CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215866
PDUFA Goal Date	May 15, 2022
OSE RCM #	2021-1826
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD
Review Completion Date	May 13, 2022
Subject	Evaluation of Need for a REMS
Established Name	Tirzepatide
Trade Name	Mounjaro
Name of Applicant	Eli Lilly and Company
Therapeutic Class	Dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist
Formulation(s)	4 prefilled single-dose pens of 2.5 mg/0.5mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, or 15 mg/0.5 mL
Dosing Regimen	Starting dose: Inject 2.5 mg subcutaneously weekly; may increase as needed for glycemic control in 2.5 mg increments at least 4 weeks after beginning current dose

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Mounjaro (tirzepatide) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Company submitted a New Drug Application (NDA) 215866 for tirzepatide with the proposed indication of adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] The risks associated with tirzepatide include: the potential to cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, hypoglycemia with concomitant use of insulin or an insulin secretagogue, hypersensitivity reactions, pancreatitis, and acute gallbladder disease which are similar to other products with glucagon-like peptide-1 receptor agonist (GLP-1 RA) activity. The Applicant did not submit a proposed REMS but did include a non-REMS risk management plan with this application consisting of routine risk minimization measures and routine pharmacovigilance activities.

DRM and the Division of Diabetes, Lipid Disorders and Obesity (DDLO) have determined that a REMS is not needed to ensure the benefits of tirzepatide outweigh its risks. The risk of thyroid C-cell tumors will be mitigated via labeling in a boxed warning, and tirzepatide will be contraindicated in these patients as are other products with GLP-1 RA activity. As in labeling with other products with GLP-1 RA activity, pancreatitis, hypoglycemia with concomitant use of insulin or an insulin secretagogue, acute gallbladder disease, and hypersensitivity reactions will be listed in warnings and precautions. Available REMS assessment data of the other approved GLP-1 RA (Bydureon, Tanzeum, Trulicity, and Victoza) indicate acceptable knowledge of these risks suggesting that these risk messages have been communicated to the relevant prescriber groups. Given the similarity of the risks associated with tirzepatide and other GLP-1 RAs, additional risk mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of tirzepatide.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Mounjaro (tirzepatide)[a] is necessary to ensure the benefits outweigh its risks. Eli Lilly and Company (Lilly) submitted a New Drug Application (NDA) 215866 for tirzepatide with the proposed indication of adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[2] This application is under review in the Division of Diabetes, Lipid Disorders, and Obesity (DDLO). The applicant did not submit a proposed REMS but did include a non-REMS risk management plan with this application.

2. Background

2.1. Product Information

[a] Section 505-1(a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Mounjaro (tirzepatide), a new molecular entity,[b] is a selective glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 dual receptor agonist (GLP-1 RA) proposed for adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. Tirzepatide's mechanism of action is via binding to either GIP or GLP-1 receptors on pancreatic beta cells and increasing the cells' sensitivity to glucose, which is the key regulator of glucose-dependent insulin secretion. Tirzepatide also appears to reduce glucagon levels during a standard mixed-meal test when compared with placebo and a selective GLP-1 receptor agonist.[3] Tirzepatide is proposed as a pack of 4 pre-filled 0.5 mL pens containing 2.5 mg/0.5mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, or 15 mg/0.5 mL for once weekly subcutaneous injection. The starting dose of tirzepatide is 2.5 mg once weekly. If additional glycemic control is necessary, the dose may be increased in 2.5 mg increments after a minimum of 4 weeks on the current dose.[3] The half-life of tirzepatide is approximately 5 days, and neither renal nor hepatic impairment appear to have a meaningful impact on tirzepatide pharmacokinetics.[4] Tirzepatide is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215866 relevant to this review:

- 09/15/2021: NDA 215866 submission for adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus received with a priority review voucher
- 01/13/2022: A Post Mid-cycle communication was sent to the Applicant by the Agency. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tirzepatide and that a final determination would be made during the review process.[5]
- 04/15/2022: Late Cycle Meeting Minutes were sent to the Applicant. It contained the notification that a REMS for tirzepatide was not needed at this time.[6]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Diabetes mellitus, which includes Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes, and maturity-onset diabetes of youth also known as latent autoimmune diabetes in adults, is a chronic[c] disease caused by impaired glucose regulation resulting in hyperglycemia. Type 1 diabetes mellitus is caused by autoimmune destruction of pancreatic beta cells and typically leads to an absolute insulin deficiency. Type 2 diabetes mellitus is caused by a progressive loss of insulin secretion by beta

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1(a) FD&C Act: *FDAAA Factor (D): The expected or actual duration of treatment with the drug.*

cells and is frequently seen with insulin resistance.[7] Over 37 million Americans have diabetes, with 90-95% of those having Type 2 diabetes.[8] Common signs and symptoms of Type 2 diabetes are polydipsia, polyuria, unintended weight loss, fatigue, blurred vision, slow-healing wounds, numbness or tingling in extremities, and darkened patches of skin, notably in the armpits and around the neck.[9]

Type 2 diabetes mellitus can lead to microvascular and macrovascular diseases such as stroke, myocardial infarction, neuropathy, retinopathy, and nephropathy. Diabetes is a leading contributing cause of kidney failure, adult blindness, and lower limb amputations.[10][d] Patients with diabetes are more than 2 times as likely to have cardiovascular disease as patients who are not diabetics, and these events occur at a younger age.[10] In 2013, diabetes was the most expensive medical condition to treat in the United States, accounting for $101.4 billion in healthcare costs.[11]

3.2. Description of Current Treatment Options

Per the 2020 American Association of Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) Guidelines,[12] Type 2 diabetes mellitus treatment should begin with proper diet, exercise, smoking cessation if the patient is a smoker, and usually metformin. As diabetes is a complex and chronic disease, individualized treatments are necessary, and include treatment for associated cardiovascular risks, including the above-mentioned lifestyle interventions. The American Diabetes Association (ADA)/European association for the study of Diabetes (EASD) consensus statement also echoes the need for individualized therapy.[13] Age and other comorbidities play a significant role in which medications are selected. Other pharmacologic interventions include additional antihyperglycemic medications, antihypertensive medications, and lipid-lowering medications to control body weight, blood glucose levels, cholesterol levels, and blood pressure.[14]

The ADA/EASD recommend if a single antihyperglycemic agent fails to achieve or maintain the hemoglobin A1c target after 3 months, another agent such as a GLP-1 RA, sodium-glucose transportor-2 inhibitor (SGLT2i), dipeptidyl peptidase inhibitor-4 (DPP-4i), thiazolidinedione (TZD), basal insulin, or sulfonylurea (SU) be added to therapy. Addition of a third agent should occur if dual antihyperglycemic therapy fail to achieve the desired HbA1c target over the subsequent three-month period.[7]

The ADA/EASD guidelines recommend the use of a (SGLT2i) or a GLP-1 RA with demonstrated cardiovascular benefit as part of the antihyperglycemic regimen for Type 2 diabetes patients with established atherosclerotic cardiovascular disease or for patients who have indicators of high atherosclerotic cardiovascular risk.[12,15] Similarly, the AACE/ACE also recommend the use of an SGLT2i or GLP-1 RA, independent of glycemic control, in patients with chronic kidney disease and/or those at high risk of having or have an established atherosclerotic cardiovascular risk.[14]

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

GLP-1 receptor agonists currently approved in the US include exenatide (a twice-daily injection), liraglutide (a once-daily injection), exenatide extended release (a once-weekly injection), albiglutide (a once-weekly injection), dulaglutide and (a once-weekly injection), lixisenatide (a once-daily injection) and combination products of liraglutide insulin degludec (a once-daily injection), lixisenatide and insulin glargine (a once-daily injection), and semaglutide (Wegovy). Exenatide (Byetta) was approved with a communication plan REMS to mitigate the risk of pancreatitis and renal failure. The REMS was eliminated upon completion of all communication activities.[16] The following GLP-1 RAs, Victoza (liraglutide), Bydureon (exenatide), Trulicity (dulaglutide), Xultophy (insulin degludec & liraglutide), and Tanzeum (albiglutide) were required to have Communication Plan REMS to address the increased risks of medullary thyroid cancer (MTC) and acute pancreatitis.[17-21] The REMS for Bydureon and Victoza, were released after the Division of Metabolism and Endocrinology Products (DMEP) and the Division of Risk Management determined that the communication activities were completed. DRM also completed reviews for both Trulicity and Tanzeum[22,23] that supported releasing these Communication Plan REMS as they were meetings the goals of the REMS, all communication plan activities were completed, and there was no new safety information that warranted the need for the REMS to be extended. Currently, no GLP-1 receptor antagonists have a REMS, and semaglutide (Wegovy) was approved without a REMS. Tanzeum (albiglutide) has been voluntarily discontinued by the Applicant.[24]

4. Benefit Assessment

The clinical reviewer states in the ongoing clinical review of tirzepatide that based upon the totality of evidence of efficacy, tirzepatide should be approved.

The Applicant submitted 19 clinical studies in support of this application. Nine global and regional Phase 2/3 trials are used to support the efficacy and safety of tirzepatide in Type 2 diabetes mellitus (T2D). During the Phase 2 trials (treatment duration from 12 to 26 weeks), varying doses of tirzepatide were compared to placebo or dulaglutide. During the Phase 3 trials (treatment durations from 40 to 104 weeks), tirzepatide at varying doses (5 mg, 10 mg, and 15 mg) was compared to placebo, insulin glargine 100 U/mL, insulin degludec 100 U/mL, dulaglutide 0.75 mg, and semaglutide 1 mg. All Phase 3 trials used the titration schedule as proposed for product labeling.

The five global trials used to support the efficacy of tirzepatide (b) (4) are as follows:

- **Trial 18F-MC-GPGK (SURPASS-1, NCT03954834):** A multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 3 trial in 478 subjects with T2D, naive to antihyperglycemic injectable therapy, inadequately controlled with diet and exercise alone, and had not been treated with any oral antihyperglycemic medication during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio of tirzepatide 5, 10, or 15 mg, or injectable placebo weekly
- **Trial 18F-MC-GPGL (SURPASS-2, NCT03987919):** A multicenter, randomized, open-label, parallel-group, active-controlled, Phase 3 trial with 1,878 subjects with T2D, inadequately controlled on ≥1500 mg/day of metformin alone during the three months preceding the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period,

and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg [dose double blinded], or semaglutide 1 mg [not blinded] weekly)

- **Trial 18F-MC-GPGH (SURPASS-3, NCT03882970):** A multicenter, randomized, open-label, parallel-group Phase 3 trial in 1,437 subjects with T2D, inadequately controlled on stable doses of metformin (≥1500 mg/day) with or without a SGLT2i during the three months preceding the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 52-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio of tirzepatide 5, 10, or 15 mg weekly, or insulin degludec daily
- **Trial 18F-MC-GPGM (SURPASS-4, NCT03730662):** A multicenter, randomized, open-label, parallel-group, active-controlled, Phase 3 trial in 1,995 subjects with T2D with increased CV risk, inadequately controlled on stable doses of at least one and no more than three oral antihyperglycemic medications during the three months preceding to the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a ≥52 to 104-week treatment period (treatment continued for ≥52 weeks from the time the last subject was randomized), and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:3 ratio (tirzepatide 5, 10, or 15 mg weekly, or insulin glargine daily). The starting dose of insulin glargine was 10 units/day at bedtime, titrated to a fasting blood glucose (FBG) <100 mg/dL, following a treat-to-target (TTT) algorithm
- **Trial 18F-MC-GPGI (SURPASS-5, NCT04039503):** A multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 3 trial with 3 study periods in 475 subjects with T2D, inadequately controlled on stable doses of titrated basal insulin glargine (>0.25 units/kg/day or >20 units/day) with or without metformin during the three months preceding the start of the trial. This trial consisted of 3 periods: a 3-week screening/lead-in period, followed by a 40-week treatment period, and a 4-week safety follow-up period. Subjects were randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, or 15 mg weekly, or injectable placebo

The primary efficacy endpoint for all five global Phase 3 trials was the mean change in baseline hemoglobin A1c (HbA1c) at the trial endpoint (Week 40 or Week 52). Across all 5 trials, the comparator-subtracted differences for each tirzepatide dose (5 mg, 10 mg, and 15 mg) favored tirzepatide therapy and were statistically significant (p value <0.05). The differences in HbA1c reductions across all 5 trials, except for the comparison of 5 mg tirzepatide to 1 mg semaglutide in trial GPGL, were clinically meaningful as well. See Appendix 10.1 for the complete Table of Primary Analysis of HbA1c Change from Baseline to Endpoint (mITT, or all patients who received at least 1 dose of tirzepatide).[25]

The clinical reviewer also noted in the ongoing clinical review that in the placebo-controlled Phase 3 trials, tirzepatide therapy resulted in a mean decrease of systolic and diastolic blood pressure of 6-9mmHg and 3-4 mmHg respectively, with subjects on placebo having a 2 mmHg and 2mmHg decrease.[24] All three tirzepatide doses in trial GPGK reduced triglycerides, very low-density lipoprotein cholesterol, and total cholesterol while increasing high density lipoprotein cholesterol levels. However, as the Applicant is not making efficacy claims for hypertension or dyslipidemia management, these findings were included in the hierarchical testing strategy and not included in the proposed labeling.[e]

[e] Section 505-1(a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

The Applicant used safety data from the 5 Phase 3 global trials listed in Section 4, as well as the following Phase 2 and Phase 3 regional trials, with a total of 7,769 subjects receiving at least one dose of tirzepatide:

Phase 2 Clinical Trials:

- **18F-MC-GPGB (NCT03131687):** Multicenter, double-blind, parallel-group placebo and active-comparator controlled, randomized Phase 2 trial of 318 subjects with 1:1:1:1:1 randomization to tirzepatide 1 mg, 5 mg, or 10 mg, dulaglutide 1.5 mg, or placebo subcutaneously weekly; may increase tirzepatide after 2 weeks, then may increase tirzepatide again up to 15 mg weekly every 4 weeks; trial duration was 26 weeks; trial purpose was to compare tirzepatide to dulaglutide and placebo with primary endpoint being HbA1c change at the endpoint
- **18F-MC-GPGF (NCT03311724):** Multicenter, double-blind, placebo-controlled, randomized, parallel-arm, dose-escalation 12 week Phase 2 trial of 111 subjects with 1:1:1:1 randomization - Group 1 used tirzepatide 2.5 mg weekly for 2 weeks, 5 mg weekly for 2 weeks, then 10 and 15 mg weekly for 4 weeks respectively, Group 2 used tirzepatide 15 mg weekly by escalating from 2.5, 7.5, 15 mg weekly for 4 weeks each, Group 3 used tirzepatide 12 mg weekly by escalating the dose every 4 weeks (4, 8, 12 mg weeks), and Group 4 used placebo weekly; trial endpoint was mean change from baseline HbA1c at Week 12

Regional Phase 3 Clinical Trials (conducted in Japan):

- **18F-JE-GPGO (SURPASS J-mono, NCT03861052):** Multicenter, randomized, double-blind, parallel, active-controlled, 52-week, Phase 3 trial of 636 subjects with 1:1:1:1 randomization to tirzepatide 5 mg, 10 mg, 15 mg weekly (starting with 2.5 mg tirzepatide weekly, and up-titrating by 2.5 mg every 4 weeks to the randomized dose), dulaglutide 0.75 mg weekly, or placebo weekly; endpoint was mean change from baseline HbA1c at Week 52

- **18F-JE-GPGP (SURPASS J-combo, NCT03861039):** Multicenter, randomized, 52-week, add-on treatment Phase 3 trial of 443 subjects with 1:1:1 randomization to tirzepatide 5 mg, 10 mg, or 15 mg weekly, beginning with tirzepatide 2.5 mg weekly and up-titrating by 2.5 mg every 4 weeks to the randomized dose; primary endpoint was the incidence of treatment emergent adverse events (TEAEs)

The Applicant submitted 5 analysis datasets (AS1, AS2, AS3, AS4, and AS5) to determine the safety of tirzepatide.

- **AS1:** (trials GPGK, GPGI): Data from these 40-week, placebo-controlled trials was used to determine a drug effect.
- **AS2:** (trials GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, and GPGP): Data from these Phase 3 trials was used to assess dose-related adverse events
- **AS3:** (trials GPGB, and GPGF and trials from AS2): This integrated Phase 2/3 analysis assessed adverse events that were more rarely found and adverse events of special interest. This safety set includes all nine Phase 2/3 trials.

- **AS4:** (trials GPGB, GPGF, GPGK, and GPGI): This safety set was used to assess additional safety signals associated with drug effect.
- **AS5:** (trials GPGB, GPGK, GPGL, GPGH, GPGM, GPGI, and GPGO): These Phase 2/3 trials with treatment durations of at least 26 weeks were used to evaluate cardiovascular safety.

In analysis dataset AS3, 71.2% of tirzepatide-treated subjects experienced a TEAE, which appear to be dose-related. Conversely, serious adverse events (SAEs) did not appear to be dose related, with subjects reporting SAEs at rates of 7.9%, 7.9%, and 7.1% in tirzepatide 5 mg, 10 mg, and 15 mg doses respectively in Phase 3 trials. SAEs were similar between comparator and pooled tirzepatide arms in all trials except GPGL. SAEs in the tirzepatide arms were 6% and comparator rates were 2.8% in trial GPGL. In the tirzepatide arm, there were 4 cases of "acute myocardial infarction" and 5 subjects experienced "acute cholecystitis." Six (2.6%) subjects in the placebo arm and 48 (6.7%) in the pooled tirzepatide arm discontinued treatment due to adverse events. "Gastrointestinal disorders" accounted for 5% of tirzepatide treated subjects' discontinuations, and 0.4% of comparator arm discontinuations.

Common TEAEs were also predominately gastrointestinal-related. Compared to the pooled placebo arms, gastrointestinal (GI) disorder adverse events (AEs) were more frequent in tirzepatide-treated subjects, occurring in approximately 40% of subjects in the pooled tirzepatide arms vs. 20% of subjects in the placebo arms. A dose-response was observed across the seven Phase 3 trials, with GI AEs reported in 38%, 44%, and 49% of subjects in the tirzepatide 5, 10, and 15 mg arms. Across all Phase 3 trials, higher proportions of tirzepatide-treated subjects experienced GI AEs compared to each control arm, although GI related AEs were seen in the active comparator arms, dulaglutide (31%) and semaglutide (41%). Unlike other GLP-1 RA products, the labeling for tirzepatide will include these sometimes-severe gastrointestinal reactions in warnings and precautions and include that tirzepatide has not been studied in, nor is recommended for, patients with severe GI disease. Patients also may experience acute kidney injury due to the severity of the GI AEs, and the instruction to monitor patients with renal impairment and severe gastrointestinal reactions is included in warnings and precautions as well. Other GLP-1 RA products contain similar language in warnings and precautions. Labeling for tirzepatide also aligns with other GLP-1 RA products to include instructions to monitor patients with diabetic retinopathy as rapid improvement in glucose control has been associated with temporary worsening of diabetic retinopathy in warnings and precautions. Other common ($\geq$5%) AEs reported for tirzepatide-treated subjects included 'nasopharyngitis', 'decreased appetite', and 'lipase increased'. In the ongoing clinical review, the clinical reviewer notes that "no new safety concerns/issues were detected following the review of the entire listing of TEAEs."

5.1. Deaths

In the nine trials, there were 80 patient deaths, with 41 occurring in the tirzepatide arms of trials and 39 occurring in the pooled comparator arm. Sixty of the subject deaths occurred in Trial GPGM, which included subjects with higher cardiovascular disease risks and had a longer treatment duration. System organ classes (SOC) "infections and infestations" accounted for 27 subjects' deaths, and "cardiac disorders" accounted for another 23 subjects' deaths.[4]

5.2. Thyroid C-cell Tumors in Rodents

Similar to other GLP-1 RA products, tirzepatide causes thyroid C-cell tumors in rats. In a 2-year carcinogenicity study submitted as part of the nonclinical program, increases in thyroid C-cell hyperplasia and neoplasia were observed in both male and female rats.[4] There is no data to determine if tirzepatide also causes these tumors, including medullary thyroid carcinoma (MTC) in humans. Tirzepatide labeling will include a boxed warning about this risk and that tirzepatide use is contraindicated in patients with a personal or family history of MTC or patients with Multiple Endocrine Neoplasia syndrome type 2. The boxed warning will also include an instruction to counsel patients on this risk and symptoms of thyroid tumors. This boxed warning is in labeling class-wide for the GLP-1 RA products.

5.3. Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

In Trial GPGK, no subjects on tirzepatide monotherapy experienced an episode of hypoglycemia. In Trial GPGI, which included add-on therapy with metformin and/or insulin glargine, clinically meaningful hypoglycemic reactions were split into 2 categories by the Applicant: Level 2 (blood glucose <54 mg/dL), and Level 3 (severe reactions - severe cognitive impairment requiring another person to administer carbohydrates, glucagon, or other resuscitative actions). In trial GPGI, none of the placebo-treated subjects had an episode of Level 3 hypoglycemia, as opposed to 2 subjects on tirzepatide 10 mg and 1 subject on tirzepatide 15 mg. Similar results were seen in Trial GPGM, in which sulfonylureas were allowed to be used in addition to trial therapy.[4] The potential for hypoglycemia with these concurrent medications will be listed in warnings and precautions and Section 6.1 of tirzepatide labeling.

5.4. Hypersensitivity Reactions

The potential for hypersensitivity reactions is included in warnings and precautions for other long-acting GLP-1 RAs. In the tirzepatide Phase 2/3 trials, hypersensitivity reactions were reported in 193 tirzepatide-treated subjects and 62 subjects in the pooled comparator arms. While there were no reported events of anaphylaxis, several tirzepatide treatment patients experienced serious hypersensitivity reactions. One subject with a past medical history of multiple antibiotic allergies experienced severe allergic rhinitis 49 days after the last tirzepatide dose, another had an episode of treatment-emergent eczema, and another patient experienced skin necrosis on his foot, resulting in the amputation of half of the foot. This subject also had a history of myocardial infarction, coronary artery disease, and heart failure.

The Applicant's proposed labeling includes a contraindication for patients with hypersensitivity to tirzepatide, as well as noting the potential for hypersensitivity reactions in the warnings and precautions.

5.5. Pancreatitis

Cases of acute pancreatitis have been reported with GLP-1 RAs, and in March 2013, the Agency issued a Drug Safety Communication on the potentially increased risk of pancreatitis or pre-cancerous findings of the pancreas from GLP-1 receptor agonists and other incretin mimetic drugs.[26] As such, GLP-1 receptor

agonists note this risk in warnings and precautions of labeling. In the Phase 2/3 trials, 61 subjects experienced 64 events of suspected pancreatitis. Of these, 17 were confirmed cases of pancreatitis as acute pancreatitis, 14 of which were categorized as acute pancreatitis in 13 tirzepatide subjects, and 1 case in the pooled comparator arm.[4] This will be included in the warnings and precautions of tirzepatide labeling.

5.6. Acute Gallbladder Disease

Patients with Type 2 diabetes have an increased risk of gallbladder-related disease. Several GLP-1 RA products that are indicated for weight-management include this in warnings and precautions in labeling. In the Phase 2/3 trials, 1.1% of tirzepatide treated subjects and 0.6% in comparator arms had events of gallbladder-related AEs. Cholelithiasis was the most frequently reported event, occurring in 0.6% and 0.2% of the tirzepatide and comparator arms, respectively.[f] Acute gallbladder disease will be included in the warnings and precautions of tirzepatide labeling.

6. Expected Postmarket Use

Tirzepatide is expected to be prescribed by the same healthcare providers currently prescribing other GLP-1 RAs, including endocrinologists, internists, and primary care providers. The prescribing population is likely familiar with the boxed warning, contraindications, and how to manage the risks of tirzepatide, as these are similar to the risks associated with GLP-1 RAs. These practitioners and patients typically meet regularly to monitor the effectiveness of therapy. Like other GLP-1 RAs, tirzepatide will be administered as a subcutaneous injection by patients, their caregivers, or healthcare providers in clinical settings in which patients with T2D receive treatment.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tirzepatide beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of tirzepatide on the basis of the currently available efficacy and safety information.

[f] Section 505-1(a) of the FD&C Act: *FDAAA factor (E); The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Type 2 diabetes is a chronic disease that increases patients' risks of fatal comorbidities if poorly controlled. Like other marketed GLP-1 receptor agonists, tirzepatide has the risks of potentially increasing the incidence of thyroid C-cell tumors in humans, hypoglycemia when used concomitantly with insulin secretagogues or insulin, hypersensitivity reactions, acute gallbladder disease, and pancreatitis. DRM and DDLO considered these risks and if a REMS was necessary to mitigate them.

The safety concerns associated with tirzepatide use are similar to other GLP-1 RAs, which use labeling to mitigate these risks. Proposed labeling for tirzepatide includes similar language to convey the risks in a boxed warning, contraindications, and warnings and precautions. We expect prescribers will be familiar with these risks as the labeling for tirzepatide will mirror other GLP-1 receptor agonists that have been on the market and widely used for years. The Communication Plan REMS for GLP-1 receptor agonists were released based on the uptake of these products and their safe use integrated into current treatment guidelines and medical practice. Available REMS assessment data of Bydureon, Tanzeum, Trulicity, and Victoza[22,23,27,28] indicate acceptable knowledge of the risks of pancreatitis and MTC suggesting that these risk messages have been communicated to the relevant prescriber groups. The risk of thyroid C-cell tumor potential in humans will be addressed in a boxed warning and tirzepatide will be contraindicated in patients who have a personal or family history of MTC. Hypersensitivity, potential for hypoglycemia when used with insulin or insulin secretagogues, hypersensitivity, and pancreatitis will be listed in warnings and precautions, as will the potential for severe GI reactions that may lead to acute kidney injury with tirzepatide. With the currently available data, tirzepatide requires no further risk mitigation beyond labeling.

9. Conclusion & Recommendations

Based on the available data, DRM and DDLO agree that a REMS is not necessary to ensure the benefits of tirzepatide outweigh the risks, which will be managed via labeling. Should DDLO have any concerns or if new safety information becomes available, please send a consult to DRM.

10. Appendices

(b) (4)

[redacted]

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

2. Gattex Prescribing Information. Daily Med. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=66b69c1e-b25c-44d3-b5ff-1c1de9a516fa. Updated June 20, 2019. Accessed June 22. 2020.
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/s/

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