre-filled (non-refillable), disposable, single user/multi-dose pen injector containing 3 ml of the drug product at a concentration of 6 mg/ml for subcutaneous injection (skin in the stomach, thigh or upper arm), and delivering user-adjustable doses of 0.6 mg, 1.2 mg and 1.8 mg of Liraglutide. (b) (4)

The Reference Listed Drug (RLD) that is the basis of this ANDA application is VICTOZA® (Liraglutide injection) 18 mg/3 mL (6 mg/mL), NDA 022341, held by Novo Nordisk Inc. (NDA 022341)

(b) (4)

The extent of the comparison between the RLD and the proposed “generic” Pen Injector includes visual review identifying [REDACTED]

(b) (4)

“Comparison between RLD and the Generic “proposed” pen injector below).

Reviewer comment – this appears reasonable since the threshold analysis may only derive from device component labeling information.

BD Medical provides the [REDACTED] components of the “Generic” Pen Injector [REDACTED]

(b) (4)

- the Letter of Authorization to the related [REDACTED] pen design [REDACTED] is included in the submission.

(b) (4)

(b) (4)

(b) (4)

Comparison between RLD and the Generic “proposed” pen injector

A “Threshold Analysis” which included a (1) labeling comparison, (2) comparative task analysis, and (3) a physical comparison was performed by Hybio and is provided in section **5.3.5.4 Other Study Reports** for identification and assessment of differences in the design of the user interface and in performing of the tasks involved with delivering the injection for the generic combination product when compared to its RLD.

There were no functional performance specifications identified for the RLD from the sources available, except for a **hold time of 6 seconds** which is similar for the proposed “Generic” Pen Injector.

Functional performance for the Generic Pen Injector was therefore based on:

1. Verification of the design inputs as determined by BD (see 7.2 Design Inputs and Outputs)
2. Control of dose accuracy in accordance with ISO 11608-1 as tested by Hybio for process verification and stability.

(b) (4)

Difference between RLD and the Generic “proposed” pen injector

(b) (4)

4.2.Steps for Using the Device

(b) (4)

(b) (4)

4.3.Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	
Reviewer Comments									
Device description is adequate									
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No									

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1.Filing Review Checklist

Filing Review Checklist				
Description	Present			
	Yes	No	N/A	Location/Notes
Description of Device Constituent	X			3.2.P.7 – container closure

Device Constituent Labeling		X			1.14 labeling, proposed user manual similar to RLD manual (name of device changed only)
Letters of Authorization		X			1.4.2 – Statement of Right of Reference
Essential Performance Requirements defined by the application Sponsor		X			(b) (4)
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X			(b) (4)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X			See 3.2.R Regional Information, Device Narrative
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X			3.2.P.2 Pharmaceutical Development for assembly process pg 132 and container closure system pg 142
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X			(b) (4)
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X			(b) (4)
	Engineering Performance	X			
	Reliability	X			
	Biocompatibility	X			
	Sterility			X	
	Human Factors	X			(b) (4) for design input validation
	Shelf Life, Aging and Transportation				The stability studies for the three submission batches (lots 3058200701, 3058200702, 3058200703) will be continued to cover the proposed shelf life
	Clinical Validation			X	Deferred to DMEPA
	Human Factors Validation			X	Note: Substitutability between generic pen injector and RLD pen injector has been confirmed by FDA through CC issued on June, 2020 (FDA response of CC#10691 for Human Factor Study Waiver is provided in Module 1.2) that generic pen injector and RLD pen injector are almost the same regarding user interface, and human factor study can be waived.

	Description of Device Manufacturing Process	X		3.2.R Regional Information, Pharmaceutical Development pg 132
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		3.2R Regional Information Device Narrative
	CAPA Procedure		X	Issue IR (DRL#1, CR#7) Refer to section 12.2.3. Corrective and Preventive Action Review
	Control Strategy provided for EPRs		X	Issue IR (DRL #4) – resolved refer to section 12.3 Control Strategy Review

Reviewer Comment

Filing Review Checklist is complete.

Items deficient include:

-
-

(b) (4)

(b) (4)

5.2.Facilities Information

Firm Name:	Hybio Pharmaceutical Co., Ltd. (Pingshan factory)
Address:	2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China.
FEI:	3011090684
Responsibilities:	(b) (4)

Inspectional History

(b) (4)

Inspection Recommendation:

☐ A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part: (b) (4)

☐ An inspection is not required because Choose an item.

5.3.Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
---	---

Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

A pre-approval inspection is recommended for Hybio Pharmaceutical Co., Ltd. (Pingshan factory) (b) (4)

5.4.Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), FEI 3011090684, 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China	
Reviewer Comments (b) (4) a Pre Approval Inspection is recommended. (b) (4)	
Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☐ No ☐ N/A	

6. LABELING

6.1.General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

Labeling included in the submission included:
 Container labeling, Carton Labeling

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Carton labeling was provided as follows:

The general device instructions for use and package labeling are adequate. The generic and RLD device share similar labeling. This labeling is reviewed by DMEPA and compared between the RLD and generic device in the ANDA.

6.2.Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
The labeling is adequate		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

7. DESIGN CONTROL SUMMARY

7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health		X	
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing			X
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

(b) (4)

7.3.Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

(b) (4)

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	Y
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products	Y	Y
ISO 11608-1:2014 (EN 11608-1:2015): Needle-based injection systems for medical use -- Requirements and test methods -- Part 1: Needle-based injection systems	Y	Y
ISO 11608-2:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 2: Needles	Y	Y
ISO 11608-3:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 3: Finished containers	Y	Y

7.4.Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments The Design Control is adequate		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. RISK ANALYSIS

8.1.Risk Management Plan

Risk Management by BD

The Risk Management Plan is included

(b) (4)

(b) (4)



9. DESIGN VERIFICATION REVIEW

9.1.Performance/Engineering Verification

9.1.1. *Essential Performance Requirement Evaluation*

(b) (4)



This Design Verification for the specific “Generic”  customized disposable pen for Liraglutide Injection was presented in summary in:

(b) (4)



(b) (4)

9.3.Discipline Specific Sub-Consulted Review Summary

- ☐ No Additional Discipline Specific Sub-Consults were requested
- ☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies

- ☐ There is no device related clinical studies for review
- ☐ There are clinical studies for review

BD does not conduct clinical investigation for BD Vystra. The ANDA does not rely on clinical evaluation.

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☐

(b) (4)

Three formative studies were done throughout different stages of the design cycle and results of the formative studies were used to improve the design and/or Instructions for Use.

As described previously, the Customer is responsible for the design validation and summative human factor study of the finished Pen – although this is ANDA and the HF comparison study was waved.

As such, BD's human factor study scope is limited to formative studies.

(b) (4)

Three rounds of usability formative testing were conducted on the (b) (4) to assess the (b) (4) itself and its associated Instructions for Use (IFU) in order to find evidence for use errors, particularly those that were safety related, and to identify ways that the use errors could be reduced or eliminated through design improvements, to optimize the usability of the (b) (4)

Validation appears adequate based on the longevity and use of the generic product. Design inputs are reasonable as compared to other pen injectors.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☐

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☐

(b) (4)

(b) (4)

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.

☒ Yes

☐ No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Components are provided from BD with Certificate of Analysis (CofA) at incoming inspection from Hybio (as found in 3.2.P.7 Container Closure System).

- Body (b) (4)
- Cartridge (b) (4)
- Pen cap (b) (4)

Shown below is the Body Subassembly COA (b) (4)

Appearance	(b) (4)	Conform to the requirement
Size	(b) (4)	Conform to the requirement
Functional structure	(b) (4)	Conform to the requirement
Volumetric accuracy	(b) (4)	Conform to the requirement

Pen Assembly (at release)

Dose Accuracy tested at release per pg 194 of 3.2.P.2 Pharmaceutical Development - Narrative

Assembly of pen injector	Assembly order	Conducted in accordance with the assembly procedure	Ensure the dose accuracy of pen injector
--------------------------	----------------	---	--

Note: The items marked "*" are critical process parameters

Essential Performance Requirements Control Strategy Table

* The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	Incoming CofA for body subassembly, final release	Y
Audible Clicking during dose increment/decrement	Incoming CofA for body subassembly	Y
Injection Force	Not in control Strategy Per IR#4 DRL response - Added to final release testing	Y
Dose selection torque	Not in control Strategy Per IR#4 DRL response - Added to incoming CofA for body subassembly	Y
Cap attachment and detachment force	Not in control strategy Per IR#4 DRL response - added to incoming CofA for Pen Cap	Y

Reviewer Comments

(b) (4)

Issue IR #4 for DRL

Per the DRL response to IR#4 in Appendix A

(b) (4)

- resolved

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☐ No ☐ N/A

Final Deficiencies:

☐ Yes ☐ No ☐ N/A

Reviewer Comments

Deficiencies #1, #4 were sent to the firm related to

(b) (4)

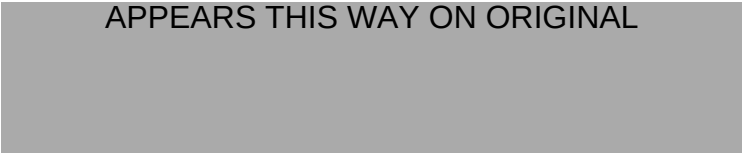
. Resolved

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

Refer to Appendix A for deficiencies #1, #4, #7

<<END OF REVIEW>>

APPEARS THIS WAY ON ORIGINAL



13.APPENDIX A (INFORMATION REQUESTS)

(b) (4)



5 Pages have been withheld in full as b4 (CCI/TS)
immediately following this page

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	10/28/2021		
To:	Jin Lee		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	N/A-OPQ/OSE led
From	Rob Nakielny OPEQ/OHT3/DHT3C		
Through (Team)	Courtney EvansChoose an item., Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Subject	ANDA 215503 Liraglutide ICC# (b) (4) Case (b) (4)		
Recommendation	Filing Recommendation Date: N/A ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 6/6/2022 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies Reviewer Comment: CDER is planning to CR this file for other review areas and we are therefore wrapping up our review with all remaining deficiencies identified in red below.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Robert Nakielny -S Digitally signed by Robert Nakielny -S Date: 2022.06.07 09:45:16 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2022.06.07 09:49:43 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	ANDA 215503
Sponsor	HIKMA PHARMACEUTICALS USA INC
Drug/Biologic	Liraglutide
Indications for Use	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Device Constituent	Pen-Injector
Related Files	(b) (4)

Review Team	
Lead Device Reviewer	Rob Nakielny

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	02/22/2022
	5/31/22 DRD

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☐ Approvable with PMC or PMR, [See Section 2.3](#)
- ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Clinical Validation			X	The clinical review is deferred to CDER/OSE/DMEPA.
Human Factors Validation			X	The human factors review is deferred to CDER/OSE/DMEPA. Per FDA response CC#10691: Additional comparative HF testing is not warranted.
Facilities & Quality Systems		X		(b) (4) A final deficiency related to (b) (4) is presented for the final CR letter

2.1. Comments to the Review Team

- ☐ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

Comment #:1

Note: (b) (4)

Comment:

1. (b) (4)
2. (b) (4)
3. (b) (4)

c.

(b) (4)

2.2.Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Major Deficiencies:

(b) (4)

2.3.Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

TABLE OF CONTENTS

1. SUBMISSION OVERVIEW.....	2
2. EXECUTIVE SUMMARY AND RECOMMENDATION	3
2.1. Comments to the Review Team	3
2.2. Complete Response Deficiencies	4
2.3. Recommended Post-Market Commitments/Requirements	4
3. PURPOSE/BACKGROUND	7
3.1. Scope	7
3.2. Prior Interactions	7
3.2.1. Related Files.....	7
3.3. Indications for Use	8
3.4. Materials Reviewed.....	8
4. DEVICE DESCRIPTION.....	8
4.1. Device Description (per 3.2.P.7 Container Closure System).....	8
4.2. Steps for Using the Device.....	10
4.3. Device Description Conclusion.....	12
5. FILING REVIEW.....	12
5.1. Filing Review Checklist.....	12
5.2. Facilities Information	14
5.3. Quality System Documentation Triage Checklist.....	14
5.4. Filing Review Conclusion.....	15
6. LABELING	16
6.1. General Labeling Review	16
6.2. Labeling Review Conclusion	18
7. DESIGN CONTROL SUMMARY.....	18
7.1. Summary of Design Control Activities.....	18
(b) (4)	
7.3. Applicable Standards and Guidance Documents	20
7.4. Design Control Review Conclusion.....	20
8. RISK ANALYSIS	20
(b) (4)	
9. DESIGN VERIFICATION REVIEW	24
9.1. Performance/Engineering Verification	24
(b) (4)	
10. CLINICAL VALIDATION REVIEW	36
10.1. Review of Clinical Studies	36
11. HUMAN FACTORS VALIDATION REVIEW	36
12. FACILITIES & QUALITY SYSTEMS	37
12.1. Facility Inspection Report Review	37
12.2. Quality Systems Documentation Review	37
(b) (4)	

	(b) (4)
12.3. Control Strategy Review	43
12.4. Facilities & Quality Systems Review Conclusion.....	44
13. APPENDIX A (INFORMATION REQUESTS)	46
	(b) (4)

3. PURPOSE/BACKGROUND

3.1.Scope

HIKMA PHARMACEUTICALS USA INC. is requesting approval of Liraglutide through an ANDA submission. The device constituent of the combination product is a Pen-Injector.

Choose an item. has requested the following [consult](#) for review of the device constituent of the combination product:

Facilities inspection consult and Technical Consult

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device Description, Labeling, Design Controls, Risk Analysis, Design Verification, Facilities & Quality Systems

This review will not cover the following review areas:

- Clinical - the review of this information is deferred to CDER/OSE/DMEPA
- Components that are part of primary packaging
- Compatibility of the drug with the device materials (deferred to CDER)
- Biocompatibility of the primary container closure, including needle (deferred to CDER)
- Sterility (primary container closure sterility deferred to CDER)
- Human Factors -the review of this information is deferred to CDER/OSE/DMEPA
- The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

- 1) FDA response of CC#01606 for Q1/Q2 confirmation;
- 2) FDA response of CC#10691 for Human Factor Study Waiver;
- 3) FDA response of CC#12118 for packaging requirement;
- 4) FDA response of CC#12332 for Q1Q2 confirmation;
- 5) ANDA-215503-PSUB-Meeting-17677

Device related details (for reviewer reference) were identified in the above related files and provided below as written in the corresponding response memos:

#2. CC#10691:

“identified differences are minor design differences in that they would not be expected to impact an external critical design attribute involving the administration of the drug product, and therefore we agree that **additional comparative human factors testing would not be warranted**”.

(b) (4)

“We acknowledge that you have submitted the performance comparison of your test device and the RLD device (b) (4)

Assessment of this data will be determined during the scientific review of the ANDA and is out of scope of the current controlled correspondence”.

“OGD recommends that you provide data on device robustness of the proposed test pen injector device up to 30 days' use, as indicated in the RLD labeling, within the ANDA submission”.

#3. CC#12118:



3.3.Indications for Use

Combination Product	Indications for Use
Liraglutide	Liraglutide injection 18 mg/3 mL (6 mg/mL) is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Pen-Injector	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	3.2.P.7 Container Closure System
0001	3.2.P.3.1 Manufacturer(s)
0001	3.2.P.8 Stability
0001	3.2.R Regional Information
0010	1.2 Responses to Discipline Review Letter (DRL) 4/14/22 (pg 83-90)
	(b) (4)

4. DEVICE DESCRIPTION

4.1.Device Description (per 3.2.P.7 Container Closure System)

Liraglutide injection is a clear, almost colorless solution. The device constituent (b) (4) of the combination product is a pre-filled (non-refillable), disposable, single user/multi-dose pen injector containing 3 ml of the drug product at a concentration of 6 mg/ml for subcutaneous injection (skin in the stomach, thigh or upper arm), and delivering user-adjustable doses of 0.6 mg, 1.2 mg and 1.8 mg of Liraglutide. (b) (4)

The Reference Listed Drug (RLD) that is the basis of this ANDA application is VICTOZA® (Liraglutide injection) 18 mg/3 mL (6 mg/mL), NDA 022341, held by Novo Nordisk Inc. (NDA 022341)

(b) (4)

The extent of the comparison between the RLD and the proposed “generic” Pen Injector includes visual review identifying [REDACTED]

(b) (4)

“Comparison between RLD and the Generic “proposed” pen injector below).

Reviewer comment – this appears reasonable since the threshold analysis may only derive from device component labeling information.

BD Medical provides the [REDACTED] components of the “Generic” Pen Injector [REDACTED]

(b) (4)

- the Letter of Authorization to the related [REDACTED] pen design [REDACTED] is included in the submission.

(b) (4)

(b) (4)

(b) (4)

Comparison between RLD and the Generic “proposed” pen injector

A “Threshold Analysis” which included a (1) labeling comparison, (2) comparative task analysis, and (3) a physical comparison was performed by Hybio and is provided in section **5.3.5.4 Other Study Reports** for identification and assessment of differences in the design of the user interface and in performing of the tasks involved with delivering the injection for the generic combination product when compared to its RLD.

There were no functional performance specifications identified for the RLD from the sources available, except for a **hold time of 6 seconds** which is similar for the proposed “Generic” Pen Injector.

Functional performance for the Generic Pen Injector was therefore based on:

1. Verification of the design inputs as determined by BD (see 7.2 Design Inputs and Outputs)
2. Control of dose accuracy in accordance with ISO 11608-1 as tested by Hybio for process verification and stability.

(b) (4)

Difference between RLD and the Generic “proposed” pen injector

(b) (4)

4.3.Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION									
Filing Deficiencies:			Mid-Cycle Deficiencies:			Final Deficiencies:			
☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	☐ Yes	☐ No	☐ N/A	
Reviewer Comments									
Device description is adequate									
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No									

5. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1.Filing Review Checklist

Filing Review Checklist				
Description	Present			
	Yes	No	N/A	Location/Notes
Description of Device Constituent	X			3.2.P.7 – container closure

Device Constituent Labeling		X			1.14 labeling, proposed user manual similar to RLD manual (name of device changed only)
Letters of Authorization		X			1.4.2 – Statement of Right of Reference
Essential Performance Requirements defined by the application Sponsor		X			(b) (4)
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X			(b) (4)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X			See 3.2.R Regional Information, Device Narrative
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X			3.2.P.2 Pharmaceutical Development for assembly process pg 132 and container closure system pg 142
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X			(b) (4)
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X			
	Engineering Performance	X			
	Reliability	X			
	Biocompatibility	X			
	Sterility			X	Deferred to DMEPA
	Human Factors	X			(b) (4) for design input validation
	Shelf Life, Aging and Transportation				The stability studies for the three submission batches (lots 3058200701, 3058200702, 3058200703) will be continued to cover the proposed shelf life
	Clinical Validation			X	Deferred to DMEPA
	Human Factors Validation			X	Note: Substitutability between generic pen injector and RLD pen injector has been confirmed by FDA through CC issued on June, 2020 (FDA response of CC#10691 for Human Factor Study Waiver is provided in Module 1.2) that generic pen injector and RLD pen injector are almost the same regarding user interface, and human factor study can be waived.

	Description of Device Manufacturing Process	X		3.2.R Regional Information, Pharmaceutical Development pg 132
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		3.2R Regional Information Device Narrative
	CAPA Procedure		X	Issue IR (DRL#1, CR#7) Refer to section 12.2.3. Corrective and Preventive Action Review
	Control Strategy provided for EPRs		X	Issue IR (DRL #4) – resolved refer to section 12.3 Control Strategy Review

Reviewer Comment

Filing Review Checklist is complete.

Items deficient include:

- (b) (4)
-

(b) (4)

5.2.Facilities Information

Firm Name:	Hybio Pharmaceutical Co., Ltd. (Pingshan factory)
Address:	2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China.
FEI:	3011090684
Responsibilities:	(b) (4)

(b) (4)

Inspection Recommendation:

☐ A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part: (b) (4)

☐ An inspection is not required because Choose an item.

5.3.Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
---	---

Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

A pre-approval inspection is recommended for Hybio Pharmaceutical Co., Ltd. (Pingshan factory) (b) (4)

5.4.Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: Hybio Pharmaceutical Co., Ltd. (Pingshan factory), FEI 3011090684, 2nd Luhui Rd, Kengzi Jinsha community, Pingshan district, Shenzhen, Guangdong 518118, China	
Reviewer Comments (b) (4)	
Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☐ No ☐ N/A	

6. LABELING

6.1.General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

Labeling included in the submission included:
 Container labeling, Carton Labeling

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Carton labeling was provided as follows:

1 Page has been withheld in full as b4 Draft Labeling

The general device instructions for use and package labeling are adequate. The generic and RLD device share similar labeling. This labeling is reviewed by DMEPA and compared between the RLD and generic device in the ANDA.

6.2.Labeling Review Conclusion

LABELING REVIEW CONCLUSION									
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A			Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A			Final Deficiencies: ☐ Yes ☐ No ☐ N/A			
Reviewer Comments The labeling is adequate									
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No									

7. DESIGN CONTROL SUMMARY

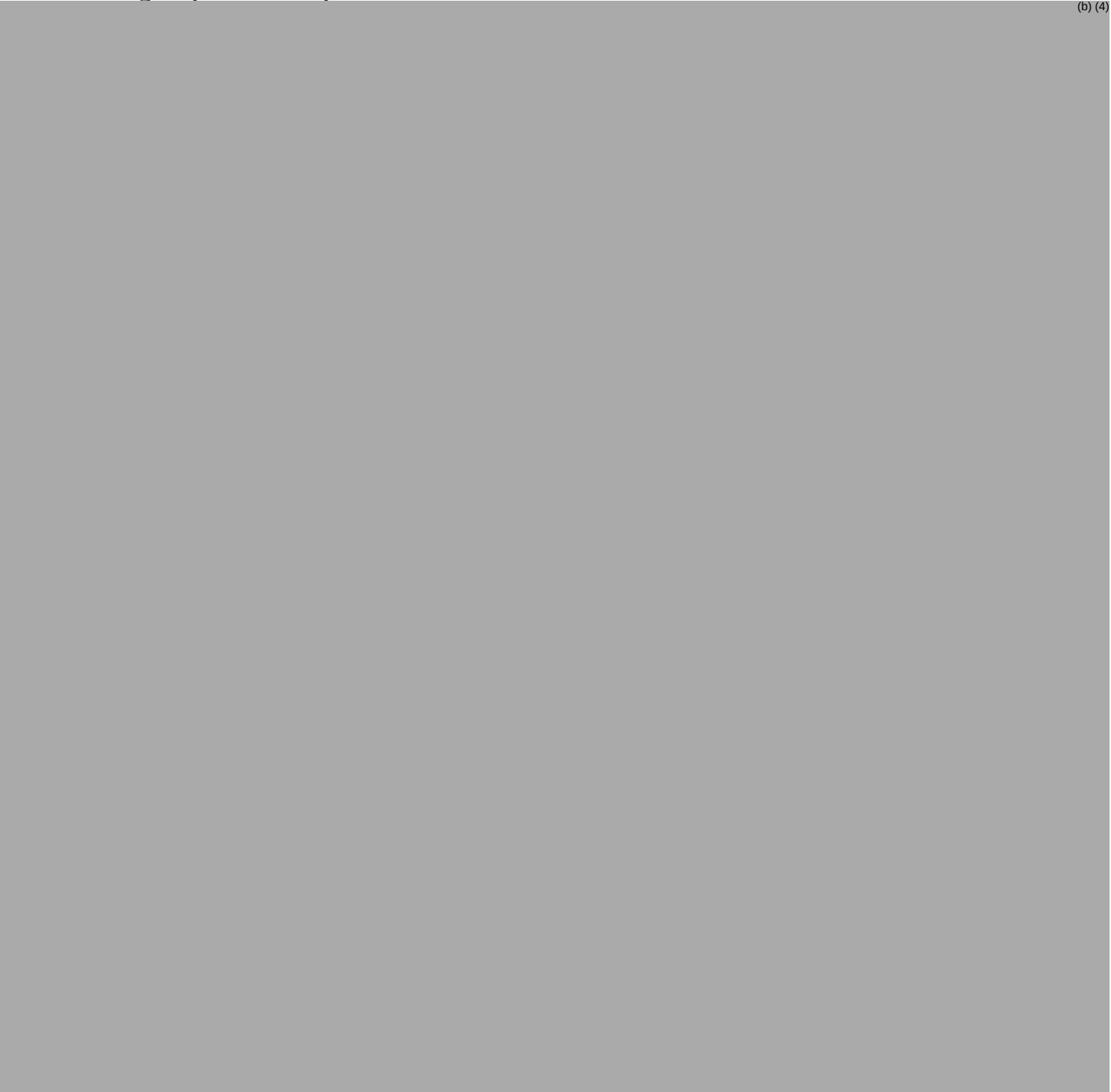
7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health		X	
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing			X
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

(b) (4)

7.2.Design Inputs and Outputs

(b) (4)



Reviewer Comments

Design inputs and Outputs appears complete
--

7.3.Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

(b) (4)

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	Y
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products	Y	Y
ISO 11608-1:2014 (EN 11608-1:2015): Needle-based injection systems for medical use -- Requirements and test methods -- Part 1: Needle-based injection systems	Y	Y
ISO 11608-2:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 2: Needles	Y	Y
ISO 11608-3:2012 Needle-based injection systems for medical use — Requirements and test methods — Part 3: Finished containers	Y	Y

7.4.Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments The Design Control is adequate		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. RISK ANALYSIS

8.1.Risk Management Plan

Risk Management by BD

The Risk Management Plan is included

(b) (4)

(b) (4)



9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. *Essential Performance Requirement Evaluation*

(b) (4)



This Design Verification for the specific “Generic”  customized disposable pen for Liraglutide Injection was presented in summary in:

(b) (4)



(b) (4)

(b) (4)

9.3.Discipline Specific Sub-Consulted Review Summary

- ☐ No Additional Discipline Specific Sub-Consults were requested
- ☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies

- ☐ There is no device related clinical studies for review
- ☐ There are clinical studies for review

BD does not conduct clinical investigation for BD Vystra. The ANDA does not rely on clinical evaluation.

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☐

(b) (4)

Three formative studies were done throughout different stages of the design cycle and results of the formative studies were used to improve the design and/or Instructions for Use.

As described previously, the Customer is responsible for the design validation and summative human factor study of the finished Pen – although this is ANDA and the HF comparison study was waved.

As such, BD's human factor study scope is limited to formative studies.

(b) (4)

Three rounds of usability formative testing were conducted on the (b) (4) to assess the (b) (4) itself and its associated Instructions for Use (IFU) in order to find evidence for use errors, particularly those that were safety related, and to identify ways that the use errors could be reduced or eliminated through design improvements, to optimize the usability of the (b) (4)

Validation appears adequate based on the longevity and use of the generic product. Design inputs are reasonable as compared to other pen injectors.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☐

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☐

(b) (4)

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Components are provided from BD with Certificate of Analysis (CofA) at incoming inspection from Hybio (as found in 3.2.P.7 Container Closure System).

- Body (b) (4)
- Cartridge (b) (4)
- Pen cap (b) (4)

Shown below is the Body Subassembly COA – Hybio BD20421A – P200410) which includes 2 EPR verifications:

Appearance	(b) (4)	Conform to the requirement
Size		Conform to the requirement
Functional structure		Conform to the requirement
Volumetric accuracy		Conform to the requirement

Pen Assembly (at release)

Dose Accuracy tested at release per pg 194 of 3.2.P.2 Pharmaceutical Development - Narrative

Assembly of pen injector	Assembly order	Conducted in accordance with the assembly procedure	Ensure the dose accuracy of pen injector
--------------------------	----------------	---	--

Note: The items marked "*" are critical process parameters

Essential Performance Requirements Control Strategy Table

* The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	Incoming CofA for body subassembly, final release	Y
Audible Clicking during dose increment/decrement	Incoming CofA for body subassembly	Y
Injection Force	Not in control Strategy Per IR#4 DRL response - Added to final release testing	Y
Dose selection torque	Not in control Strategy Per IR#4 DRL response - Added to incoming CofA for body subassembly	Y
Cap attachment and detachment force	Not in control strategy Per IR#4 DRL response - added to incoming CofA for Pen Cap	Y

Reviewer Comments

(b) (4)

Issue IR #4 for DRL

Per the DRL response to IR#4 in Appendix A, (b) (4)

- resolved

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☐ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☐ No ☐ N/A

Final Deficiencies:

☐ Yes ☐ No ☐ N/A

Reviewer Comments

Deficiencies #1, #4 were sent to the firm related t

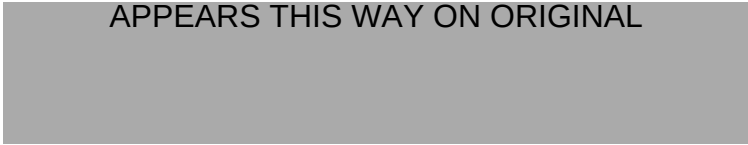
(b) (4)

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No

Refer to Appendix A for deficiencies #1, #4, #7

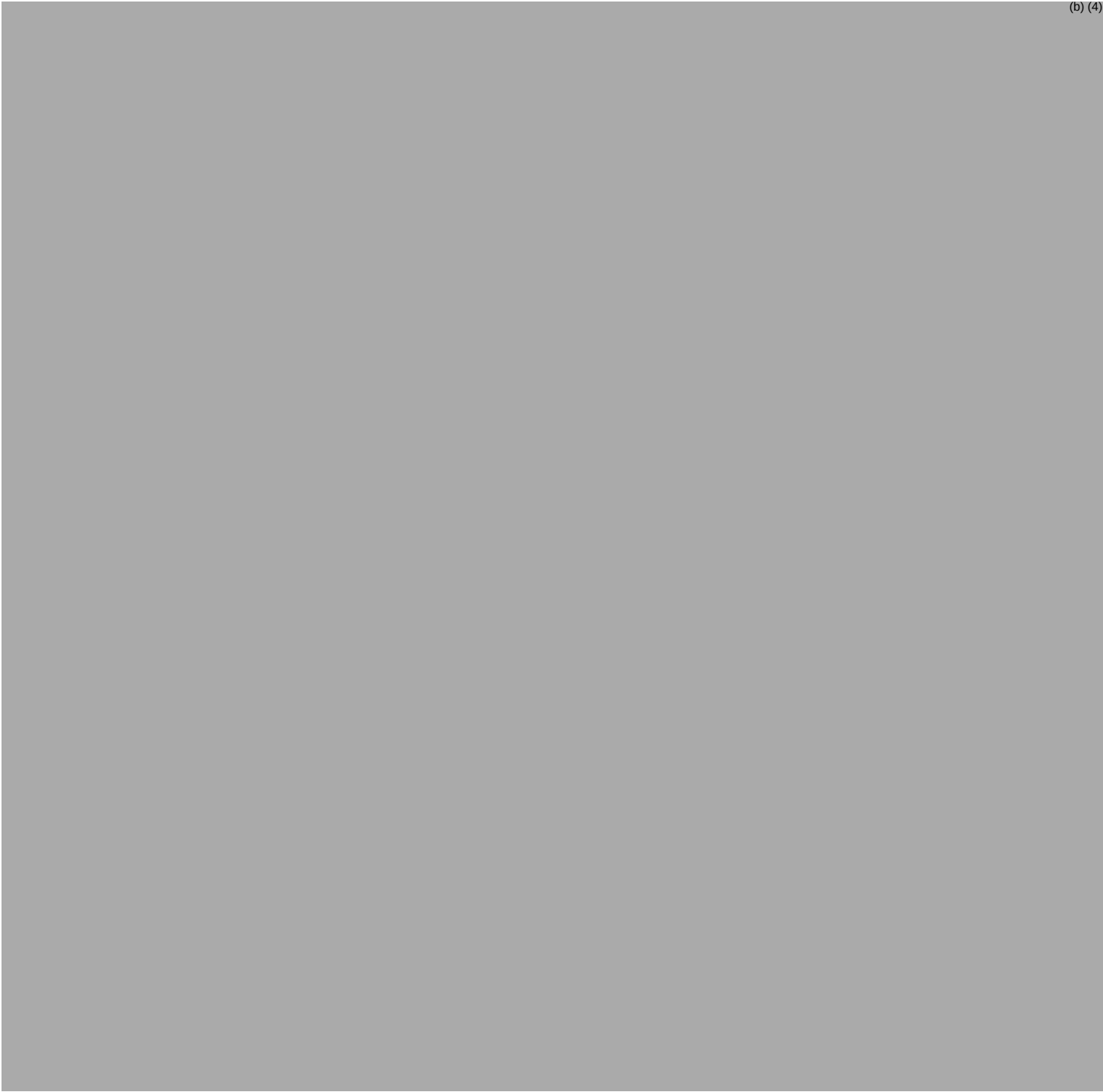
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APPEARS THIS WAY ON ORIGINAL



13.APPENDIX A (INFORMATION REQUESTS)

(b) (4)



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ANDA 215503

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Hikma Pharmaceuticals USA, Inc.
703 Palomar Airport Road
Suite 280
Carlsbad, CA 08003
Attention: Jonathan Endo
Manager, Regulatory Affairs

Dear Jonathan Endo:

This is in reference to your amendment received on September 23, 2024, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is December 23, 2024.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Kimberly
McCullough

Digitally signed by Kimberly McCullough

Date: 9/26/2024 09:55:24AM

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ANDA 215503

NOTIFICATION
New Regulatory Project Manager

Hikma Pharmaceuticals USA, Inc.

703 Palomar Airport Road
Suite 280
Carlsbad, CA 92011
Attention: Jonathan Endo
Manager, Regulatory Affairs

Dear Jonathan Endo:

Please refer to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of the new Regulatory Project Manager, Kimberly McCullough, for the above-indicated ANDA. We look forward to working with you on this important application for the American Public.

If you have any questions, contact Regulatory Project Manager, Kimberly McCullough, at (240) 402-9021, Kim.McCullough@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough, BS, RPh, MBA

Regulatory Project Manager
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Kimberly
McCullough

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ANDA 215503

**INFORMATION REQUEST
QUALITY**

Hikma Pharmaceuticals USA Inc
2325 Camino Vida Roble
Suite B
Carlsbad, CA 92011
Attention: Jonathan Endo
Manager, Regulatory Affairs

Dear Jonathan Endo:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 21, 2024, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection 18 mg/3 mL (6 mg/mL).

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Manufacturing

a.

(b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional

requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a complete written response, no later than April 8, 2024 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request¹, the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY
MINOR**

If you do not submit a complete written response by April 8, 2024, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

¹ Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 4/04/2024 09:01:07AM

GUID: 56f4536500ea9700421d7152e24f140d



ANDA 215503

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Hikma Pharmaceuticals USA Inc.
2325 Camino Vida Roble, Suite B
Carlsbad, CA 92011
Attention: Jonathan Endo
Manager Regulatory Affairs

Dear Jonathan Endo:

This is in reference to your amendment received on March 21, 2024, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient-Use Prefilled Pens.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is June 21, 2024.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Parth Soni, Regulatory Project Manager, at (301) 796-7673.

Sincerely,

{See appended electronic signature page}

Parth Soni, PharmD, MBA
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Parth
Soni

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Date: 3/27/2024 05:25:23PM

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ANDA 215503

AMENDMENT ACKNOWLEDGEMENT
Standard
Major

Hikma Pharmaceuticals USA Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Tamara Elder
Director Regulatory Affairs

Dear Tamara Elder:

This is in reference to your amendment received on June 30, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) Single-Patient Use Prefilled Pens.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard major amendment. If FDA determines that an inspection is not required to validate the information contained in this standard major amendment, the GDUFA goal date for review of this standard major amendment is February 29, 2024. If this standard major amendment requires an inspection, the goal date for review of this standard major amendment is April 30, 2024. Two possible goal dates are provided because FDA is unable to determine if an amendment requires an inspection at the time of submission. FDA will make this determination during the assessment of the amendment. For more information, see FDA's Guidance for Industry, *ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA*.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to

help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Parth Soni, Regulatory Project Manager, at (301) 796 - 7673.

Sincerely,

{See appended electronic signature page}

Parth Soni
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Alli
Schaefer

Digitally signed by Alli Schaefer

Date: 7/06/2023 01:30:57PM

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Comments: on behalf of Parth Soni



ANDA 215503

INFORMATION REQUEST

Hikma Pharmaceuticals USA Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) pre-filled single-use pen.

Reference is also made to your amendment dated December 3, 2021.

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product and we require additional information in order to complete our Clinical review.

1. We recommend that your proposed Instructions for Use (IFU) wording should reflect your proposed pen physical characteristics. (b) (4)

[REDACTED]

[REDACTED] We recommend that you revise the wording in your proposed IFU as follows:

- a. Revise Step C. Dial to the Flow Check Symbol to state, “Turn dose selector until the black line of flow check symbol [insert symbol] lines up with pointer (See Figure E).”
- b. Revise Step D. Prepare the Pen to state, “Keep needle pointing up and press dose button until the black line of 0 mg lines up with pointer (See Figure G).”
- c. Revise Step G. Dial the Dose to state,
 - i. “Turn the dose selector until the black line of your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L).”
 - ii. “If you select a wrong dose, change it by turning the dose selector backwards or forwards until the black line of the correct dose lines up with the pointer.”
- d. Revise Step H. Inject the Dose to state, “Press down on the center of the dose button to inject until the black line of 0 mg lines up with the pointer (See Figure M).”

2. [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED] we recommend that you revise your proposed IFU figures to [REDACTED] (b) (4)
- [REDACTED], consistent with the figures in the RLD IFU.

3. [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]. We recommend that you revise the carton labeling to state, “Intended for use with compatible disposable pen needles” to be consistent with your proposed IFU.

4. Submit revised labeling to ensure that modifications in your proposed IFU and carton labeling are adequate based on the recommendations above. We refer you to the FDA Draft Guidance for Industry “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA” (January 2017).

We request a complete written response no later than March 11, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
CLINICAL
LABELING

If you do not submit a complete written response by March 11, 2022, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research



Nitin K.
Patel

Digitally signed by Nitin K. Patel

Date: 3/04/2022 03:30:33PM

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ANDA 215503

DISCIPLINE REVIEW LETTER

Hikma Pharmaceuticals USA Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 08, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) pre-filled single-use pen.

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiencies:

- Your waiver request of in-vivo bioequivalence (BE) study requirements for your test product, Liraglutide Injection, 18 mg/3 mL (6 mg/mL), cannot be granted at this time. There are deficiencies related to (b) (4) which should be communicated to you by the Office of Pharmaceutical Quality (OPQ). Please address all outstanding deficiencies and communicate with OPQ for further evaluation.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **April 1, 2022**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition,

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Olubunmi Jaiyeola, Bioequivalence Project Manager, at Olubunmi.Jaiyeola@fda.hhs.gov or (301) 796 - 4126.

Sincerely,

{See appended electronic signature page}

Olubunmi Jaiyeola
Project Manager
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Olubunmi
Jaiyeola

Digitally signed by Olubunmi Jaiyeola

Date: 3/02/2022 09:54:38AM

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ANDA 215503

**DISCIPLINE REVIEW LETTER
QUALITY**

Hikma Pharmaceuticals USA Inc
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell
Director Regulatory Affairs

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, 18mg/3ml.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1.

2.

3.

4.

(b) (4)

(b) (4)

5.

6.

7.

8.

9.

10.

11.

B. Drug Product

(b) (4)

1.

(b) (4)

6.

C. Manufacturing

a. Process

(b) (4)

1.

2.

3.

4.

5.

(b) (4)



b. Facility

1.

(b) (4)



2.

D. Microbiology

1.

(b) (4)



2.

10.

11.

12.

13.

(b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**DISCIPLINE REVIEW LETTER
QUALITY**

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit

a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 2/28/2022 01:16:22PM

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ANDA 215503

INFORMATION REQUEST

Hikma Pharmaceuticals USA Inc
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell
Director Regulatory Affairs

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, Solution, 18mg/3ml.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Drug Product

a. (b) (4)

1.

2.

(b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional

requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than **February 10, 2022** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 2/07/2022 04:45:26PM

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ANDA 215503

INFORMATION REQUEST

Hikma Pharmaceuticals USA Inc
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell
Director Regulatory Affairs

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, Solution, 18mg/3ml.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. CDRH

1.

2.

3.

(b) (4)

4.

5.

6.

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than **February 02, 2022** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information

that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 1/26/2022 10:01:13AM

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ANDA 215503

INFORMATION REQUEST

Hikma Pharmaceuticals USA Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003
Attention: Sarah Ansell

Dear Sarah Ansell:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on September 8, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Liraglutide Injection, 18 mg/3 mL (6 mg/mL) pre-filled single-use pen.

The Clinical Discipline is reviewing your comparative (threshold) analyses for your proposed product. At this time, in order to complete our review of your proposed prefilled delivery device (pen injector), the review team will need to look at physical samples, and we will make arrangements to access the physical samples. We request three samples of the to-be-marketed proposed product and three samples of the RLD for evaluation. The proposed product should be affixed with the to-be-marketed immediate container label, or a label that closely resembles the to-be marketed product. For the proposed product, samples with a mocked label, i.e., noncommercially produced, depicting the actual label in size, shape and font would be acceptable. It is preferred that the **samples should not be refrigerated during shipment**, since the drug content will not be tested, and it will prevent the need for a bulky cooler box during shipment. Rather, the samples will be evaluated by physical manipulation to assess the user interface.

The requested samples should be submitted under a separate cover letter and mailed to the following address. **Please specify to the delivery courier that a signature receipt is not required, so that the package can be placed outside the office, without anyone being present. For overseas shipments, it is advisable to first ship the samples to your domestic office** and then use (b) (4) to ship the samples from your domestic office to the FDA. During this COVID-19 pandemic, some overseas couriers have not been able to cross the security checkpoint to be able to leave the package outside the FDA office door. Additionally, please provide the tracking number to the Clinical Project Manager listed below by email.

Shipment address:

Denise Conti, PhD
Clinical Review Team
Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Bldg. 75, 4th floor, Room 4715
10903 New Hampshire Ave,
Silver Spring, MD 20993

We request a complete written response no later than November 23, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
CLINICAL**

If you do not submit a complete written response by November 23, 2021, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:
www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at
Nitin.Patel@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Nitin K. Patel, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Safety and Clinical Evaluation
Office of Generic Drugs
Center for Drug Evaluation and Research



Nitin K.
Patel

Digitally signed by Nitin K. Patel

Date: 11/16/2021 03:34:17PM

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