

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208583Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: November 2, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 208583

Product Name and Strength: Xultophy 100/3.6 (insulin degludec and liraglutide) injection, 300 units insulin degludec and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)

Submission Date: September 28, 2016

Applicant/Sponsor Name: Novo Nordisk

OSE RCM #: 2016-1328-3 and 2016-1934-1

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader (Acting): Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised commercial carton labeling, commercial container label, sample carton labeling, and sample container label for Xultophy 100/3.6 (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to the recommendations that were made in a previous proprietary name review and labeling review.^a

^a Conrad A. Proprietary Name Memorandum for Xultophy 100/3.6 (NDA 208583). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Sept 20. 5 p. OSE RCM No.: 2016-10049878.

Conrad A. Review of Revised Labeling Memorandum for Xultophy 100/3.6 (NDA 208583). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Sept 28. 5 p. OSE RCM No.: 2016-1328-2 and 2016-1934.

2 CONCLUSION

The revised commercial carton labeling, commercial container label, sample carton labeling, and sample container label for Xultophy are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARIANE O CONRAD
11/02/2016

HINA S MEHTA
11/02/2016



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Division of Pediatric and Maternal Health Review

Date: September 22, 2016 **Consult Received:** January 7, 2016

From: Carol H. Kasten, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatric and Maternal Health

To: Division of Metabolism and Endocrinology Products

Drug: XULTOPHY (Insulin degludec and liraglutide)

Drug Class: Insulin analog (insulin degludec), GLP-1 Receptor Agonist
(liraglutide)

NDA: 208-583

Applicant: Novo Nordisk

Subject: Pregnancy and Lactation Labeling

Proposed Indication: XULTOPHY is indicated as an adjunct to diet and exercise to
improve glycemic control in adults with type 2 diabetes mellitus.

Consult Request: Assistance with PLLR labeling

Documents Reviewed:

Citizen's Petition: Docket No. FDA-2012-P-0404, dated March 25, 2014.

DPMH Reviews

- DPMH review of pioglitazone, NDA 21-073/S-048, Miriam Dinatale DO, Medical Officer, Primary Author. March 9, 2016. DARRTS Reference ID 3898973.
- DPMH review of Lixisenatide, NDA 208-471, Christos Mastroyannis, MD, March 10, 2016. DARRTS Reference ID: 3912226
- DPMH review of pioglitazone, NDA 21-073/S-048. Miriam Dinatale DO, Medical Officer. April 28, 2016. DARRTS Reference ID 3921521.
- DPMH review of Fiasp (insulin aspart), NDA 20-8751. Jane Liedtka, MD. May 6, 2016. DARRTS Reference ID: 3928027

Novo Nordisk Responses to Agency

- December 22, 2015: Response to 74-day letter, review and summary of all available published literature, supporting information for the Pregnancy and Lactation Labeling Rule (PLLR). NN9068 Insulin degludec/ liraglutide.
- June 28, 2016: Novo Nordisk Response to FDA Information Request and PLLR Compliance. Pharmacovigilance Database Information for Liraglutide, provided in Module 1.11.3.
- August 9, 2016: Novo Nordisk Response to FDA Information Request dated August 3, 2016, PLLR Compliance Pharmacovigilance Database for Liraglutide Clarification, provided in Module 1.11.3.

INTRODUCTION and REGULATORY HISTORY

This original 505(b)(1) application was received on September 14, 2015 for Xultophy (insulin degludec and liraglutide), NDA 208-583. Patents for both insulin degludec and liraglutide are owned by the applicant,

- Insulin degludec: TRESIBA (NDA 203-314) is indicated to improve glycemic control in adults with diabetes mellitus. Approved September 25, 2015.
- Liraglutide is approved under two different trade names for two different indications:
 - VICTOZA (NDA 22-341): indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Approved January 25, 2010.
 - SAXENDA (NDA 206-321): indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of either 30 kg/m² or greater (obese) or, 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition. Approved December 23, 2014.

In the 74-day letter sent on November 27, 2015 the Agency requested the applicant provide a review and summary of the published literature on the use of insulin degludec and liraglutide in pregnant and lactating women and reports of adverse effects on the

reproductive potential of both sexes. The applicant was also requested to revise the labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and to incorporate in the labeling any pertinent new data noted in their literature review. The applicant submitted the revised labeling and supporting data on December 22, 2015.

DMEP consulted the Division of Pediatric and Maternal (DPMH) on January 7, 2016 to review and provide recommendations for the Xultophy Pregnancy (Section 8.1) and Lactation (Section 8.2) labeling. The Agency sent an IR to the applicant on June 14, 2016 requesting a cumulative review and summary of cases from the applicant's pharmacovigilance database on liraglutide exposures during pregnancy, lactation and reports of infertility or reduced fertility. The applicant submitted the requested data on June 28, 2016. A second IR was sent on behalf of DPMH requesting the applicant revise the pharmacovigilance data received on August 9, 2016 in order that the data presented in tabular form match the descriptive data and to assure chromosomal abnormalities were accurately reported.

BACKGROUND

Diabetes and Pregnancy

Adverse outcomes of diabetes during pregnancy relate to the onset of diabetes mellitus (DM), its duration, and the degree of vasculopathy. Women with pregnancies complicated by DM may be separated into one of two groups:

1. Gestational diabetes (GDM): women with carbohydrate intolerance of variable severity, with onset or first recognition during the present pregnancy. This means the glucose intolerance may have antedated the pregnancy but was not recognized by the patient or the physician.
2. Pregestational diabetes (PGD): women known to have DM before pregnancy.

Ninety percent of all pregnant diabetic women have GDM, whereas type 1 (T1DM) insulin-dependent, and type 2 (T2DM), non-insulin dependent, account for the remaining 10%.¹

Gestational Diabetes

The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the U.S. The likelihood of developing GDM is significantly increased among certain subgroups, these include women with a family history of type 2 DM, advancing maternal age and obesity. Infants born to women diagnosed with GDM do not have an increased risk of congenital anomalies when compared to infants born to women without GDM. GDM usually is diagnosed later in pregnancy when the risk of MCM has passed. PGD that is well controlled is not associated with an increased risk either, however, infants of women with poorly controlled PGD have an increased risk of multiple congenital malformations (MCM). The incidence of GDM varies in different study populations and is estimated to occur in 3–5% of all pregnant women in the United States.

¹ Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008.

Pregestational Diabetes

Poorly controlled PGD during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SABs), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia. In addition, poorly controlled DM during pregnancy increases the risk of fetal malformations, including neural tube defects, cardiovascular malformations, oral clefts, genitourinary abnormalities (absent kidneys, double ureter), and sacral agenesis or caudal regression. Fetal complications include macrosomia, which may result in brachial plexus injury or shoulder dystocia at delivery. Also directly related to metabolic control are neonatal hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.

Infants of diabetic mothers in unsatisfactory glycemic control often develop hypoglycemia during the first few hours of life. The reported incidence ranges from 25% to 40% of infants of diabetic mothers. Poor glycemic control during pregnancy and high maternal plasma glucose levels at the time of delivery increase the risk of hypoglycemia in the infant. Clinical studies suggest that euglycemia during organogenesis in pregestational pregnant diabetics is critical in the prevention of congenital anomalies.² Achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.^{3,4,5}

Poorly controlled PGD in the first 14 weeks after conception is associated with a major congenital malformation (MCM) in 5-10% of fetal exposures and SABs in 15-20%.⁶ The higher the fasting serum glucose level is at diagnosis, the higher the incidence of MCM.⁷ The Micromedex database states that pregestational diabetes mellitus in pregnant women with poor control during organogenesis is associated with a three-fold increase in congenital anomalies that include cardiac malformations, lumbosacral agenesis, hyperbilirubinemia, polycythemia, and renal vein thrombosis. Infants of mothers with poorly controlled PGD have a mortality rate that is five times higher than that of non-diabetic mothers; the mortality rate is higher at all gestational ages.⁸

The American College of Obstetricians and Gynecologists (ACOG) in a statement issued in 2005 and reaffirmed in 2012 for PGD, states that HbA1c of 5-6% is associated with a

² See Reece.

³ Mills J. Malformations in infants of diabetic mothers. *Teratology*.1982;25:385-94.

⁴ Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. *Diabetes Med*. 2014;31:1047-54.

⁵ www.cdc.gov Problems of Diabetes in Pregnancy. Accessed December 30, 2015.

⁶ Ornoy, et al. Effect of Maternal Diabetes on the Embryo, Fetus, and Children: Congenital Anomalies, Genetic and Epigenetic Changes and Developmental Outcomes. *Birth Defects Research, Part C: Embryo Today: Reviews*. 2015;105:53-72.

⁷ Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165-1171.

⁸ The Behrman RE, Kleigman RM, Nelson WE, et al: *Nelson Textbook of Pediatrics*, 14th. WB Saunders Company, Philadelphia, PA, 1992.

fetal malformation rate close to what is seen in normal pregnancies. A HbA1c near 10% is associated with a fetal anomaly rate of 20-25%.⁹

Reviewer's Comment

The DPMH, Maternal Health Team has completed four reviews of drugs to treat diabetes in the past four months. Two MHT reviewers, Miriam Dinatale, DO and Christos Mastroyannis, MD, working with DMEP, have developed estimates of the risk of birth defects and miscarriage in the indicated population, pregnant women with diabetes based on the published literature. These estimates will be included in the background risk statement that is part of the information provided in Pregnancy (8.1) in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) published on June 30, 2015. The four previous DPMH reviews form the basis for much of this review.

Drug Characteristics

The Xultophy drug device combination consists of a pre-filled injector pen that contains two drugs, insulin degludec and liraglutide, in fixed ratio that is administered subcutaneously once daily.

*Insulin degludec*¹⁰

- Class: long-acting human insulin analog
- Mechanism of action: the same as that of endogenous insulin
- Plasma half-life: 13 hours
- Percent protein bound: 98%

*Liraglutide*¹¹

- Class: GLP-1 receptor agonists (GLP1RA)
- Mechanism of action:
 - activates the GLP-1 receptor and increases intracellular cyclic AMP leading to insulin release in the presence of elevated glucose concentrations
 - enhances insulin synthesis and secretion in the presence of elevated glucose concentrations;
 - causes delayed gastric emptying, reduced food intake, contributing to a slower rate of rise of plasma glucose after meals.
- Plasma half-life: 13 hours
- Percent protein bound: 98%

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹² also

⁹ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. 2005; 60:675-685.

¹⁰ Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: May 19, 2016. Accessed July 16, 2016.

¹¹.Xultophy labeling

¹² *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹³ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Note for Reference: Current labelings for Reference Listed Drugs (RLDs) have been excerpted and are located in Appendix A (Tresiba) and Appendix B (Victoza)

Nonclinical Experience

Insulin degludec

Studies in rats and rabbits at five times (rats) and 10 times (rabbits) the human exposure at a dose of 0.75 U/kg/day did not demonstrate any increase in adverse outcomes in pregnant animals or their offspring relative to the comparator, human insulin (NPH insulin). No maternal toxicity was observed. The reader is referred to the Pharmacology/Toxicology Review by Miyun Tsai-Turton, PhD, MS for complete details.¹⁴

Liraglutide

Animal reproduction studies in rats and rabbits demonstrated some adverse effects in embryofetal development. Specifically, early embryonic death and an imbalance in some fetal abnormalities were observed in pregnant rats administered liraglutide at exposures approximating the exposure at the maximum recommended human dose (MRHD) of 1.8 mg/day. Similar studies in rabbits administered liraglutide at exposures that were less than those approximating the exposure at the MRHD produced a decrease in fetal weight and an increase in major fetal abnormalities. The reader is referred to the Victoza original application by the primary Pharmacology/Toxicology author, Anthony Parola, PhD for complete details.¹⁵

Review of Literature

Insulin Degludec

The applicant completed a literature search of major biomedical databases including Biosis, Current Contents, Embase and Medline to identify publications regarding the use of insulin degludec during pregnancy. No publications were found in English.

¹³ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

¹⁴ Dated June 4, 2012, DARRTS Reference ID: 3138839

¹⁵ Dated July 10, 2009.

Liraglutide

The applicant completed a literature search of the databases noted above regarding the use of liraglutide in pregnant women and identified one publication by Greco that is described below.

Greco D, 2015¹⁶

This publication is a case report of a 37-year-old woman with T2DM diagnosed when she was 33 years old. The patient had been treated with liraglutide (1.8 mg/day) and metformin (2000 mg/day) when she was diagnosed as 13 weeks pregnant. The patient's medications were changed to insulin aspart and insulin detemir for the remainder of the pregnancy. The patient's HbA1C was reported to have remained below 6.3% throughout the remainder of her pregnancy when she delivered a healthy female at 37 weeks gestation weighing 3790 grams (97%) and 52 cm long (96%).¹⁷ From this case report, the applicant concluded that the Xultophy labeling did not require any changes.

DPMH review of literature

This reviewer found 11 references in English in a search with terms "liraglutide or Victoza" and "pregnant or pregnancy." Among these were found the Greco reference noted above. No other publications were found that were relevant to use of insulin degludec and/or liraglutide during pregnancy. This reviewer agrees with the applicant that the Greco publication does not contain new data that should be included in the labeling.

Review of Reproductive Toxicology Databases

The TERIS¹⁸ review of liraglutide noted that the magnitude of teratogenic risk was considered undetermined as there are no epidemiological studies of liraglutide use during pregnancy.

The Reprotox¹⁹ review of liraglutide stated that the increase in abnormal embryo development in the animal studies was equivocal. The review also noted the following:

According to the product labeling, liraglutide treatment of pregnant rats and rabbits produced an increase in birth defects at dose levels below therapeutic levels in humans based on plasma concentration (AUC). The studies were summarized in considerably more detail on the FDA website ([Drugs@FDA.gov](http://www.fda.gov/Drugs/Drugs@FDA.gov)) and the purported increases in malformations in rats do not appear to be dose related. In rabbits, overall malformations were equivocally increased, but individual malformations generally showed no relationship to dose. All dose levels used in

¹⁶ Greco D. Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with Type 2 diabetes. *Diabet Med.* 2015; 32: e29-30.1

¹⁷ See PediTools <http://peditools.org/fenton2013/index.php>>

¹⁸ TERIS is the TERatology Information Service located at University of Washington. Search April 5, 2016 2015. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidenceexpert/ND_PR/evidencexpert/CS/ Accessed July 16, 2016.

¹⁹ Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed April 5, 2016.

the rabbit resulted in decreased maternal weight gain, and it is difficult to conclude that liraglutide had selective effects on embryo development.

There was no review of liraglutide in Shepard's;²⁰ however, there was a review of animal data for another GLP-1 receptor agonist, exenatide.²¹ The review noted that the number of umbilical hernias was increased; however, the review stated the malformations occurred at the same doses as those that caused maternal toxicity. In the presence of maternal toxicity, adverse animal findings such as malformations may be secondary to illness in the mother animal.

Review of Pharmacovigilance Database

Insulin Degludec

The applicant did not include pharmacovigilance data for insulin degludec as the drug was approved on September 25, 2015. In addition, there are no animal data that indicated a possible teratogenic effect from prenatal exposure to insulin degludec.

Liraglutide

In view of the nonclinical data that suggested a potential teratogenic risk with use of liraglutide during pregnancy and following discussion with the Division, an information request for liraglutide pharmacovigilance data was sent to the applicant, as noted above. The applicant provided a cumulative review and summary of cases of liraglutide use in pregnancy, lactation and infertility in females or males of reproductive potential from the Novo Nordisk safety database (NNSD). Per the applicant, the NNSD is an internal database that includes reports from clinical trials, observational studies, published literature, solicited and unsolicited cases. The applicant notes that spontaneous reporting systems have limitations such as under-reporting, variable data quality and lack of precise information on drug exposure.

A total of 271 liraglutide-exposed pregnancies were identified through May 31, 2016 in the NNSD. Of those, 16 cases were duplicative reports of the mother and her infant, which reduced the total number of cases to 255. Per the applicant, pregnancy outcome data was available for 111 cases. Table 1 below is intended to describe the 111 pregnancies and lists them by outcome. Abbreviations used: congenital anomalies (CA); spontaneous abortion (SAb); elective abortion (ElAb); hypertension (HTN).

²⁰ 2016 Shepard's®: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. Accessed April 6, 2016.

²¹ Byetta (exenatide) NDA 21-773 approved April, 2003.

Table A: Liraglutide Exposed Pregnancies^{22,23}		
Total Pregnancies	255	100%
Pregnancy Outcomes Unknown or Not Reported	144	56.5%
Known Outcomes	111	43.5%
Live births	53	20.8%
<ul style="list-style-type: none"> • 51 no CA 		
<ul style="list-style-type: none"> • 2 with CA <ol style="list-style-type: none"> 1) Trisomy X syndrome ('cytogenetic abnormality') 2) Univentricular heart 		
SABs - no CA reported	32	28.8%
Ectopic	2	1.8%
Stillbirths	2	1.8%
<ul style="list-style-type: none"> • 1 Stillbirth – no CA 		
<ul style="list-style-type: none"> • 1 Stillbirth – with CA <ol style="list-style-type: none"> 3) placental insufficiency, fetal microsomia and cardiac hypertrophy & maternal T2DM, HTN poorly controlled 		
EIABs	20	18%
<ul style="list-style-type: none"> • 6 with CA reported <ol style="list-style-type: none"> 4) Trisomy 21 5) fetal exencephaly 6) "rare genetic brain damage disease" 7) fetal death (@ 6 weeks approx) 8) congenital hydrocephalus 9) Osteogenesis Imperfecta 		
<ul style="list-style-type: none"> • 2 No CA reported 		
<ul style="list-style-type: none"> • 12 Reason not reported 		

²² Novo Nordisk Response to FDA Information Request and PLLR Compliance. Pharmacovigilance Database Information for Liraglutide, received June 28, 2016. Module 1.11.3.

²³ Response to FDA Information Request Clinical/Safety Information, received August 9, 2016. Module 1.11.3.

Reviewer's Comment

The tabulation of the applicant's reported pregnancy outcomes above, contains data on 109 pregnancies, not 111 as reported by the applicant. No further clarification will be requested from the applicant to reconcile the 111 versus the 109 outcomes described. This reviewer has captured 9 CAs reported for 9 infants which are analyzed below.

Liraglutide Exposed Pregnancies with CAs

Case 1 – Live Birth -Trisomy X Syndrome (Cytogenetic Abnormality)

This CA is a result of chromosomal non-disjunction and does not represent a teratogenic effect of liraglutide.

Case 2 - Live Birth - Univentricular Heart

Univentricular heart is a MCM and may represent a teratogenic effect of liraglutide.

Case 3 - Stillbirth - Placental Insufficiency, Fetal Microsomia, Cardiac Hypertrophy associated with Poor Control Maternal T2DM and Hypertension

The IR response provides information that the mother had poorly controlled diabetes and hypertension, which are risk factors for adverse pregnancy outcomes. Poor glycemic control may also have contributed to the stillbirth and placental insufficiency and microsomia are often present with poorly controlled maternal hypertension.

Case 4 – Termination - Trisomy 21

This is a result of chromosomal non-disjunction and does not represent a teratogenic effect of liraglutide.

Case 5 - Termination - Fetal Exencephaly

Exencephaly is a MCM in which the early brain tissue is not enclosed by the skull.²⁴ Exencephaly is less common than most neural tube defects. There are some data suggesting exencephaly may be caused by mutations in one of the ciliopathy genes associated with Bardet-Biedl, Alstrom or Meckel-Gruber syndromes.²⁵ In summary, this CA may be caused by a genetic disorder or it may represent a teratogenic effect of liraglutide.

Case 6 – Termination - “Rare Genetic Brain Damage Disease”

Review of the August 9, 2016 detailed IR response did not include any further descriptors of this CA. No mention of any genetic testing was found. This CA may be caused by a genetic disorder as or it may represent a teratogenic effect of liraglutide.

²⁴ National Institute for Neurological Disorders and Stroke, What are Cephalic Disorders? Accessed September 5, 2016. <http://www.ninds.nih.gov>

²⁵ Badano J, Mitsuma, N *et al* . The Ciliopathies: An Emerging Class of Human Genetic Disorders. *Annu Rev Genomics Hum Genet* 2006;7:125–48. doi 10.1146/annurev.genom.7.080505.115610

Case 7 – Termination - Fetal Death at 6 Weeks Approximately

The August 9, 2016 detailed IR response indicated this case was a termination for fetal defects, with no fetal defects described. The data stated that the fetus had died with the termination following this. This case may represent a teratogenic effect of liraglutide

Case 8 – Termination - Congenital Hydrocephalus

Hydrocephalus refers to excessive accumulation of cerebrospinal fluid in the brain which results in an abnormal widening of the cerebral ventricles. The causes are not well understood, although it is known that a genetic mutation may cause hydrocephalus, or a brain injury occurring in premature infants or infection. This CA may be caused by a genetic disorder as or it may represent a teratogenic effect of liraglutide.

Case 9 – Termination - Osteogenesis Imperfecta

Osteogenesis Imperfecta is caused by a mutation in either the COL1A1 or COL1A genes. This abnormality is very likely the result of a *de novo* mutation and is not the result of a teratogenic effect of liraglutide.

The liraglutide-exposed pregnancies with a CA are listed below. Those which are the result of a cytogenetic abnormality and not the result of a teratogen are struck through.

1. ~~Trisomy X Syndrome~~
2. Univentricular Heart
3. Stillbirth with Placental Insufficiency & poor maternal disease control
4. ~~Trisomy 21~~
5. Exencephaly
6. Rare Genetic Brain Damage Disease
7. Fetal Death at 6 Weeks
8. Hydrocephalus
9. ~~Osteogenesis imperfecta~~

The number of remaining cases that should be included as a possible result of a teratogen is six. The CAs are 5.4% (6/111) of the total number of liraglutide-exposed pregnancies. Also, the type of MCMs found in this review, cardiovascular and neural tube defects are reported to be common in fetuses and infants of women with PGDM or GDM.

As discussed above, DPMH with DMEP have developed estimates for the risk of serious birth defects and miscarriage in pregnant women with DM based on the published literature. The rate of congenital malformations, or birth defects, is estimated to be approximately 6 to 10%. Therefore, the rate of congenital malformations 5.4% for liraglutide-exposed pregnancies in the NNSD is consistent with the DPMH-DMEP estimates for the occurrence of birth defects in pregnant women with DM. The following Background Risk statement will be included in labeling:

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1C < 7 and has been reported to be as high as 20-25% in women with a HbA1C >10. The estimated background risk of miscarriage in the indicated population is unknown. In the U.S. general

population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

The rate of SAbS reported in these pharmacovigilance data is 29%. This is higher than that expected in the U.S. general population of 15-20%; however, these are women with either GDM or PGDM. This reviewer was unable to identify references that provided a rate for the occurrence of SAbS among pregnant women with diabetes. That said, it is known that pregnancies in women with diabetes are at high risk for adverse pregnancy outcomes.

Summary

Insulin Degludec

The mechanism of action for insulin degludec is the same as that for insulin. Structurally the drug has the same amino acid sequence as human insulin with the omission of threonine in the B30 position and a C16 fatty acid side-chain attached. Once injected, the drug forms a depot in the subcutaneous tissues, which appears to slow the drug's absorption. In view of the structural and apparent mechanistic similarity of insulin degludec to endogenous insulin, the teratogenic risk would appear to be low. The animal data demonstrated no teratogenic effects. There are no data demonstrating a risk; however, absent human pharmacovigilance data or large published studies, the risk is not known.

Liraglutide

The nonclinical data of prenatal exposure to liraglutide demonstrate some embryo-fetal malformations. The Reprotox database review does not find the nonclinical data on congenital malformations to be as compelling as described in the labeling of the. Assessment of the liraglutide teratogenic risk was discussed with the Pharmacology/Toxicology Team and the Division at the June 9, 2016 labeling meeting. The pregnancy pharmacovigilance data were assessed. Less than half of the known exposed pregnancies were linked to an outcome. Among these, the incidence of congenital malformations was 5.4% (6/111), which would be a high rate if the background rate of congenital malformations in pregnant women with DM were assumed to the same as that for non-diabetic pregnant women. However, given that the birth defect background rate in the indicated population is estimated to be between 6% and 10%, the congenital malformation rate estimated from the applicant's liraglutide pregnancy pharmacovigilance data could be considered within the expected range for the population.

LACTATION

Nonclinical Experience

Both insulin degludec and liraglutide have been found in the milk of lactating rats. Insulin degludec was present in rat milk at a concentration that was lower than that found in the lactating rat plasma. The liraglutide concentration in rat milk was reported to be approximately half that measured in the lactating rat plasma.

Animal carcinogenicity studies conducted in mice and rats demonstrated increased incidences of thyroid C-cell tumors at clinically relevant liraglutide exposures. The human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. However, based on these carcinogenicity studies, liraglutide has a boxed warning. The reader is referred to the Victoza original application Pharmacology/Toxicology review by Anthony Parola, PhD for further details.²⁶

Review of Literature

In their review, the applicant stated no publications were identified for insulin degludec or liraglutide and lactation.

DPMH's search of the literature regarding insulin degludec or liraglutide in human breast milk found no publications. There was no review in LactMed²⁷ for either insulin degludec or liraglutide.

Review of Pharmacovigilance Database

There were no lactation pharmacovigilance data reported by the applicant.

Summary

Both insulin degludec and liraglutide have been found in the breast milk of rats. At this time, it is not known if a drug is present in animal milk whether that predicts the drug will be present in human milk. It is also not known if insulin degludec or liraglutide can be absorbed enterally when either drug is present in the breast milk of a treated lactating woman. The effect of either drug on the breastfeeding infant is not known. However, there is a serious risk of tumorigenicity demonstrated with liraglutide exposure in animals. It is not known if there is similar risk in humans. Due to the potential serious risk of tumorigenicity from liraglutide to the breastfed infant, a woman should not breastfeed during treatment with liraglutide.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There were no animal data demonstrating an adverse effect on reproductive potential for either sex with either insulin degludec or liraglutide.

Review of Literature

The applicant did not report finding any references related to insulin degludec or liraglutide and fertility. This reviewer found one case report relevant to adverse effects of liraglutide on male fertility that is discussed below.

²⁶ Dated July 10, 2009.

²⁷ LactMed[®]: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. Accessed April 5, 2016.

Fontoura P, 2014²⁸

This is a case report of a 35-year-old man with a history of primary infertility.

- October, 2011: treatment with liraglutide initiated
- November, 2011: normal sperm analysis
- March, 2012: decreased sperm count and all sperm non-motile
 - Liraglutide treatment interrupted
- May 2011: sperm count decreased (0.01×10^6 sperm/mL), sperm non-motile
- July, 2012: sperm count low but increased (8.7×10^6 sperm/mL), normal motility
- August, 2012: all sperm count parameters normal

This is the only report of decreased fertility associated with liraglutide that this reviewer found. Without additional reports suggesting liraglutide induced infertility in males of reproductive potential, this reviewer does not recommend changes to the Xultophy labeling.

Review of Pharmacovigilance Database

The applicant did not submit pharmacovigilance for insulin degludec. In response to the Agency's IR issued June 14, 2016, the applicant stated, "No significant safety information has been identified concerning fertility disorders in male and female subjects of reproductive potential associated with liraglutide use based on data available from different sources."

Summary

There is one published case report suggesting liraglutide may be associated with sperm abnormalities; however, this reviewer did not find the report significant enough to consider changes in liraglutide labeling.

CONCLUSIONS.

- **Pregnancy, Section 8.1**
 - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
 - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," (b) (4) and "Data" sections.
- **Patient Instructions, Section 17**
 - The "Patient Instructions" section of the labeling was reformatted to include the "Pregnancy" section.

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling

²⁸ Fontoura P, Cardoso M, *et al.*, The effects of liraglutide on male fertility: a case report. *Reprod Biomed Online*. 2014 Nov;29:644-6. doi: 10.1016/j.rbmo.2014.07.009. Epub 2014 Jul 29. PMID: 25246122

CONCLUSIONS

DPMH Proposed Pregnancy and Lactation Labeling

----- USE IN SPECIFIC POPULATIONS -----

(b) (4)

FULL PRESCRIBING INFORMATION

BOXED WARNING

WARNING: RISK OF THYROID C-CELL TUMORS

- **Liraglutide, one of the components of XULTOPHY, causes** (b) (4) **thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY 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)].**
- **XULTOPHY 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** (b) (4) **and** (b) (4) **symptoms of thyroid tumors** (b) (4) **[see Contraindications (4), Warnings and Precautions (5.1)].**

1 INDICATIONS AND USAGE

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with XULTOPHY, insulin degludec or liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. There are clinical considerations the risks of poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

For insulin degludec, rats and rabbits were exposed in animal reproduction studies at 5 times (rat) and 10 times (rabbit) the human exposure of 0.75 U/kg/day. No adverse outcomes were observed for pregnant animals and offspring [see *Data*].

For liraglutide, animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with (b) (4) 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 Data]. (b) (4)

The estimated background risk of major birth defects (b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, 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, stillbirth and delivery complications (b) (4)

(b) (4) Poorly controlled diabetes increases the fetal risk for (b) (4) still birth, macrosomia related morbidity (b) (4)

Data

Animal Data

Insulin degludec

Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec was given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall, the effects of insulin degludec were similar to those observed with human insulin.

Liraglutide

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating, during mating and the period of organogenesis, 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, 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 maternal body weight gain during the dosing period. 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 or insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. In lactating rats, insulin degludec and liraglutide, the two components of XULTOPHY, were present in milk;

(b) (4)

Data

Insulin degludec

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

Liraglutide

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

17 PATIENT COUNSELING INFORMATION

Pregnancy

Instruct female patients of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

(b) (4)



APPENDIX A
RLD Labeling Excerpt

TRESIBA (insulin degludec)
NDA 203-314
Labeling Approved September, 2015

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no well-controlled clinical studies of the use of insulin degludec in pregnant women. Patients should be advised to discuss with their health care provider if they intend to or if they become pregnant. Because animal reproduction studies are not always predictive of human response, insulin degludec should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

Subcutaneous reproduction and teratology studies have been performed with insulin degludec and human insulin (NPH) as a comparator in rats and rabbits. In these studies, insulin was given to female rats before mating throughout pregnancy until weaning, and to rabbits during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin as both caused pre-and post-implantation losses and visceral/skeletal abnormalities in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to maternal hypoglycemia.

8.3 Nursing Mothers

It is unknown whether insulin degludec is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when insulin degludec is administered to a nursing mother. Women with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

In rats, insulin degludec was secreted in milk and the concentration in milk was lower than in plasma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75 U/kg/day, based on U/body surface area) prior to mating and in female rats during gestation had no effect on mating performance and fertility.

APPENDIX B
RLD Labeling Excerpt

VICTOZA (liraglutide)
NDA 22-341
Labeling Approved April, 2016

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of VICTOZA in pregnant women. VICTOZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Liraglutide has been shown to be teratogenic in rats at or above 0.8 times the human systemic exposures resulting from the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma area under the time-concentration curve (AUC). Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below human exposure at the MRHD based on plasma AUC.

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.

8.3 Nursing Mothers

It is not known whether VICTOZA is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, a decision should be made whether to discontinue nursing or to discontinue VICTOZA, taking into account the importance of the drug to the mother. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

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/s/

CAROL H KASTEN
09/22/2016

TAMARA N JOHNSON
09/23/2016

LYNNE P YAO
09/28/2016

MEMORANDUM
REVIEW OF REVISED LABELING

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

Date of This Memorandum: September 27, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 208583

Product Name and Strength: Xultophy 100/3.6 (insulin degludec and liraglutide) injection, 300 units insulin degludec and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)

Submission Date: August 24, 2016

Applicant/Sponsor Name: Novo Nordisk

OSE RCM #: 2016-1328-2 and 2016-1934

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader (Acting): Hina Mehta, PharmD

DMEPA Deputy Director: Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the prescribing information (PI), Medication Guide, Instructions for Use (IFU), carton labeling, and the proposed pen dial redesign for Xultophy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review^a and advice from DMEP^b. In addition, DMEP requested we provide additional comments regarding options considered to determine

^a Conrad A. Label and Labeling and Labeling Comprehension Study Results Review for Xultophy (NDA 208583). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 July 13. 28 p. OSE RCM No.: 2016-1328.

^b Petruccelli M. COR-NDAIR-10 (General Advice Letter) for insulin degludec and liraglutide. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 Aug 18. NDA 208583.

the most appropriate term of measure to communicate the dose of Xultophy in the labeling from a medication error prospective.

2 DISCUSSION

As discussed in our previous reviews^{a,c}, we considered various options for the term of measure that would be most appropriate to communicate the dose of Xultophy in the labeling. We discussed multiple options with the DMEP and the Office of Policy for Pharmaceutical Quality (OPPQ) and these are outlined below:

1. No term of measure as proposed by Novo Nordisk
 - a. We determined that this was not a viable option because (1) expressing a dose without a term of measure would result in miscommunication of the dosing information and we anticipate that electronic prescribing systems would not be able to support a lack of a measure term and (2) this approach was studied in the label comprehension study done by Novo with results that indicate that prescribers may assign their own measure term (i.e., “units”) to designate the dose in the absence of a defined term^a.
2. Introduction of the novel term (b) (4) as proposed by Novo Nordisk
 - a. Based on our experience, we determined that the introduction of a novel term for this product (and others in this class) would introduce confusion (b) (4). In addition, we believe that electronic prescribing systems would have difficulty accommodating this non-standardized measure term.
3. Use of the terms (b) (4) or “mg” alone
 - a. The numbers on the current pen dial are designed to correspond to the dose of insulin. We determined that using terms such as (b) (4) or “mg” would be confusing for end users, especially considering that the pen design requires dialing the Xultophy dose (b) (4). In order to accommodate either of these options, the pen would have to be redesigned to indicate either the dose of both medications or the GLP-1 component alone on the pen dial.
4. Use of the term “units”
 - a. We acknowledge that this term may be considered misleading since it only references the insulin component and does not impart the presence of two medications. However, we determined that this term is the least problematic of the options available considering that the applicant has based the dosing strategy for Xultophy on the number of insulin units contained in the dose and designed the pen device to dial based on the units of insulin. In addition, healthcare practitioners and patients are familiar with the measure term “units” and electronic prescribing systems are already designed to accommodate this term.

^c Conrad A. Label and Labeling and Human Factors Results Review for Xultophy (NDA 208583). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 April 12. 32 p. OSE RCM No.: 2015-2086.

These recommendations were discussed with the DMEP and DMEP determined that use of the term “units” would be the least problematic strategy for communicating the dose for this product in the labeling. We acknowledge that there are some residual risks with the use of the measure term “units” in instances where prescribers do not read the prescribing information and are not familiar with the contents of Xultophy and assume that the product only contains insulin. Thus, we have provided recommendations to revise the product label and labeling to increase the clarity and prominence of critical dosing information. Furthermore, following discussion with DMEP, numerical modifiers were added to the proprietary name to help convey to healthcare providers that the formulation contains two ingredients (i.e., Xultophy 100/3.6). This nomenclature is similar to that currently used for marketed insulin/insulin mixtures, where the numerical modifier conveys the percentage of each insulin in the mixture.

In addition, the sponsor revised the pen dial by starting the pen dial at 10 units and replaced (b) (4) with a priming symbol as recommended by the Division of Metabolism and Endocrinology Products (DMEP)^b. The product labeling was updated to reflect these changes.

3 CONCLUSION

The revised dial for the Xultophy pen device, Medication Guide, and carton labeling are acceptable from a medication error perspective. This review identified several deficiencies in the prescribing information (PI) and the Instructions for Use (IFU). We provide recommendations in Section 4 and recommend their implementation prior to approval of this NDA.

4 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Highlights of Prescribing Information: Dosage Forms and Strengths
 - a. We recommend revising the current statement as follows for improved clarity: “Xultophy contains 100 units/mL insulin degludec and 3.6 mg/mL liraglutide in a 3 mL pre-filled disposable pen.”
2. Full Prescribing Information: Section 2.1 Important Administration Instructions
 - a. We recommend moving the bulleted statement (b) (4) to Section 2.2 General Dosing Instructions as the first bulleted statement for improved visibility of this information. In addition, we recommend bolding the statement (b) (4) to improve visibility of this reference to the dosing table.
3. Full Prescribing Information: Section 2.2 General Dosing Information

a. Consider moving the bulleted statement [REDACTED] (b) (4) to a higher location in the section to improve visibility of this information in the section.

b. Consider revising the statement directly above the dose table (Table 1) as follows: “The dose of Xultophy must be individualized based on the patient’s need for glycemic control and is titrated based on the dose of insulin degludec.” This revision is recommended to clarify that the dose is prescribed and dialed to correlate with the number of insulin units prescribed.

4. Full Prescribing Information: Section 16.1 How Supplied

a. We recommend modifying the statement [REDACTED] (b) (4) as follows for improved clarity: “Xultophy is supplied as a clear, colorless solution containing 100 units insulin degludec and 3.6 mg liraglutide per mL in a 3 mL pre-filled, disposable, single-patient use, multiple dose pen.”

b. We recommend removing the statement [REDACTED] (b) (4) from this section.

c. We recommend revising the statement [REDACTED] (b) (4) as follows for improved clarity: “Xultophy 3 mL disposable prefilled pen (Package of 5) NDC 0169-2911-15”.

B. Instructions for Use (IFU)

1. Under step 10, we recommend bolding and creating a separate bullet for the statement “If there is not enough Xultophy left in your pen for a full dose, do not use it. Use a new Xultophy pen.” to increase prominence of this information.

APPENDIX A. LABELING SUBMITTED ON AUGUST 24, 2016

Pen dial



Carton labeling



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/s/

ARIANE O CONRAD
09/28/2016

HINA S MEHTA
09/28/2016

LUBNA A MERCHANT
09/28/2016



GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: 9/7/2016

To: Marisa Petruccelli, Project Manager
Division of Metabolic Products
Office of New Drugs
Center for Drug Evaluation and Research (CDER)

From: Sapana Patel, PharmD.
Pharmacist/Lead Reviewer

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for NDA 208583/ICC 1600591

Applicant	Novo Nordisk
Indication for Use	Indicated as an adjunct to diet and exercise to improve glycemc control in adults with type 2 diabetes mellitus
Drug / Biologic Constituent	Insulin degludec and liraglutide
Device Constituent	(b) (4)

Recommendation: Approval

Note to CDER: Please ensure patient labeling is updated to reflect the dial changes. Current patient labeling reflects (b) (4)

Digital Signature Concurrence Table	
Reviewer	Sapana Patel -S Digitally signed by Sapana Patel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sapana Patel -S, 0.9.2342.19200300.100.1.1=2001554957 Date: 2016.09.07 10:53:25 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.09.08 10:13:48 -04'00'

I. Purpose / Background

The Center for Drug Evaluation and Research (CDER) has requested CDRH to provide a review of the proposed new design for the pen dial display. This NDA originally came in September 14, 2015 with a PDUFA date of September 14, 2016. CDRH's original review dated May 13, 2016 recommended approval of the device constituent. Since CDRH's original review the sponsor was asked by CDER to change the display on the pen dia. CDER is requesting review of the change.

Please note a full review of the device constituent is provided in the previous review

II. Administrative

Documents Reviewed:

NDA 208583/Novo Nordisk Response to comments dated August 17, 2016

CDRH Review Team:

Sapana Patel, PharmD.

III. Device Description



Figure 1 PDS290 IDegLira pen-injector

The device constituent PDS290 IDegLira pen-injector is similar to the currently marketed prefilled disposable insulin delivery device Flex Touch. PDS290 IDegLira pen-injector is developed for the injection of the combination product insulin degludec/liraglutide, whereas FlexTouch was developed for the injection of insulin. Both pens are based on the same PDS290 pen-injector platform design. The design similarities are that both are pen-shaped injectors with prefilled cartridges, where the intended dose is given by turning the dose selector and pressing the button to deliver the intended dose. PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 ml cartridge with drug. Therefore the drug is not in contact with the device. The device is intended to function with a standard needle thread **1** or a needle with a bayonet coupling.

IV. Review

FDA (CDER) response to sponsor on August 18, 2016 in response to proposed dial change.

We have reviewed your August 16, 2016, response to the inquiry below. In light of the revised indication, the recommended starting dose should be 16 units. It would be acceptable to redesign the Pen to display units starting at 10 so that clinical discretion can be used in the case of illness or other conditions necessitating a dose reduction.



(b) (4)

NovoNordiskResponse

Based on the revised indication as per the Agency's comments to the Physician Insert dated August 17, 2016, Novo Nordisk agrees that the recommended starting dose will be 16 units when converting from basal insulin or GLP-1 RA treatment.

The scale drum component (pen dial) of the pen will be updated as requested by the Agency to display units starting at 10 so that clinical discretion can be used in the case of illness or other conditions necessitating a dose reduction. Novo Nordisk will configure the pen dial in a manner that will provide for administration of volumes necessary to prime the pen, ie. a priming symbol (••→), consistent with the FDA approved Saxenda pen-injector which shares the same PDS290 platform with the Xultophy pen. The updated pen dial is shown below in [Figure 1](#).

(b) (4)

Reviewer Comments:

The sponsor is proposing starting the pen dial at 10 units. The previously reviewed pen dial started at (b) (4). The sponsor has conducted dose accuracy testing to 11608-1 on (b) (4) unit doses. The revised minimum dose of 10 units is covered with the existing data submitted in the application. The sponsor has also proposed to replace (b) (4) with a priming symbol at required priming volume. The sponsor is not making specification changes to the dial or pen. The changes requested are acceptable.

V. Recommendation

Approval of amendment.

Note to CDER: Please ensure patient labeling is updated to reflect the dial changes. Current patient labeling reflects (b) (4)

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/s/

MARISA PETRUCCELLI
09/09/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 29, 2016

To: Marisa Petruccelli, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208583
OPDP labeling comments for XULTOPHY® (insulin degludec and liraglutide), for subcutaneous injection

On September 17, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Medication Guide, carton/container and Instructions for Use (IFU) for XULTOPHY® (insulin degludec and liraglutide), for subcutaneous injection. OPDP's comments on the proposed draft labeling are based on the version sent by Marisa Petruccelli via email on August 18, 2016, and are marked on the version provided directly below.

OPDP does not have any comments on the proposed carton/container labeling at this time.

Comments on the Medication Guide and IFU are provided in a collaborative review between DMPP and OPDP under a separate cover.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
08/29/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 29, 2016

To: Jean-Marc Guettier, MD
Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): ZULTOPHY (insulin degludec and liraglutide [rNDA origin] injection)

Dosage Form and Route: Solution, for subcutaneous use

Application Type/Number: NDA 208583

Applicant: Novo Nordisk

1 INTRODUCTION

On September 15, 2015, Novo Nordisk submitted for the Agency's review an original New Drug Application (NDA) for XULTOPHY (insulin degludec and liraglutide [rNDA origin] injection) solution for subcutaneous injection indicated as an adjunct to diet and exercise to improve glucemic control in adults with type 2 diabetes mellitus. Novo Nordisk is filing for approval of the fixed ration combination of insulin degludec/liraglutide.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on September 20, 2015, and September 17, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XULTOPHY (insulin degludec and liraglutide [rNDA origin] injection).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 12, 2016.

2 MATERIAL REVIEWED

- Draft XUTOPHY (insulin degludec and liraglutide [rNDA origin] injection) MG, and IFU received on September 15, 2015, and received by DMPP and OPDP on August 18, 2016.
- Draft XULTOPHY (insulin degludec and liraglutide [rNDA origin] injection) Prescribing Information (PI) received on September 15, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 18, 2016.
- Approved VICTOZA (liraglutide) comparator labeling dated April 22, 2016.
- Approved TRESIBA (insulin degludec injection) comparator labeling dated September 25, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
08/29/2016

CHARUNI P SHAH
08/29/2016

LASHAWN M GRIFFITHS
08/29/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: August 19, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 208583

Product Name and Strength: Xultophy (insulin degludec and liraglutide) injection, 300 units insulin degludec and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)

Submission Date: July 22, 2016

Applicant/Sponsor Name: Novo Nordisk

OSE RCM #: 2016-1328-1

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader (Acting): Hina Mehta, PharmD

1 PURPOSE OF MEMO

DMEP requested that we review the revised commercial container label and carton labeling and professional sample label and labeling for Xultophy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised commercial and professional sample container label and carton labeling for Xultophy are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Conrad A. Label and Labeling and Labeling Comprehension Study Results for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jul 13. 29 p. OSE RCM No.: 2016-1328.

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/s/

ARIANE O CONRAD
08/19/2016

HINA S MEHTA
08/19/2016

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 2, 2016

TO: Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of New Drugs

FROM: Li-Hong Paul Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Establishment Inspection Report (EIR)
covering Study **NN9068-4026** submitted in support of **NDA
208583** sponsored by Novo Nordisk Inc., Plainsboro, NJ.

Inspection Summary

This was a FY2016 GDUFA in vivo bioequivalence clinical site inspection. The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of Study **NN9068-4026** conducted by Profil Institute, Neuss, Germany in support of **NDA 208583**.

At the conclusion of the inspection, no significant issues were observed and no Form FDA 483 was issued. The final classification for this inspection is no action indicated (NAI). Based on the inspectional findings, I recommend that the data from the clinical portion of the audited study be accepted for further Agency review.

The following study was audited during the inspection:

NDA 208583

Study #: NN9068-4026

Study Title: "A trial to demonstrate bioequivalence between
two insulin degludec/liraglutide formulations, B5
and V2, in healthy subjects"

Clinical Study Conduct: 08/05/2013 - 11/04/2013

Clinical Site: PROFIL Institut für Stoffwechselforschung GmbH,
Hellersbergstraße 9, D-41460 Neuss, Germany

Clinical investigator: Dr. med. Christoph Kapitza

The inspection of the clinical portion of the above study was conducted by ORA investigator Mark A. Jackson at Profil Institut, Neuss, Germany from March 14 to 18, 2016. The inspection included a thorough examination of study records, informed consent process, protocol compliance, institutional review board approvals, adverse event reporting, test article accountability and storage, blinding/randomization, clinical data validation, and IRB and sponsor communications.

At the conclusion of the inspection, no objectionable findings were observed and no Form FDA 483 was issued.

Recommendations:

Following review of the EIR, the clinical data from Study **NN9068-4026** conducted by Profil Institut, Neuss, Germany, were found to be reliable. Therefore, I recommend that the data from the clinical portion of the audited study be accepted for further Agency review.

Li-Hong Paul Yeh, Ph.D.
Chemical Engineer

Final Classification:

Clinical Site:

NAI- Profil Institut, Neuss, Germany
FEI#: 3003421648

E-mail cc:

OTS/OSIS/Kassim/Haidar/Taylor/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au

Draft: PY 07/28/2016

Edit: RCA 07/28/2016;AD 8/2/2016

Page 3 - NDA 208583, Insulin degludec/liraglutide, sponsored by
Novo Nordisk Inc.

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Inspections/BE Program/Clinical
Sites/Profil Institut, Neuss, Germany

OSIS File #: BE 7029 (NDA 208583)

FACTS: 11603460

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/s/

LI-HONG P YEH
08/02/2016

ARINDAM DASGUPTA
08/02/2016

LABEL AND LABELING AND LABELING COMPREHENSION STUDY RESULTS REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 13, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 208583

Product Name and Strength: Xultophy (insulin degludec and liraglutide) injection, 300 units insulin degludec and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)

Product Type: Multi-ingredient and Combination Product

Rx or OTC: RX

Applicant/Sponsor Name: Novo Nordisk

Submission Date: June 2, 2016 and June 3, 2016

OSE RCM #: 2016-1328

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader (Acting): Hina Mehta, PharmD

DMEPA Associate Director for Human Factors (Acting): QuynhNhu Nguyen, MS

DMEPA Deputy Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA evaluate the labeling comprehension study report and updated labels and labeling submitted under NDA 208583 for Xultophy (insulin degludec and liraglutide). The Agency requested that Novo Nordisk complete this study during the mid-cycle meeting on February 18, 2016.¹ Novo Nordisk submitted the protocol for this labeling comprehension study, which we reviewed and provided comments.²

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Labeling Comprehension Study	C
Labels and Labeling	D

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For this product, we reviewed the labeling comprehension study report and the proposed Prescribing Information (PI) submitted by Novo Nordisk on June 3, 2016. Novo Nordisk also submitted updated container label and carton labeling for review on June 2, 2016.

3.1 LABELING COMPREHENSION STUDY

The labeling comprehension study for Xultophy was conducted with a total of 20 prescriber participants: five diabetes specialists (DS), five primary care physicians (PCP), five physician assistants (PA), and five nurse practitioners (NP). The study was designed to simulate prescribing tasks and provide data that various prescriber types are able to use the prescribing information (PI) to appropriately prescribe, make dose titrations, and make conversions from

¹ Petruccelli M. Mid-Cycle Communication for insulin degludec and liraglutide injection. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 February 18. NDA 208583.

² Conrad A. Labeling Comprehension Study Protocol Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 12. RCM# 2016-651.

other drug therapies to Xultophy (refer to Appendix C). We reviewed the study protocol and we agreed with the proposed methodology in terms of objectives, participants, and simulated use environment. However, we recommended modifications to the proposed moderator script to ensure that the protocol was representative of the real world environment.² We reviewed the protocol with this submission and confirmed that Novo Nordisk made the recommended changes to the study protocol. The study tested the prescribers' comprehension using five different patient scenarios and the nine tasks associated with these scenarios; we provide a summary of the study results and our evaluation on each scenario in the following sections.

Scenario 1: Participants (n=20) were presented with a written patient profile of a type 2 diabetic patient treated with an oral anti-hyperglycemic agent. They were then asked to determine (1) a starting dose of Xultophy for this patient and (2) the number of insulin units and milligrams of liraglutide in a dose of 10.

Task 1: Sixteen of 20 participants were able to successfully determine the recommended starting dose for this patient case scenario based on the recommendations in the PI. Four participants recommended the wrong starting dose for this case scenario.

Two participants (NP4 and DS3) used the dosing instructions in the PI. Participant NP4 selected the wrong dose because the participant was uncomfortable prescribing the medication with the limited information provided and chose to prescribe a low dose of 2 based on personal experience. Participant DS3 determined that the recommended starting dose of 10 was too low based on the participant's prior medical experience. Therefore, this participant prescribed a dose higher than that recommended in the PI (16 prescribed instead of 10). We attributed these errors to be related to the physician's own practice; therefore, we do not have any recommendations to modify the PI.

Two participants (DS2³ and PCP3) elected not to use the dosing instructions in the PI to complete the task and used the "Highlights of Prescribing Information" on the first page of the PI instead. Participant DS2 used the information to determine that the product was a multi-ingredient product then recommended a lower starting dose than the participant would normally use for basal insulin in a single injection. This error would represent a very small difference in dose, which could result in clinically insignificant hyperglycemia. Participant PCP3 used the information from the "Dosage Forms and Strengths" section of the

³ Participant DS2 failed each of the dosing tasks (Tasks 1, 3, 5, 6, 8, and 9).

Highlights, which indicated the strength of the insulin component to be 100 units/ml, and subsequently prescribed 100 instead of the dose of 10 that he intended to prescribe. This error is concerning because it would result in clinically significant hypoglycemia. Participant PCP3 was reported to be nervous during the task and he realized the error when conducting the next task. It is unclear why the prescriber would refer to the “Dosage Forms and Strengths” section instead of the “Dosing and Administration” section of the PI. It is also unclear why the participant selected a dose of 100 units as this dose is generally considered high and the recommended starting dose of basal insulin in an insulin naïve patient would usually be 10 units per day. We do not have any recommendation to modify the PI at this time.

Task 2: All 20 participants were able to correctly determine the number of units of insulin degludec and milligrams of liraglutide in a Xultophy dose of 10.

Scenario 2: Participants were presented with a written patient profile of a type 2 diabetic patient treated with a GLP-1 receptor agonist and asked to (1) determine the starting dose of Xultophy for this patient, (2) determine the number of insulin units and milligrams of liraglutide in a dose of 16, and (3) determine if the patient’s current diabetes treatment should be changed after adding Xultophy.

Task 1 (noted as task 3 in the study): Sixteen of 20 participants were able to successfully determine the recommended starting dose for this patient case scenario based on the recommendations in the PI.

Four participants (DS2³, PCP2, PCP5, and DS5) recommended the wrong starting dose for this case scenario. Three of the four participants (DS2, PCP2, and PCP4) prescribed doses lower than recommended (5 or 10 instead of a dose of 16). One of the four participants (DS5) prescribed a dose higher than recommended (20 instead of 16) based on an assumption that the patient was already on a GLP-1 agonist and would not be subject to the side effects associated with the GLP-1 agonist component in Xultophy; thus, he did not determine that the patient would require the lower dose of Xultophy. Our review of the PI indicates that the initiation dose should be lower for improved tolerability of the GLP-1 side effects. Additional subjective feedback from these study participants indicated that they did not use the dosing instructions in the PI to complete the task and determined a starting dose based on personal experience with dosing basal insulin in this type of patient. We do not have any recommendations to modify the PI at this time.

Task 2 (noted as task 4 in the study): All 20 participants were able to correctly determine the number of units of insulin degludec and milligrams of liraglutide in a Xultophy dose of 16.

Task 3 (noted as task 5 in the study): Nineteen participants recommended discontinuation of the patient's current therapy after starting Xultophy, per the recommendations in the PI. One participant (DS2³) failed to recommend discontinuation of the case patient's current therapy. This participant stated that he did not use the dosing instructions in the PI but rather his own clinical judgment to determine that the patient could remain on the current therapy because the dose of Xultophy that the participant prescribed was below the recommended starting dose of 10 and therapy could be adjusted later based on the patient's glucose readings. We do not have any recommendation to modify the PI at this time.

Scenario 3: Participants were presented with the patient profile of a type 2 diabetic patient treated with 20 units of basal insulin and they were asked to (1) determine the starting dose of Xultophy for this patient and (2) determine if the patient's current diabetes treatment should be changed after starting Xultophy.

Task 1 (noted as task 6 in the study): Fifteen of 20 participants were able to successfully determine the recommended starting dose for this patient case scenario based on the recommendations in the PI. Five participants (DS2³, PCP2, PA3, PCP5, and DS5) recommended the wrong starting dose for this case scenario. Of these, four participants (DS2, PCP2, PA3, and DS5) decided to prescribe an "equivalent" Xultophy dose of 20, instead of the 16 units recommended in the PI, based on their determination that the patient's glucose must be uncontrolled on the current 20 unit dose of basal insulin. They believed that addition of the second medication would improve glucose control. One participant (PCP5) decided to prescribe 10 units for this case based on personal experience and a general discomfort with prescribing a higher dose with the limited information available. During the follow-up interviews, the participants expressed understanding of the dose recommendations in the PI; however, they made their decisions based on their prior experience with dosing basal insulin. We noted that the PI does clearly indicate the recommended dose of Xultophy when switching from basal insulin and those prescribers that used the PI for dosing information were able to complete the task successfully. Thus, we did not identify any concerns with the PI.

Task 2 (noted as task 7 in the study): All participants recommended discontinuation of the patient's current therapy after starting Xultophy, as recommended in the PI.

Scenario 4: Participants were presented with the patient profile of a type 2 diabetic patient currently treated with 80 units of basal insulin and asked to make a recommendation regarding initiation of Xultophy for this patient.

Task 1(noted as task 8 in the study): Thirteen participants correctly determined that Xultophy is not a recommended therapy option for a patient taking 80 units of basal insulin, based on the information in the PI. These 13 participants used the dosing instructions in the PI to make this determination. Seven participants (PCP1, DS2³, PCP2, PCP3, DS3, PCP5, and DS5) incorrectly determined that this case patient would be a candidate for Xultophy therapy.

Three participants used the dosing instructions in section 2.4 of the PI to inform their recommendation to start Xultophy in this patient. Participant PCP1 and PCP3 decided to stop the patient’s basal insulin to start Xultophy but the sponsor noted that they did not read the entire section. After prompting to read the entire section, participant PCP1 correctly determined that the patient was not a candidate for Xultophy therapy. Participant PCP3 persisted in recommending Xultophy because this participant did not interpret the statement “Xultophy has not been studied in patients taking >50 units of basal insulin daily, and alternate treatment regimens should be considered” to mean that the patient wasn’t a candidate for therapy. Thus, we recommend changes to this statement in the PI to improve clarity regarding the patients for whom Xultophy is not an appropriate therapy.

Four participants did not use the dosing instructions in the PI to inform their recommendation to start Xultophy in this patient.

Participants DS2 and DS5 recommended starting Xultophy at a dose of 50 and lowering the current dose of basal insulin to 30 units to maintain the patient’s current insulin dose. Participant DS2 indicated that he based his/her recommendation for the dose of Xultophy on the statement in the “Highlights of Prescribing Information” section that indicates the pen is (b) (4). During the follow-up interview, they were both prompted to read section 2.4 of the PI and were able to determine that this patient was not a candidate for Xultophy. Our review of the PI indicates that there is no statement regarding the maximum dosing for Xultophy in the “Highlights” section of the PI. Thus, we recommend adding this information to improve clarity regarding the dose recommendations for this product.

Participant PCP2 recommended lowering the patient's dose to 60 of Xultophy to be cautious instead of prescribing a dose of 80. The participant realized that patient was not a candidate for therapy after reading section 2.4 of the PI during the follow-up session but expressed the desire to use the drug anyway based on his own clinical judgment.

Participant PCP5 decided to cut the current insulin dose in half and proscribed 40 of Xultophy after expressing discomfort with making a recommendation based on the limited information provided in the case. We agree with the sponsor and consider this failure to be a study artifact. We note that the PI describes that the maximum dose of Xultophy is 50 and that it has not been studied for patients taking more than 50 units of basal insulin per day. However, study participants that did refer to the PI for this task still failed to interpret this information as contraindications for therapy. Therefore, we provide some additional revisions to the language in the PI to help further mitigate for this type of error.

Scenario 5: Participants were asked to titrate the dose of Xultophy for a type 2 diabetic patient. There was no specific patient case provided for this task.

Task (noted as task 9 in the study): Fifteen participants correctly determined how to titrate Xultophy based on the titration information provided in Section 2.5 of the PI. Five participants (DS1, DS2³, PCP2, PCP5, and DS5) failed to titrate Xultophy based on the recommendations provided in the PI. Participant DS1 did use the titration table in Section 2.5 to determine a titration dose of 2 but failed to recommend the correct interval for dose adjustments without reading the entire section. Participants DS2, PCP2, PCP5, and DS5 failed to use the PI to determine a titration dose and determined a titration schedule based on personal experience with dosing and titrating basal insulin. Each of these participants used recommended longer titration schedules than recommended in the PI based on their own clinical judgment. While the PI does contain recommendations regarding a rate of dose titration, we provide some additional revisions to the language in the PI to help further mitigate for this type of error.

3.2 LABELS AND LABELING

The labeling comprehension study results indicate that the majority of the errors occurred when the prescribers did not use the PI and relied on their own experience with dosing insulin products. However, several prescribers that did use the PI for dosing information chose to deviate from the PI as well because they incorporated their clinical experience into their decisions. We realize that this particular aspect is a practice of medicine issue and is beyond

the scope of the labels and labeling. However, we do provide recommendations in sections 4.1 and 4.2 to improve the prominence of certain information and recommend their implementation prior to approval of this NDA.

Additionally, we note that Novo is proposing to communicate the Xultophy dose without using any terms of measure in the labeling. This was studied in this labeling comprehension study and their human factors validation study. However, we believe that expressing a dose without a term of measure would result in miscommunication of the dosing information and we anticipate that computerized order entry programs would not be able to support the lack of a measure term. Study participants' verbatim responses⁴, submitted in response to DMEPA's June 29, 2016 information request, demonstrate that users may subjectively develop terms to use if they are not predefined. For example, we noted that 17 of the 20 prescriber participants in this labeling comprehension study referred to the Xultophy dose using the term "units" at least once when completing the written prescribing tasks during the study. In addition, multiple participants expressed uncertainty about how to refer to the dose and asked for assistance to determine if the dose would be considered units.

In our review of the human factors validation study results⁵, we considered that the use of the term "units" would be the least problematic strategy for dosing this multi-ingredient product but that terminology fails to impart the presence of two drugs. We are also considering the use of both dosage units (units for insulin and mg for liraglutide) but this may create confusion for end users of the pen device, considering that the proposed device dials doses based on the insulin component alone. If the use of both dosage units is desired, the device design may require significant modifications. However, considering the current design of the pen injector and user familiarity with the term for insulin products, "units" may be the least problematic strategy for the Xultophy labels and labeling. We are discussing multiple options with the Division of Metabolism and Endocrinology Products (DMEP) and the Office of Policy for Pharmaceutical Quality (OPPQ) to determine the best terminology to use for dosing this product but a final recommendation is pending.

⁴ The summaries are available through FDA GlobalSubmit Review:

<\\cdsesub1\evsprod\nda208583\0050\m1\us\re-fda-req-20160216-resub.pdf>

⁵ Conrad A. Label and Labeling and Human Factors Results Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 12. RCM No. 2016-2086.

4 CONCLUSION & RECOMMENDATIONS

The labeling comprehension study results indicate that prescribers should be able to prescribe Xultophy safely when they use the PI. Although some failures occurred, the majority of errors occurred because the prescribers used their personal experience and clinical judgment when prescribing basal insulin. There were few errors that occurred when prescribers referred to the PI; thus, we have provided specific recommendations to revise the PI to increase the clarity and prominence of critical dosing information.

In addition, we continue to have concerns regarding the most appropriate term of measure to use to communicate the dose of Xultophy in the labeling. We are discussing multiple options with the Division of Metabolism and Endocrinology Products (DMEP) and the Office of Policy for Pharmaceutical Quality (OPPQ) to determine the best terminology to use for dosing this product but a final recommendation is pending.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on the results of the labeling comprehension study, we identified the following areas for improvement:

A. Prescribing Information (PI) Labeling

1. We continue to have concerns with the Applicant's proposal to communicate the Xultophy dose without using any terms of measure in the labeling. We believe that expressing a dose without a term of measure would result in miscommunication of the dosing information and we anticipate that computerized order entry programs would not be able to support the lack of a measure term. Additionally, as seen in the study, users may subjectively develop terms to use if they are not predefined. We recommend revising the dosing information throughout the PI to include a term of measure (i.e., units or units/mg) once a determination is made on the best terminology to use based on the ongoing discussion with DMEP, DMEPA and OPPQ.
2. Highlights of Prescribing Information:
 - a. In the Dosage and Administration section, add the following statement regarding the maximum recommended dose immediately following the bulleted statement (b) (4)
 "The maximum recommended daily dose of Xultophy is 50."
3. Section 2.1 Dosing

- a. We recommend reformatting this section into bullet statements for improved readability.
- b. Consider adding the following statement directly above the dose table:
“The dose of Xultophy is titrated based on the patient’s need for insulin. The Xultophy dose is increased or decreased based on the insulin degludec dose.” This information may help to clarify that the dialed dose on the pen correlates to the number of insulin units prescribed.
- c. We recommend omitting the (b) (4) “dose counter display” columns of the dose table to improve clarity of the information presented in this table. The numbers provided in these columns overlap with the number provided in the (b) (4) column making it more difficult to determine the numbers that users need to determine the dose.

4. Section 2.4 Converting to Xultophy from Basal Insulin

- a. For improved clarity, consider rephrasing the statement (b) (4)
[REDACTED]
[REDACTED] as follows:
“Xultophy is not recommended for use in patients taking >50 units of basal insulin daily; alternate treatment regimens should be considered.”

5. Section 2.5 Titration of Xultophy

- a. We recommend adding the statement “titrate every 3-4 days” to Table 2 to increase visibility of this information.

4.2 RECOMMENDATIONS FOR NOVO NORDISK

We provided container label and carton labeling comments on May 25, 2016⁶ and we have additional recommendations, which are noted below. We have noted that the previously recommended changes were not fully implemented and we request that the following changes are made for both carton presentations, container labels, and the professional sample label and labeling:

A. Carton Labeling

⁶ Petruccelli M. Labeling PMR/PMC Discussion Comments for insulin degludec and liraglutide (NDA 208583). Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2016 May 25.

1. On the primary display panel, consider adding line spaces between the proprietary name, established name, “For Single Patient Use Only” warning, and concentration statement since this information appears cluttered on the label. Since there is a large amount blank space available, this modification should improve readability.
2. Revise the statement [REDACTED] ^{(b) (4)} to “See prescribing information” for improved clarity.
3. Revise the statement [REDACTED] ^{(b) (4)} to “Must be refrigerated”.
4. Include the statements “Date of first opening ___/___/___ . Discard unused portion 21 days after first opening.” Since there will be multiple pens in each carton, we recommend including space for users to make note of the date for each pen in the box.
5. On the primary display panel, add the following statement immediately below the product concentration information: “Each unit of Insulin from this pen also delivers 0.036 mg of liraglutide”.

B. Commercial Container Label

1. Add the following statement immediately below the product concentration information: “Each unit of Insulin from this pen also delivers 0.036 mg of liraglutide”. Consider minimizing the font size or relocating the statements “RX only” and “For subcutaneous use only” to provide space for the above statement.

C. Professional Sample Label and Labeling

1. Increase the size and prominence of the “Sample. Not for Resale” statement on the drug sample’s label and the “Sample” statement on the drug sample container’s labeling so that it is clear that these are drug samples, per 21CFR 203.38(c).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xultophy that Novo Nordisk submitted on June 3, 2016.

Table 2. Relevant Product Information for Novo Nordisk			
Initial Approval Date	N/A		
Active Ingredient	insulin degludec and liraglutide		
Indication	Type 2 diabetes mellitus		
Route of Administration	Subcutaneous		
Dosage Form	Solution		
Strength	100 units insulin degludec and 3.6 mg liraglutide per mL		
Dose and Frequency	Individualized dose given once daily		
How Supplied	3 mL prefilled pens dispensed in boxes of (b) (4) 5 pens		
Storage	Prior to first use		
	After first use		
	Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
	Until expiration date		21 Days

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 16, 2016, we searched the L:drive and AIMS using the terms “degludec liraglutide” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews and we confirmed that our previous recommendations were implemented or considered.

<u>Review Title</u>	<u>RCM Number</u>	<u>Full Citation</u>
Labeling Comprehension Study Protocol Review for Xultophy (insulin degludec and liraglutide)	2016-651	Conrad A. Labeling Comprehension Study Protocol Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 12. RCM No. 2016-651.
Label and Labeling and Human Factors Results Review for Xultophy (insulin degludec and liraglutide)	2015-2086	Conrad A. Label and Labeling and Human Factors Results Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 12. RCM No. 2016-2086.
Human Factors Study Protocol Review for Insulin Degludec and Liraglutide Injection (IND 109121)	2012-2754	Vee S. Human Factors Study Protocol Review for Insulin Degludec and Liraglutide Injection (IND 109121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. RCM No. 2012-2754.

APPENDIX C. LABELING COMPREHENSION STUDY

C.1 Study Design

1 Test Objective

The objective of the labeling comprehension test was to assess if prescribers were able to find and comprehend the information in the draft PI – Dosage and Administration section, to appropriately:

- Prescribe and dose IDegLira
- Make dose titrations
- Convert patients to IDegLira from other therapies

2.3 Number and type of test participants

The test included the user group who will prescribe and dose IDegLira, make dose titrations and convert patients to IDegLira from other therapies, namely prescribing HCPs.

The prescribing HCP user group includes the following sub-groups:

- Diabetes Specialists (i.e., Endocrinologists)
- Primary Care Physicians (non-specialists)
- Physician Assistants
- Nurse Practitioners

Each sub-group included 5 participants.

No training was provided to the test participants as it is likely that prescribing HCPs in real life would not receive any training other than their formal education.

To test this, the participants completed the following five scenarios with a total of nine knowledge tasks:

- Scenario 1 - Initiation of Xultophy[®] for a Type 2 diabetic patient currently treated with oral anti-diabetic agents
- Scenario 2 – Conversion to Xultophy[®] for a Type 2 diabetic patient currently treated with GLP-1 receptor agonists
- Scenario 3 – Conversion to Xultophy[®] for a Type 2 diabetic patient currently treated with basal insulin
- Scenario 4 – Recommendation for a Type 2 diabetic patient currently treated with 80 units of basal insulin
- Scenario 5 - Titration of Xultophy[®] for a Type 2 diabetic patient

The draft PI was available for use at the discretion of the HCP. Results have been evaluated for whether the participants could find and comprehend the information in the draft PI. This

included collecting data regarding the number of participants that refer to the draft PI and those that did not use the dosing instructions in the PI. The number of correct and incorrect responses during the knowledge tasks were collected and separated based on participant use of the PI to facilitate comparison of prescribing performance.

C.2 Results

A majority of the incorrect responses were given while participants did not use the dosing instructions in the PI. The participants based their recommendations their prior medical experience.

Scenario 1 - Initiation of Xultophy[®] for a Type 2 diabetic patient currently treated with oral anti-diabetic agents

Task 1: Determine a starting dose of Xultophy[®]

16 of 20 participants performed the task and responded correctly:

- 12 of 16 participants used the dosing instructions in the PI.
- 4 of 16 participants did not use the dosing instructions in the PI.

4 of 20 participants performed the task and responded incorrectly:

- 2 of 4 participants used the dosing instructions in the PI.
- 2 of 4 participants did not use the dosing instructions in the PI.

TASK 1				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.2 in the draft PI.
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.2 in the draft PI.
3 (PCP1)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.2 in the draft PI.
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.2 in the draft PI.
5 (DS1)	Yes	Yes	Yes	The participant stated that she based her decision on table 1 in the draft PI.
6 (DS2)	No	Yes	No	The participant incorrectly determined a starting dose of 5, and stated that she based her decision on personal experience of other long acting insulins "normally I would start at 10, but because it is a combination product I would start at 5". Notably, during follow up the participant was directed to the draft PI (b) (4). (b) (4) Nevertheless, the participant would not correct her initial recommendation "right here 2.2. I would go under what it says right here. I would rather underdose than overdose".
7 (PCP2)	Yes	Yes	No	The participant stated that he based his decision on personal experience regarding long acting insulin.
8 (PA2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.2 in the draft PI.
9 (NP3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.2 in the draft PI.
10 (PCP3)	No	Yes	No	The participant stated that he would prescribe "the lowest dose" and proceeded to incorrectly prescribe a dose of 100. The participant stated that he based his decision on "the dosage forms and strengths" in the highlight section of the PI. Notably, the participant changed his decision to a dose of 10 during task 2 (b) (4) but did not understand the gravity of his initial decision.
11 (NP4)	No	Yes	Yes	The participant incorrectly prescribed a dose of 2 based on her personal experience. Notably, the participant expressed to feel uncomfortable prescribing medication to a patient with the limited information provided on the patient.

12 (DS3)	No	Yes	Yes	<p>The participant immediately changed her answer to a dose of 10 during follow-up at the end of the session.</p> <p>The participant recognised that the PI recommended (b) (4) but ultimately and incorrectly decided on a starting dose of 16. She stated that she based her decision on her personal experience and the limitations in section 2.4 ("the recommended starting dose [of 16] should not be exceeded") "Oh (b) (4) but I will not change my decision. 10 is a pretty low dose to start with [...] I usually start on 20 units with the long acting. 16 is kind of in the ballpark".</p>
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Incorrect responses when using the dosing instructions in the PI

Root cause analysis

Prior exposure to the PI. Novo Nordisk attributes one participant's (DS3) incorrect response to her exposure to the PI prior to being introduced to the first scenario. After reading the task instruction, she quickly made her dosing decision based on her prior exposure to the PI, and only used the PI to confirm that her recommendation (a dose of 16) was in fact stated in the PI somewhere.

Test artefact. Novo Nordisk attributes two participant's (DS3, NP4) incorrect response due to test artefact. The participants did not feel comfortable making a dosing decision with the limited patient profile information they were provided. One participant (DS3) attributed the lack of additional patient profile characteristics which, in her medical opinion, invited her to diverge from the recommendation in the PI.

Prior medical experience. Novo Nordisk attributes one participant's (DS3) incorrect response to her prior medical experience. The participant did ultimately find and understand (b) (4) (b) (4) but chose to let her prior medical experience supersede the recommendation in the PI.

Task 2: Determine the units of insulin degludec and milligrams of liraglutide in a Xultophy[®] dose of 10

20 of 20 participants performed the task and responded correctly:

- 16 of 20 participants used the dosing instructions in the PI.
- 4 of 20 participants did not use the dosing instructions in the PI.

Scenario 2 – Conversion to Xultophy[®] for a Type 2 diabetic patient currently treated with GLP-1 receptor agonists

Task 3: Determine a starting dose of Xultophy[®]

16 of 20 participants performed the task and responded correctly:

- All 16 participants used the dosing instructions in the PI.

4 of 20 participants performed the task and responded incorrectly:

- All 4 participants did not use the dosing instructions in the PI.

TASK 3				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
3 (PCP1)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.3 in the draft PI.
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
5 (DS1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
6 (DS2)	No	Yes	No	The participant incorrectly prescribed a starting dose of 5 based on personal experience. The participant did not use the PU during this task, but recalled the information she had used during a previous task (task 1) "the same for this one [as in task 1]. A dose of 5". Notably, during follow up at the end of the session the participant recognized the draft PI recommended a starting dose of 16 and she corrected her decision to a starting dose of 16. Although, the participant did not appear convinced this was a more suitable approach than her own "there is a lot of rules with this one".
7 (PCP2)	No	Yes	No	The participant incorrectly prescribed a starting dose of 10. The participant stated that he based his decision on personal experience "I like to start low and work my way up". Notably, during the follow up at the end of the session the participant recognized that the draft PI recommends a starting dose of 16. However, the participant did not correct his initial recommendation "They recommend 16 I will start on 10 and come up to 16".
8 (PA2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
9 (NP3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
10 (PCP3)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.3 in the draft PI.
11 (NP4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
12 (DS3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
17 (PCP5)	No	Yes	No	The participant incorrectly prescribed a starting dose of 10 based on personal experience. During the follow up at the end of the session the participant was directed to the PI and recognized that the PI recommended a starting dose of 16. However, the participant stated that she would not change her initial recommendation "I have no experience with the medication, I will see how it goes and then maybe start at 16".
18 (DS5)	No	Yes	No	The participant incorrectly prescribed a starting dose of 20 based on personal experience "I just doubled it [compared to previous test-patient in task 1]". Notably, during the follow up at the end of the interview the participant corrected his recommendation to a starting dose of 16 based on section 2.3

Task 4: Determine the units of insulin degludec and milligrams of liraglutide in a Xultophy[®] dose of 16

20 of 20 participants performed the task and responded correctly:

- 16 of 20 participants used the dosing instructions in the PI.
- 4 of 20 participants did not use the dosing instructions in the PI.

Task 5: Determine if current diabetes treatment should be changed

19 of 20 participants performed the task and responded correctly:

- 15 of 19 participants used the dosing instructions in the PI.
- 4 of 19 participants did not use the dosing instructions in the PI.

1 of 20 participants performed the task and responded incorrectly:

- The participant did not use the dosing instructions in the PI.

TASK 5				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
3 (PCP1)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.3 in the draft PI.
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.3 in the draft PI.
5 (DS1)	Yes	Yes	Yes	The participant stated that she based her decision on personal experience that was confirmed by section 2.3 in the draft PI "you know that the product cannot go with insulin, and it is stated here [points to section 2.3 in the draft PI]".
6 (DS2)	No	Yes	No	The participant incorrectly determined that the patient should continue on her current treatment. Notably, the participant had prescribed a very low starting dose (dose of 5) in a previous task (task 3) and believed the
				current treatment and/or Xultophy should be adjusted based on the participant bloodsugar-level after initiating her on Xultophy "If she becomes hyperglycaemic I would decrease the current treatment or the Xultophy". During the follow-up at the end of the session the participant was directed to the draft PI and recognized that patient should discontinue her current treatment (and be prescribed a higher starting dose; starting dose of 16).

Scenario 3 – Conversion to Xultophy® for a Type 2 diabetic patient currently treated with basal insulin

Task 6: Determine a starting dose of Xultophy®

15 of 20 participants performed the task and responded correctly:

- 14 of 15 participants used the dosing instructions in the PI.
- 1 of 15 participants did not use the dosing instructions in the PI.

5 of 20 participants performed the task and responded incorrectly:

- All 5 participants did not use the dosing instructions in the PI.

TASK 6				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on table 1 in the draft PI.
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
3 (PCP1)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.4 in the draft PI.
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
5 (DS1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI "it is pretty clear from 2.4".
6 (DS2)	No	Yes	No	The participant incorrectly prescribed a dose of 20, and stated that she based her decision on personal experience "the same [insulin dose] as it is clearly not cutting it [...] keep the insulin and adding the second agent". Notably, during the follow-up at the end of the session the participant was directed to the PI and corrected her decision to a starting dose of 16 but stated she would "titrate him relatively rapidly according to the directions [in the PI]" to avoid a

7 (PCP2)	No	Yes	No	hypoglycaemic incident. The participant incorrectly prescribed a dose of 20, and stated that he based his decision on personal experience and the assumption the patients' blood-sugar was high "I am assuming his sugar is high, so I start him on 20 units". Notably, during the follow-up at the end of the session the participant was directed to the PI and corrected his decision to a starting dose of 16 "if it says 16, it should be 16".
8 (PA2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
9 (NP3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
10 (PCP3)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.4 in the draft PI.
11 (NP4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
12 (DS3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
13 (DS4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
14 (PCP4)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.4 in the draft PI.
15 (PA3)	No	Yes	No	The participant incorrectly prescribed a dose of 20, and stated that he based his decision on the text under figure 7 (section 14 "converting from basal insulin therapy (insulin glargine)"). The participant incorrectly interpreted the text to indicate that Xultophy and patient profile C's current medication was "1-to-1", thus the starting dose of Xultophy should be the same as the current medication "[a starting dose of] 20 – it is 1-to-1". Notably, during follow up at the end of the session the participant corrected his recommendation to a starting dose of 16. The participant attributed his correction to section 2.4 in the draft PI, which he had discovered prior to the follow-up session (task 8).
16 (NP5)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
17 (PCP5)	No	Yes	No	The participant incorrectly prescribed a dose of 10, and stated that she based her decision on personal experience. At the beginning of the task the participant several times stated that she did not have sufficient information to base a dosing decision on "I have almost no information on this patient! [...] if he is controlled on basal, what is the point in changing him? [...] I have no information to make a clinical decision on this patient!" Notably, the participant appeared annoyed and behaved uncooperative "[I based my decision on] whatever comes to mind". During follow up at the end of the session the participant was directed to the PI and recognized the recommended starting dose was a dose of 16. Consequently, the participant corrected her recommendation to a starting dose of 16.
18 (DS5)	No	Yes	No	The participant incorrectly prescribed a dose of 20, and stated that he based his decision on personal experience "[he is] already on 20 units, I would give the equivalent of the 20 units that is in this drug". Notably, during follow up at the end of the session the participant is directed to use the PI and recognize the recommended starting dose is 16 and is open to starting the patient on the recommended starting dose "sure [I would start the patient on the recommended starting dose]".
19 (PA4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 and table 1 in the draft PI.
20 (PA5)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 and table 1 in the draft PI.

Task 7: Determine if current diabetes treatment should be changed

20 of 20 participants performed the task and responded correctly:

- 15 of 20 participants used the dosing instructions in the PI.
- 5 of 20 participants did not use the dosing instructions in the PI.

Scenario 4 – Recommendation for a Type 2 diabetic patient currently treated with 80 units of basal insulin

Task 8: Determine a recommendation regarding initiation onto Xultophy[®]

13 of 20 participants performed the task and responded correctly:

- All 13 participants used the dosing instructions in the PI.

7 of 20 participants performed the task and responded incorrectly:

- 3 of 7 participants used the dosing instructions in the PI.
- 4 of 7 participants did not use the dosing instructions in the PI.

TASK 8				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI "I actually wouldn't start her on Xultophy".
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI "Don't do it!"
3 (PCP1)	No	Yes	Yes	The participant stated that he used the information from section 2.4. Notably, the participant did not appear to actually use the section during this task (task 8), but rather recall the information probably he used in the previous task (task 7) with a patient also on basal insulin. The participant did not realize that this was a different type of task and repeated his decision to "stop basal insulin" presumably to start the patient onto Xultophy. During the follow-up at the end of the session, the participant was prompted to read the entire section 2.4 and immediately corrected his recommendation to not initiate the patient onto Xultophy "If you don't have any data on Xultophy you shouldn't prescribe it to her".
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI "I wouldn't do it".
5 (DS1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
6 (DS2)	No	Yes	No	The participant incorrectly recommended initiating the patient onto a dose of 50 Xultophy in addition to 30 units of basal insulin. She stated to base her decision on the fact that the pen did not deliver a dose above 50 "the amount the pen is allowed to deliver", which she found in the highlight section. During the follow-up at the end of the session the participant was directed to the draft PI and recognized it did not recommend to start patients currently on >50 units of basal insulin onto Xultophy. However, this did not change the participants decision "I would take a chance on this one [...] I am coming up with my own new regiment. It just states that it have not been tried, not that you cannot do it".
7 (PCP2)	No	Yes	No	The participant stated to aim at a low starting dose, which he felt was a starting dose of 60 "I might be a little chicken; I will drop her down to 60". The participant expressed that he did not have the sufficient information to make a decision "I am going completely in the dark here". During the follow-up at the end of the session the participant was first directed to the PI section 2.4, where he realized the dose only goes to 50 and accordingly changed his recommendation to a starting dose of 50. Following, he was directed to the last sentence of section 2.4 and recognize the PI does not recommend patients currently on >50 units to be initiated onto
				Xultophy. The participant was very unsure "It is complicated because I really want to refer to this drug", but ultimately decided not to initiate the patient onto Xultophy. Notably, at all attempts to perform the task the participant expressed a wish to refer an endocrinologist.
8 (PA2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI "She actually can't take it".
9 (NP3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
10 (PCP3)	No	Yes	Yes	The participant stated to use section 2.4. The participant recommended stopping the basal insulin and a start on Xultophy with a starting dose of 16. The participant vocalized that the patient was currently on 80 units, but still would recommend a starting dose of 16 to not exceed the recommended starting dose. During the follow-up at the end of the session the participant was prompted to read the last two sentences of section 2.4 out loud and discovered the information regarding conversion from patient currently on >50 units of basal insulin. He stated that the information "did not add a clinical weight" (in his dosing-decision presumably), and persisted on his initial recommendation. Notably, the participant appeared incoherent and uncertain of himself during the entire session.
11 (NP4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
12 (DS3)	No	Yes	Yes	The participant recognised it was not recommended to start patients currently on >50 units of basal insulin onto Xultophy. "it says not to, but it makes sense to me [to start the patient on Xultophy]". Ultimately, she recommended either starting the patient on 50 of Xultophy® and watch blood sugar levels closely, or reduce the patients current basal insulin amount from 80 to 60 units and adding an injection of liraglutide on top dependent on patient preference.
13 (DS4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
14 (PCP4)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.4 in the draft PI.
15 (PA3)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.4 in the draft PI "based on 2.4 here [points to PI]. Xultophy is not studied in patients on >50 units of basal insulin".
16 (NP5)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.4 in the draft PI.
17 (PCP5)	No	Yes	No	The participant stated to not be comfortable making the decision with the information provided on patient. She ultimately and incorrectly determined to initiate the patient onto Xultophy with a starting dose of 40 "I will give her half of Xultophy
				[compared to current medication]". Notably, during follow up at the end of the session the participant was prompted to read the entire section 2.4 and immediately recognised that the patient was not eligible for Xultophy "so this is not a good candidate. She should not be on it".
18 (DS5)	No	Yes	No	The participant incorrectly decided to initiate the patient onto Xultophy with a starting dose of 50 in addition to 30 units of basal insulin. The participant stated to base his decision on personal knowledge on liraglutide, which should not exceed 1.8 mg (equivalent to a Xultophy dose of 50)and the patients current treatment of 80 units of basal insulin that he wanted to maintain "I want to keep up the 80 units of degludec". During follow up at the end of the interview the participant was directed to section 2.4 in the PI and ultimately recanted his initial decision "She is better off with another regiment of insulin".

Incorrect responses when using the dosing instructions in the PI

Root cause analysis

Negative transfer from previous tasks. Novo Nordisk attributes one participant's (PCP1) incorrect response due to negative transfer from the previous tasks. In the previous tasks (1-7), the participant had recommended dosing decisions for patients who should be initiated/converted onto Xultophy®. The participant continued this line of thought, and performed the task as if the patient was supposed to be converted onto Xultophy®. Notably, he did not focus on all information provided, e.g. that the patient was currently treated with 80 units of basal insulin daily.

Nervousness or Lack of knowledge on this type of patient and medication. Novo Nordisk attributes one participant's (PCP3) incorrect response to lack of knowledge on this type of medicine and patient. The participant's reasoning suggested that he did not have the sufficient knowledge regarding this type of medication and patient. However, based on the participants' occupation, it is possible that nervousness also contributed.

Prior medical experience. Novo Nordisk attributes two participants' (PCP3, DS3) incorrect responses to their prior medical experience. One participant (PCP3) did not agree with the recommendations in the PI and went with his prior medical experience. The other participant (DS3) recognised that Xultophy® has not been studied in patients taking > 50 units of basal insulin daily, but chose to let her prior medical experience supersede this information.

Scenario 5 - Titration of Xultophy® for a Type 2 diabetic patient

Task 9: Determine how to titrate

15 of 20 participants performed the task and responded correctly:

- All 15 participants used the dosing instructions in the PI.

5 of 20 participants performed the task and responded incorrectly:

- 1 of 5 participants used the dosing instructions in the PI.
- 4 of 5 participants did not use the dosing instructions in the PI.

TASK 9				
Participant	Correct response	Refer PI	Use dosing instructions in PI	Subjective feedback (paraphrased) including description of task performance when relevant
1 (PA1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
2 (NP1)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
3 (PCP1)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.5 in the draft PI.
4 (NP2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
5 (DS1)	No	Yes	Yes	The participant stated Xultophy should be titrated by increments or decrements of 2, however she only briefly touched upon intervals between titration and incorrectly recommended an interval of "a week". The participant stated to base her decision

6 (DS2)	No	Yes	No	on table 2 in the draft PI. Notably, during the entire task the participant was focused on the “target” and not intervals. During the follow up at the end of the session, the participant chose to use section 2.5 instead of table 2 and accordingly referenced the correct intervals of 3-4 days.
7 (PCP2)	No	Yes	No	The participant incorrectly determined to titrate by increments or decrements of 5 every month. The participant stated to base her decision on personal experience on titrating patients. The participant stated to usually start a new patient on normal long acting insulin prior to a product with two agents like Xultophy, when initiating a patient on a product like Xultophy the participant would start at the patient’s current dose. Notably, during the follow-up at the end of the session the participant decided to correct his recommendation and titrate patients with increments or decrements of 2 every 4 days. She stated to base his latter decision on section 2.5 in the PI.
8 (PA2)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
9 (NP3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
10 (PCP3)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.5 in the draft PI.
11 (NP4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
12 (DS3)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI. The participant stated that with a higher starting dose e.g. 50 she would titrate with a higher dose. Notably, the participant did recognise that the PI did not recommend a higher starting dose than 16, but did not personally agree.
13 (DS4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
14 (PCP4)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.5 in the draft PI. In addition, the participant stated that he personally would use intervals of 2-5 days.
15 (PA3)	Yes	Yes	Yes	The participant stated that he based his decision on section 2.5 in the draft PI.
16 (NP5)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
17 (PCP5)	No	Yes	No	The participant incorrectly determined to use increments of “a few units” every second day. She stated to base her decision on her prior experience with long acting insulin “as I would long acting insulin [...] start by 10 and increase by a few units every few days if they are not controlled”. During follow-up at the end of the session the participant recognize that the PI recommends increments of 2 and intervals of 3-4 days. However the participant stated to “do as with basal” when titrating Xultophy, notably, the participant now stated “2 units every few days”.
18 (DS5)	No	Yes	No	The participant incorrectly determined to “start with a low dose and go up” based in personal experience. Notably, the participant did not appear particular invested in the task: “these things are trial and error”. Notably, during follow up at the end of the interview the participant recognised the recommended titration process in the draft PI. However, the participant did not change his response much “you would start with the recommended and if you learn something different you apply it to the next patient”.
19 (PA4)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.
20 (PA5)	Yes	Yes	Yes	The participant stated that she based her decision on section 2.5 in the draft PI.

Incorrect responses when using the dosing instructions in the PI

Root cause analysis

Prior medical experience: Novo Nordisk attributes this participant’s (DS1) response to prior medical experience. The participant quickly realized that titration should be done in a similar manner as what she normally does, and started explaining her own medical practice regarding titration instead of looking in the PI for information to confirm her recommendation.

Sponsor Conclusion

Overall, the test participants fully understood the instructions in the PI as currently written for prescribing and dosing IDegLira, making dose titrations, and converting patients to IDegLira from other therapies. No further modifications of the PI are assessed as being needed based on the clear understanding of the PI as determined by the number of correct responses on the tasks and subjective feedback. Moreover, for the incorrect responses, the follow up interview revealed that participants who did not use the dosing instructions in the PI understood the relevant PI text when finding it in the relevant section of the PI.

In conclusion, the labeling comprehension test of the PI demonstrated that users could find the PI text needed for dosing related tasks, and they comprehended how to prescribe and dose IDegLira, make dose titrations, and convert patients to IDegLira from other therapies.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HINA S MEHTA
07/13/2016

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07/13/2016

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07/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Devices and
Radiological Health
ODE-WO-66
10903 New Hampshire Avenue
Silver Spring, MD 20993

InterCenter Consult Memorandum ICC1500488/NDA208583

Date: 5/13/2016
To: Marisa Petruccelli
Regulatory Project Manager
OND/ODEII

From: Sapana Patel, PharmD.
Pharmacist
WO66 Rm 2562
CDRH/ODE/DAGRID/GHDB

Subject: CDRH Consult for ICC1500488/NDA208583
Insulin Degludec/liraglutide (100units and 3.6mg/ml)/Novo Nordisk

Recommendation: **APPROVAL**

I. Consult Purpose

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 208583. Novo Nordisk has submitted an NDA which is a combination product consisting of a pen-shaped, prefilled device containing a 3ml cartridge with drug. CDER is requesting review of the device constituent of the prefilled pen injector

II. Review Summary

The CDRH reviewer performed a review of the prefilled pen-injector, device constituent part for the drug insulin degludec/liraglutide (100U/3.6mg/ml)s drug is to be administered subcutaneously and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Consultants for this file:

Robert Meyer- Engineering review of pen-injector
Sarah Mollo Ph.D-Biocompatibility review of pen-injector
Patricia Beaston Ph.D. M.D. - Clinical consult

The review of this application covered the following:

Pen-Injector

The review of this application did not cover the following:

- Review of the prefilled cartridge (primary container closure) including biocompatibility and sterility
- Review of the drug product
- Manufacturing of the drug product
- Review of the safety and efficacy of the drug product after contacting the device constituent parts or while stored in the device constituent parts,
- Review of the final drug kit packaging
- Device Constituent part usability or human factors validation information
- Stability of the drug product after aging

III. Documents reviewed

Documents reviewed related to the design of the device constituent parts for the combination product. This review is limited to the design requirements and verification/validation information to support the device constituent.

This review does not cover the review of the primary container closure system (prefilled syringe (PFS)), manufacturing or process validation of the device, nor usability.

NDA 208583

IV. Review

Insulin degludec/liraglutide will be referred to within this review memo as IDegLira as referenced in the submission.

Indications for Use:

Insulin degludec/liraglutide (100units and 3.6mg/ml) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dosage and Administration:

IDegLira is dosed once daily (b) (4) (b) (4)

It is to be injected subcutaneously in the thigh, upper arm, or abdomen. Insulin degludec/liraglutide (IDegLira) is a fixed ratio combination of the basal insulin, insulin degludec (IDeg), and the GLP-1 analogue liraglutide (marketed as Victoza®). IDegLira will be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The recommended daily starting dose of IDegLira is (b) (4) units insulin degludec and (b) (4) mg liraglutide. (b) (4) (b) (4)

(b) (4) The maximum dose for IDegLira will be 50 units insulin degludec and 1.8 mg liraglutide which will not exceed the maximum approved liraglutide dose of 1.8 mg for T2DM. Each increment contains 1 unit of insulin degludec and 0.036 mg liraglutide.

IDegLira is available as a 3ml pre-filled, multi-dose pen containing 100 units insulin degludec and 3.6ml liraglutide per ml.

Device Description:

The device constituent PDS290 IDegLira pen-injector is similar to the currently marketed prefilled disposable insulin delivery device Flex Touch. PDS290 IDegLira pen-injector is developed for the injection of the combination product insulin degludec/liraglutide, whereas FlexTouch was developed for the injection of insulin. Both pens are based on the same PDS290 pen-injector platform design. The design similarities are

that both are pen-shaped injectors with prefilled cartridges, where the intended dose is given by turning the dose selector and pressing the button to deliver the intended dose.

Container Closure System:

Information on the container closure system was found in Section 3.2.P.7. This part of the review serves as identifying the components and specifications of the primary closure.

PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 ml cartridge with drug. Therefore the drug is not in contact with the device. The device is intended to function with a standard needle thread 1 or a needle with a bayonet coupling.

The container closure for the drug is a 3ml cartridge system which consists of:

- A 3ml cartridge made of type 1 glass, colorless
- A rubber plunger made of (b) (4)
- A (b) (4) rubber disk. The rubber disc is made of (b) (4)

The cartridge system 3 ml may contain (b) (4)

Physical characteristics:

Length and thickness: Approximately 138 mm without cap and 156 mm with cap. Thickness is approximately Ø19 mm

Dose button displacement: Approximately 2 mm, non-rotating dial during injection

(b) (4)
Components: (b) (4) 1 cartridge
(b) (4)

End-of-dose click

PDS290 IDegLira pen-injector was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Needle-based injection systems for medical use - requirements and test methods –Part 1: Needle-based injection systems).



Figure 1 PDS290 IDegLira pen-injector

The pen consists of (b) (4) parts and a 3 ml cartridge, as shown in Figure 2.



Figure 2 Exploded view of the PDS290 IDegLira pen-injector

Generic figure with neutral product colour.

The pen mechanism can be considered as two interacting systems:

- Dose system
- Dial system

During dose setting, the dial mechanism consisting of dial (b) (4) rotates (b) (4) sequentially (b) (4)

(b) (4)

Dose system

(b) (4)

Dial system

Setting the dose

The dose is set and corrected if necessary by turning the dial

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Reset / adjustment of a dose

[Redacted]

(b) (4)

[Redacted]

(b) (4)

turning the dial either up or down.

(b) (4)

The dose can be adjusted by

Delivering a dose

To deliver a set dose, the dose button (1) is pushed by the user.

(b) (4)

[Redacted]

It is possible to stop/start a dose at any time by pushing/releasing the dose button during injection.

[Redacted]

(b) (4)

End-of-dose (EoD) click

The basic idea of an EoD click is to give a distinct feedback to the user, telling the mechanism is at the end of the dose position. After the click (and the display showing the figure 0) the user must slowly count to 6 to ensure that full dose has been delivered. This feature will compensate for the lack of a moving dose button during injection such as in the currently approved FlexPen[®] and other manual injection devices.

(b) (4)

(b) (4)

Comparison to Flex Touch:

The PDS290 IDegLira pen-injector is similar to the currently marketed prefilled disposable insulin delivery device FlexTouch.

FlexTouch[®] was developed for the injection of insulin, whereas the PDS290 IDegLira pen-injector is developed for the injection of the combination product insulin degludec/liraglutide, with both pens being based on the same PDS290 pen-injector platform design. The design similarities are that both are pen-shaped injectors with prefilled cartridges, where the intended dose is given by turning the dose selector and pressing the dose button to deliver the intended dose.

Table 1 Comparison of PDS290 IDegLira pen-injector to FlexTouch[®]

Feature	PDS290 IDegLira pen-injector	FlexTouch [®]
Length (approximately)	156 mm	156 mm
Diameter (approximately)	19 mm	19 mm
Weight (excluding cartridge) Approximately	24 g	24 g
Dose accuracy specification	ISO 11608-1 ref 1	ISO 11608-1 ref 1
Injection force	(b) (4) N	(b) (4) N
Dose button extension @ maximum dose size	0 mm	0 mm

Dose increment	1 increment contains (1 unit of insulin degludec and 0.036 mg liraglutide)	1 unit per increment
Maximum dose	50 (50 units of insulin degludec and 1.8 mg liraglutide)	80 units
Priming steps	(b) (4)	2 units
Number of components (needle and cartridge excluded)	(b) (4)	(b) (4)
Basic pen colour	Dark blue	Dark blue
Cartridge holder colour	According to approved product colour	According to approved product colour
Dose button colour	According to approved product colour	According to approved product colour
Materials (needle and cartridge excluded)	(b) (4) (see Table 2).	(b) (4) (see Table 2).
Click during dose setting	Yes	Yes
Click during dosing	Yes	Yes
Click at end of dose	Yes	Yes
Dials back to zero during injection	Yes	Yes
Dose accuracy	ISO 11608-1 ref 1	ISO 11608-1 ref 1
Intended use	Intended for the subcutaneous injection of insulin degludec/liraglutide	Intended for the subcutaneous injection of insulin
Indications for use	Incorporates a design containing 3 ml cartridges to assist in the subcutaneous injection of insulin degludec/liraglutide drug product for the treatment of individuals with type 2 diabetes mellitus	Incorporates a design containing 3 ml cartridges to assist in the subcutaneous injection of insulin drug products for the treatment of individuals with diabetes mellitus
Product type	Pre-filled, multiple-dose, disposable pen containing a 3 ml cartridge with insulin degludec/liraglutide	Pre-filled, multiple-dose, disposable pen containing a 3 ml cartridge with insulin
Target population/age group	Adult	Adult and pediatric
Biocompatibility	ISO 10993-1 ref 2 Only external skin contact during injection.	ISO 10993-1 ref 2 Only external skin contact during injection.
Anatomical sites	As recommended in the Physician Insert	As recommended in the Physician Insert
Where used	Home or in hospital	Home or in hospital
Energy used and/or delivered	Manual	Manual
Human factors	Needle attachment needed before injection	Needle attachment needed before injection
Performance test	Dose accuracy test Function test Physical stress test	Dose accuracy test Function test Physical stress test
Standards met	ISO 11608-1 ref 1	ISO 11608-1 ref 1
Sterility	N/A	N/A
Mechanical safety	N/A	N/A

Table 2 Material abbreviations



PDS290 IDegLira pen-injector with cap demounted

Figure 4 FlexTouch® (PDS290 pen-injector) with cap demounted

Device Review (Engineering):

Robert Meyer reviewed the engineering component of the device constituent. The following review was provided:

The Sponsor claims that risk management for the device was performed in accordance with ISO 14971:2007 Medical Devices - Application of risk management to medical devices.

Use Error Risk Analysis (UERA) (Volume 0010-3.2.P.7 IDegLira. Pen injector Product Risk Management Summary): risk analysis pertaining to foreseeable user errors.

The following intended functions have been identified by the Sponsor:

- Receiving the device
- Preparing the device including mounting a needle
- Setting and resetting a dose
- Injection of IDegLira
- Removing the used needle
- Storage and caring (climate and chemicals)

The identified hazards for the user analysis are:

- Wrong dose size is selected
- The user is injured when using the needle
- Device is damaged by wrong handling or storage and caring
- Risk of using drug delivery products different from IDegLira

The results from the UERA analysis are tabulated below. After evaluation, ten (10) hazards are designated ALARP, after which eight (8) have been mitigated to a probability rating P_{harm1} . The hazards are still possible after mitigation, yet are not considered intolerable. The two hazards which are not rated P_{harm1} are mitigated through instructions (see Table 6 below). The instructions inform the user of proper storage conditions.

Table 5 Summary of Use Error Risk Analysis risk evaluation

Risk class	No. of hazards before mitigations	No. of hazards after mitigations
Broadly Acceptable	135	135
ALARP	10	10
Intolerable	0	0
Total	145	145

Table 6 UERA hazards in ALARP with a probability rating higher than P_{Harm1}

Description of Deviation or Failure mode	Type of mitigations	User error analysis reference ID	IFU section	Conclusion
(b) (4)	The information for safety must include instructions to keep the device away from dirt, dust and liquid.	7.A.1	'Storage'	ALARP according to NNAS risk priority, but risk accepted due to the very low overall probability and acceptable risk benefit profile.
	The information for safety must include instructions to keep the device away from dirt, dust and liquid.	7.A.2	'Storage'	ALARP according to NNAS risk priority, but risk accepted due to the very low overall probability and acceptable risk benefit profile.

Technical Risk Analysis- Failure Mode Effects and Criticality Analysis (FMECA): risk analysis pertaining to risk associated to the product design and manufacturing process.

Three hundred eighty four (384) hazards associated to the product design and manufacturing were identified by the sponsor, of which sixty eight (68) were concluded to have the status of ALARP .. According to the Sponsor all hazards have been mitigated and none are considered intolerable. After review the risk identified appear to be mitigated as low as possible, and the analysis is deemed adequate. Three hazards designated ALARP with the probability higher than P_{Harm1} are listed below.

Table 4 FMECA hazards in ALARP with a probability higher than P_{Harm1}

Hazard ID	Deviation / Failure mode	Mitigations	Conclusion
05.10.G.01.B	(b) (4)	N/A	ALARP according to NNAS risk priority, but risk accepted due to the very low overall probability and acceptable risk benefit profile.
09.00.-.04.A		SOP describing (b) (4) procedure (b) (4) [QBIQ number 038549]	ALARP according to NNAS risk priority, but risk accepted due to the very low overall probability and acceptable risk benefit profile.
12.11.O.02.B		Process inspection	ALARP according to NNAS risk priority, but risk accepted due to the very low overall probability and acceptable risk benefit profile.

Design Verification:

The list of device specifications shown below has been provided by the Sponsor. The list references various analysis and laboratory verification tests; however the test reports have not been located, thus they were requested. In response to deficiency (1) below the Sponsor has provided the associated test reports. The Sponsor states that vibration, shipping, and drop testing are completed in accordance to ISO 11608-1, and the results are verified via visual inspection, and during dose accuracy testing (PDS290 IDegLira pen-injector Summary Report of Qualification Testing, page 6). The list shown below is comprehensive for verification; yet additional functional requirements may be needed based on the device functions (e.g. injection depth, injection time). The Sponsor was asked to provide a traceability matrix that identifies all device features and

functions, the associated requirements, and the supporting verification/ validation documents (e.g. spring specifications, needle specifications, connection features etc.). **The sponsor has provided an adequate traceability matrix which identifies the product development design requirements and references the associated tests (volume 0024- pen-injector-dev-perf-safety-just.pdf, page 4 through 9).**

Deficiency Previously Sent:

- (1) **You have provided a list of device specifications (Table 1: Functional design Requirements as Verification Activities). The list is comprehensive; yet additional functional requirements may be needed based on the device functions (e.g. injection depth, injection time). The list references various analysis and laboratory verification tests; however the test reports have not been located. You should provide a traceability matrix that identifies all device features and functions, the associated requirements, and the supporting verification/ validation documents (e.g. spring specifications, needle specifications, connection features etc.).**

Sponsor’s Response

In 3.2.P.7 Essential device performance and safety requirements, Table 1, the functional design requirements and the corresponding verification activities are listed. This table has been updated to include references to the verification reports and a traceability matrix, which correlates the device features or functions associated with the specific requirement.

The device features or functions associated with the requirements are:

- Quality perception
- Stability
- Robustness
- Biocompatibility
- Portability
- Identification of pen-injector type
- Prepare the pen-injector
- Setting the dose

CDRH’s Comment

The provided functional design requirements list is adequate, and properly identifies the associated verification test reports.

Table 1 Functional design requirements and verification activities

Functional requirement	Verification method
(b) (4)	Tolerance stack-up analysis
	Laboratory verification test
	Tolerance stack-up analysis
	Visual inspection
	Tolerance stack-up analysis
	Laboratory verification test
	Visual inspection
	Laboratory verification test
	Visual inspection
	Visual inspection
	Visual inspection
	Laboratory verification test

Functional requirement	Verification method
(b) (4)	Laboratory verification test
	Laboratory verification test

(b) (4)	Laboratory verification test
	Expert analysis
	Laboratory verification test
	Laboratory verification test
	Expert analysis
	Laboratory verification test
	Laboratory verification test
	Tolerance stack-up analysis
	Visual inspection
	Laboratory verification test
	Visual inspection

Route of injection depth

The clinical development program investigated insulin degludec/liraglutide (100 U/ 3.6 mg/ ml) for treatment of adults with type 2 diabetes mellitus and utilized the PDS290 IDegLira pen-injector and NovoFine® needles.

The Sponsor identifies literature that states the use of 4-8 millimeter needles effectively delivers the drug solution in the subcutis for people with diabetes. The full details can be found in 3.2.P.7 Validation of depth and route of injection.

The Sponsor states the skin and subcutaneous adipose layer thickness has been studied in 388 subjects (type 1 or type 2 diabetes mellitus) with BMI 19.4-64.5 kg/m² in different ethnic groups (3). Of the 388 subjects, more than 100 subjects had BMIs ≥ 30 kg/m². The Sponsor determined the thickness of the skin (epidermis and dermis) is quite consistent across injection sites, ages, races, BMI and gender, and states “It is rarely larger than 3.0 mm at the injection site.” The Sponsor notes their conclusion is supported by the clinical studies they have completed.

Dose Accuracy

Because this is a combination drug product with one drug (insulin) being dosed in “units” and the other drug (liraglutide) being dosed in “mg” the Sponsor refers to the markings on the pen injector as “increments”. These increments represent the number of units of insulin to be delivered at the time of injection.

Dose accuracy testing has been summarized by the Sponsor, and the following statements have been noted during review:

- Testing is completed to demonstrate that the volume/weight of drug/biological product expelled through the injector is the same as the set dose
- Testing is completed that multi-dose (variable dose) cartridge injectors are designed to accurately deliver each successive randomly set dose
- Testing to ensure that dose settings/markings correlate with the volume of drug/biological product delivered
- The dose accuracy was investigated at three dose sizes; dose [redacted] (b) (4) [redacted] representing the minimum, midpoint and maximum dose that can be selected, respectively.
- IDegLira pen-injector meets the specifications for total content of device, dose accuracy of last dose, dose accuracy after free fall and vibration pre-conditioning and visual inspection according to ISO 11608-1:2012.

- Per the life time of the fixed cartridge, the pen-injector has been verified to be able to deliver the entire labelled volume (300 increments).

The method used to assess the dose accuracy is (b) (4)

(b) (4) It is noted by the Sponsor that a dose (b) (4) is delivered before each measurement per the instructions to assure product flow (b) (4). **It is noted that the lower limit of delivery accuracy for (b) (4) is (b) (4) units (b) (4) μ L.** Review of the data for dose accuracy testing supports compliance with ISO 11608-1. However Gage R&R verification was not provided to demonstrate the accuracy and precision of the test and additional information was requested. **In response to deficiency (2) below the Sponsor has provided adequate Gage R&R testing results.**

Previously sent deficiencies

- (2) You have completed dose accuracy verification per ISO 11608-1:2012, and the results appear to comply, however Gage R&R verification has not been provided to demonstrate the accuracy and precision of the test. Per ISO 11608-1:2012 “The repeatability and reproducibility (Gage R&R) of the test apparatus shall be no greater than 20 % of the allowed tolerance range for any given measurement.” You should provide Gage R&R testing results which demonstrates the provided test protocol for dose accuracy is adequate.**

Sponsor’s response

On March 4, 2016 the Sponsor provided a Gage R&R report to demonstrate the dose accuracy verification test challenges the requirement properly, and controls the measurements accuracy and precision (document: gauge-rr-dose-acc-measure- volume 0024). The dose accuracy test is verified (b) (4) which according to the Sponsor is “closest in weight of the real liquid holder in dose accuracy test.” The Sponsor states: The allowed tolerance range is chosen as the worst case range in dose accuracy measurement, (b) (4) The allowed tolerance range is defined as (b) (4) ml in standard ISO 11608-1:2012. This corresponds to (b) (4) mg, (b) (4) The result of Gage R&R analysis shows a Gage R&R of (b) (4)%, which is below the specification limits of 20% defined by ISO 11608-1:2012.

CDRH Comment

The provided Gage R&R study is appropriate. The measurement limit is in the units of milligrams, and it is demonstrate that the scale is able to measure in microgram units precisely.

The device is for multiple dosages, (b) (4) To demonstrate the device delivers the desired dose the device was tested repeatedly (b) (4) one time however; all units met specification.

In Table 7 below dose accuracy for 1U increment is verified for 60 devices. (b) (4)

(b) (4) Dose accuracy (b) (4) has been verified as compliant with ISO 11608-1:2012 (shown below).

Table 4 Acceptance criteria according to ISO 11608-1:2012

(b) (4)



PDS290 IDegLira pen-injector
 Summary of Qualification Testing
 290.QA.1235
 novoDOCS ID 002004304

4 Test results according to ISO 11608-1

ISO 11608-1 subject	Requirements related to <u>system designation C with no electronics</u> = multi dose needle-based injection device with integrated non-replaceable container and no electronics	Results	Comments
5.5a	(b) (4)	This was visually inspected during the tests in 290.QA.123R and found true.	No comments
5.5b		Total content of device fulfils the acceptance criteria. See Table 5	No comments
5.5d		This was visually inspected during the tests in 290.QA.123R and found true.	No comments
5.5e		This was visually inspected during the tests in 290.QA.123R and found true.	No comments
5.5f		This was visually inspected during the tests in 290.QA.123R and found true.	No comments
5.5g		This was visually inspected during the tests in 290.QA.123R and found true.	No comments
ISO 11608-1 subject		Results	Comments
5.5h		This was visually inspected during the tests in 290.QA.123R and found true.	No comments
5.5j		This has been verified in 290.QA.123R by dialling to End Of Content and is found true.	PDS290 IDegLira pen-injector does not allow a larger dose to be pre-set than is left in the container (5.5j 1).
5.5l		The PDS290 IDegLira pen-injector is specified to function with a NovoTwist [®] needle or a NovoFine [®] needle. All tests have been performed with the specified needle - either NovoTwist [®] needles or NovoFine [®] needles.	No further comments
5.5m	The PDS290 IDegLira pen-injector is specified to function with a Novo Nordisk 3 ml non-replaceable cartridge. The device is assembled with this specified container and all tests have been performed with this specified container.	No further comments.	

Additional comments:

It appears in Table 7 that 60 samples were tested at one (1) unit increments (b) (4) you should provide the related protocol to clarify the procedure and results (Summary Report of Qualification Testing). We recommend you note if the needle was replaced in between each application.

In Table 4 shown below it is noted that the lower limit for a (b) (4) dosage is (b) (4) µL. Please justify the clinical acceptability of this requirement.

Table 4 Acceptance criteria according to ISO 11608-1:2012

(b) (4)



Sponsor's Response

The Sponsor has confirmed the needle was not replaced and the priming function not repeated for each dose measurement taken during the Dose Accuracy Testing at Standard Atmosphere (Table 7). The protocol provided states the device was used repeatedly at various increments to support accuracy verification. The last dose accuracy measurement after repeated deliveries (b) (4) is per specifications. The average last dose for the 60 samples tested is (b) (4) mg and the standard deviation is .831 (acceptance criteria: (b) (4) mg min ; (b) (4) mg max).

CDRH's Comment

The dose accuracy verification for the last dose is per ISO 11608-1:2012, thus it is considered adequate. The Sponsor has not provided testing results which demonstrate the device is capable of delivering the minimum dosage, the maximum amount of times, while maintaining dose accuracy. After discussion such testing is deemed unnecessary. As shown in Table 4, 7 8, and 9 the Sponsor has demonstrated the device is able to deliver 1 unit as specified.

According to discussions with the consulting CDRH Medical Officer (Dr. Patricia Beaston) although the ISO standard allows for 100 % dose error at 1 increment (1 unit of insulin/.036 mg liraglutide) this error would be unlikely to result in harm to the patient as the recommended starting dose for IDegLira is 10 increments (10 units of insulin/.036 mg liraglutide). However, the final decision regarding the acceptability of the potential dosing error at the lower range is deferred to the Primary Clinical Reviewer in DMEP.

Clinical Studies:

In Clinical Study NN9068-3632, there was record of 1 device related adverse reaction which was reported as hematoma which was related to the needle not the pen-injector.

No other device related adverse reactions were reported during the clinical studies.

BIOCOMPATIBILITY REVIEW OF DEVICE CONSTITUENT:

The Biocompatibility of the device constituent was reviewed by Sarah Mollo, Ph.D. DAGRID/GHDB.

The sponsor states that the PDS290 IDegLira pen-injector implies brief, repeated contact to intact skin by handling of the device; therefore, the PDS290 IDegLira pen-injector is categorized as a surface device with contact to intact skin, Category B –prolonged duration of contact (>24 h to 30 d). Based on this contact classification the sponsor has considered the following biological endpoint: Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity.

Table 1 Components of the PDS290 IDegLira pen-injector and the user

Component	(b) (4) masterbatch	User contact
Housing and cap	(b) (4)	Brief, repeated contact to intact skin by handling of the device
Cartridge Holder	(b) (4)	
Dial	(b) (4)	
Dose button #	(b) (4)	
Dose button #	(b) (4)	
Dose button #	(b) (4)	

The Dose button includes either (b) (4) masterbatch OR (b) (4) masterbatch

The sponsor has provided the following statement:

All manufacturing processes with a potential to change the chemical properties of materials with user contact listed in section 6.1.4 of ISO/TR 15499 (2) are (b) (4)

Housing and cap – (b) (4) masterbatch

The blue housing and cap of the PDS290 IDegLira pen-injector consist o (b) (4)

Also, the manufacturing processes are (b) (4)

Reviewer Comment:

The reviewer agrees that (b) (4) no further biocompatibility evaluation is necessary for these components.

The sponsor has provided a rationale for not performing sensitization and irritation on the cartridge holder, dial, and dose button components (b) (4) The cartridge holder, dial, and dose button of the PDS290 IDegLira pen-injector have passed an in vitro cytotoxicity test in cultured in accordance with EN ISO 10993-5:2009 “Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity”. The sponsor states that “based on the concordance between in vivo irritation and in vitro cytotoxicity, and the weight of evidence for irritation as a prerequisite in the sensitization pathway, a negative in vitro cytotoxicity

test is considered sufficient to rule out any relevant hazard for skin irritation and sensitization caused by dermal exposure to leaching substances.”

Reviewer Comment

The reviewer does not agree with the rationale that a negative cytotoxicity score negates the need for an irritation or sensitization test. Non-cytotoxic chemicals can be irritating or sensitizing. An IR was sent to the sponsor requesting an evaluation of the irritation and sensitization endpoints.

The sponsor provided the chemical composition of the (b) (4) masterbatch for the dose button. They also provided a table which evaluated the substances for their potential to cause sensitization and irritation. This did not include the (b) (4) substances (b) (4) table for the potential leachables for the (b) (4) masterbatch of the dose button.

Table 2 Potential leachables from (b) (4) masterbatch

Cas no.	Substance	Skin irritation	Skin sensitization	Sources
(b) (4)	(b) (4)	No potential	No potential	(10,11)
(b) (4)	(b) (4)	No potential	No potential	(11)
(b) (4)	(b) (4)	Irritating	No potential	(11)
(b) (4)	(b) (4)	No potential	No potential	(11)
(b) (4)	(b) (4)	No potential	No potential	MSDS (b) (4) (b) (4) – see also Appendix C
(b) (4)	(b) (4)	No potential	No potential	Non-irritating to skin and eyes and non-sensitizing to skin (negative GPMT) according to MSDS (b) (4) – see also Appendix D
(b) (4)	(b) (4)	No potential	No potential	MSDS (b) (4) (b) (4) – see also Appendix E
(b) (4)	(b) (4)	No potential	No potential	(11,12)

Reviewer comment

The sponsor provided a table for evaluating the chemicals (b) (4)

(b) (4) for the dose button. They did not provide the same information for the cartridge or the dial components. This analysis does not address the potential impurities (b) (4)

The Agency has sent an IR to the sponsor recommending that biocompatibility testing (including sensitization and irritation testing is performed on the final finished product.)

Interactive Review History

The following IR was sent to the sponsor February 16, 2016:

You state that all PDS290 IDegLira pen-injector device components which come into direct or indirect contact with users consist of (b) (4)

We are unable to locate test reports for cytotoxicity, sensitization, and irritation within the NDA for the proposed device constituent of your combination product. Please submit the test reports as an amendment to the NDA or submit a letter of authorization from the device manufacturer and location within the DMF of the requested test reports within one week.

Sponsor Response

Novo Nordisk has performed a biological evaluation of the PDS290 IDegLira pen-injector considering all parts of the device which come in direct or indirect contact with users in accordance with EN ISO 10993-1: 2009 "Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process" and FDA Draft Guidance for Industry "Use of International Standard ISO- 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", please see the full Biological Evaluation Report 3.2.P.7 Biological Evaluation of PDS290 IDegLira pen-injector.

Table 1 provides an overview of the biological documentation basis and location of the documentation in this report for components and materials of the pen-injector. All available biological evaluation tests report can be found in Appendix G of the Biological Evaluation Report.

Table 1 The biological documentation basis for components and materials in the PDS290 IDegLira pen-injector with direct or indirect contact to the user

Component	Material	Biological evaluation basis	Section
Housing and cap	(b) (4)	(b) (4) No further biological evaluation necessary.	7.1.1
Cartridge holder	(b) (4)	(b) (4) Further, (b) (4) has passed an <i>in vitro</i> cytotoxicity test Appendix G. No further biological evaluation necessary.	7.1.2
Dial	(b) (4)	The (b) (4) material meets USP Class VI requirements and has passed tests for irritation and delayed-type hypersensitivity in accordance with ISO 10993-10. Further, (b) (4) has passed an <i>in vitro</i> cytotoxicity test Appendix G. No further biological evaluation necessary.	7.1.3
Dose button #	(b) (4)	(b) (4) has passed an <i>in vitro</i> cytotoxicity test Appendix G. No further biological evaluation necessary.	7.1.4.1
Dose button #	(b) (4)	(b) (4) has passed an <i>in vitro</i> cytotoxicity test Appendix G. No further biological evaluation necessary. Information on the chemical composition on the masterbatch in combination with literature data, and in some cases, worst case exposure assessments for constituents assessed as potential leachables. No further biological evaluation necessary.	7.1.4.2

*Please note that the (b) (4) was wrongly stated as (b) (4) in the previously submitted 3.2.P.7 Summary Report of Biological Evaluation.

The Dose button includes either (b) (4) masterbatch OR (b) (4) masterbatch

The following IR was sent to the sponsor on April 21, 2016:

The dial, dose button, and the cartridge holder are made with (b) (4). You state within the Biological Evaluation of PDS290 that cytotoxicity testing is sufficient to evaluate these components because “epidermal inflammation caused by cytotoxicity is a prerequisite in the sensitization pathway”; therefore, a negative cytotoxicity result means the components will not cause sensitization and irritation reactions. This rationale does not address the fact that non-cytotoxic chemicals can be irritating or sensitizing. Therefore, a negative cytotoxicity test result is not sufficient to demonstrate the device is non-sensitizing and non-irritating. To address the use (b) (4) you also provided a table that lists the chemical composition for the “potential leachables” from the masterbatch; however, this table does not address the potential impurities (b) (4). Please provide biocompatibility tests on the

final finished dial, dose button, and cartridge holder for cytotoxicity, sensitization and irritation. Alternatively, you may provide a scientific justification (b) (4)

Sponsor Response on April 28, 2016- Updated May 12, 2016

Novo Nordisk would like to clarify (b) (4) in the PDS290 IDegLira pen injector for the dial (b) (4)

As described in the 3.2.P.7 Biological Evaluation of PDS290 IDegLira pen-injector, and noted by the Agency, (b) (4) A scientific justification (b) (4) is provided below.

In accordance with ISO 10993-1, biocompatibility of the final PDS290 IDegLira pen-injector was evaluated with respect to (b) (4) (master batches) for the dose button and cartridge holder (b) (4). The evaluation of safety was based on both the risk of material (i.e. the level of toxicological concern) and the nature of the user exposure (i.e. duration and bioavailability). The dose button and cartridge holder will only come into brief/transient contact with a small area of intact skin with the handling of the device. Also, the only vehicle for migration available is the limited amount of natural skin moisture available on the palm of a hand. Therefore, the overall risk was assessed to be very low.

In accordance with FDA Draft Guidance for Industry and Food and Drug Administration Staff, Use of International Standard ISO- 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", April 23, 2013, the biological evaluation of (b) (4) the dose button and cartridge holder is based on the full chemical composition (b) (4):

- Cartridge holder: (b) (4)
- Dose button: (b) (4) or (b) (4)
- (b) (4)
- (b) (4)

All (b) (4) are listed (b) (4) and manufactured under change control. All constituents of the (b) (4) (master batches) with a potential to migrate were evaluated for their potential to cause irritation and sensitization based on four websites containing toxicological data publicly available in scientific literature. Based on this, supplier data and/or a worst-case exposure assessment, it was concluded that (b) (4) do not contain any constituent with a potential to cause skin irritation or sensitization reactions.

Moreover, (b) (4) the dose button and cartridge holder are considered to be (b) (4) and implicitly do not result in any leachables. Therefore, in accordance with the FDA Draft Guidance stated above, the (b) (4) are not considered to be bioavailable, have any direct or indirect user contact, and no further toxicological information is necessary.

In conclusion, the biological evaluation is sufficient to assess the biological safety of PDS290 IDegLira pen-injector when used as intended (b) (4) and hence, do not result in any leachables. Therefore, the (b) (4) are not considered to be bioavailable or have any direct or indirect user contact.

The following IR was sent to the sponsor on April 29, 2016 (memo updated May 12, 2016):

The Agency recommends that you perform testing on the final finished device and not on the raw materials as manufacturing and processing could alter the physicochemical characteristics of the device that could lead to

changes in the biocompatibility response. In order to use a risk assessment to address the necessary biocompatibility endpoints, in this case cytotoxicity, sensitization, and irritation, both the materials (b) (4) as well as manufacturing should be included. You have provided information on either (b) (4) and manufacturing for the various components; however, the reviewer was unable to locate all the necessary information. The reviewer has included a table, summarizing the information provided and highlighting the missing information. Please provide the CAS # (and if available MSDS sheets) and provide a risk assessment of the sensitization and irritation potential for:

- (b) (4) the cartridge holder
- (b) (4) the dose button
- (b) (4) the dose button
- (b) (4) the dial

Additionally, please provide a rationale for why the manufacturing and processing will not impact the biocompatibility (b) (4). Alternatively, you may perform the requested testing on the final finish device (or components).

Component	Cytotoxicity testing on final finished component	Sensitization and Irritation testing on final finished component	(b) (4) risk information (b) (4)	(b) (4) risk information (b) (4)
Housing and cap	(b) (4)	(b) (4)	Not needed	Not needed
Cartridge holder	Testing performed	(b) (4) Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials	(b) (4)	Information (b) (4) not provided
Dial	Testing performed	(b) (4) Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials	Testing performed on base (b) (4) material used for the dial (b) (4) in compliance with ISO-10993-10	(b) (4) CAS number and/or MSDS needed
Dose button 1 (b) (4)	Testing performed	(b) (4) Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials	MSDS sheet provided	No information (b) (4)
Dose button 2 (b) (4)	Testing only	(b) (4) Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials	No information on base material	Table of potential leachables including CAS#s and an assessment of the sensitization and irritation potential

Sponsor Response on May 4, 2016- Updated May 12, 2016

Device Biocompatibility – Risk assessment

Novo Nordisk would like to clarify that biocompatibility testing (cytotoxicity) was performed on representative samples of the final finished PDS290 IDegLira pen-injector and not on the raw materials.

Moreover, to address the necessary biocompatibility endpoints, sensitization and irritation, a risk assessment for the following materials (including (b) (4) as well as the manufacturing and processing) was performed in accordance with section 6.1 in ISO 10993-1:2009 “Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process”:

- (b) (4) the cartridge holder (b) (4)
- (b) (4) the dose button (b) (4)
- (b) (4) dose button (b) (4) (potential leachables information table)

This risk assessment was provided as a scientific justification in Novo Nordisk's response on April 28, 2016 to address the Agency's April 21, 2016 information request (b) (4)

The biological evaluation of (b) (4) the dose button and cartridge holder was based on the full chemical composition. In addition, the (b) (4) above have a long history of safe use in medical devices (b) (4)

All constituents of the (b) (4) (master batches) with a potential to migrate were evaluated for their potential to cause irritation and sensitization based on four websites (1,2,3,4) containing toxicological data publicly available in scientific literature and MSDS information from the supplier (see Table 2, Table 3 and Table 4 of Appendix A for list of potential leachables (b) (4)).

Based on data from the literature, supplier and/or a worst case exposure assessment, it was concluded that (b) (4) do not contain any constituent with a potential to cause skin irritation or sensitization reactions.

Importantly, also contributing to the biocompatibility risk assessment for the endpoints sensitization and irritation is that (b) (4) the dose button and cartridge holder are considered to be (b) (4) and implicitly do not result in any leachables. (b) (4)

Therefore, the risk assessment is justified (b) (4), do not have any direct or indirect user contact, and no further toxicological information regarding sensitization and irritation is necessary per the FDA Draft Guidance for Industry and Food and Drug Administration Staff, Use of International

Standard ISO- 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", April 23, 2013 (b) (4) do not result in leachables.

Table 1 below provides a summary of the requested the CAS # and MSDS sheets which are provided in Appendix A and Appendix B, respectively.

Table 1 Requested CAS # and MSDS

Component	(b) (4)
Cartridge holder	(b) (4)
Dial	(b) (4)
Dose button 1	(b) (4)
Dose button 2	(b) (4)

Reviewer Comment- Updated May 12, 2016

The reviewer does not agree with the sponsor's rationale "that (b) (4) the dose button and cartridge holder are considered to be (b) (4)

(b) (4) and implicitly **do not** result in any leachables. (b) (4)
" However, the sponsor provided the requested MSDS and CAS # (b) (4)
and evaluated the sensitizing and irritation potential for "all constituents of the
(b) (4)". The sponsor concluded that based on a worst case exposure assessment, (b) (4)
do not contain the potential to cause irritation or sensitization reactions.

Manufacturing and processing – impact on device biocompatibility

The manufacturing and processing of the PDS290 IDegLira pen-injector do not impact the biocompatibility
(b) (4) A scientific rationale is provided below.

According to section 6.1.4 in ISO/TR 15499:2012 Biological evaluation of medical devices - Guidance on the conduct of biological evaluation within a risk management process, the following aspects of the manufacturing process have a potential to change the chemical properties of materials and should therefore be considered when test data on the final finished device is not available:

- intended additives, e.g. colorants, lubricants, pigments, surface treatments, ink;
- potential process aids, e.g. cleaning/disinfection/sterilization agents, etching agents, mould release agents, cutting fluids and particles, machine contaminants such as lubricants;
- potential process residuals of chemicals and additives
- degradation during manufacturing and processing

All manufacturing processes for the PDS290 IDegLira pen-injector with a potential to change the chemical properties of materials with user contact listed above per section 6.1.4 of ISO/TR 15499 are (b) (4)

The components of the PDS290 IDegLira pen-injector that come in direct or indirect contact with the user are (b) (4)

. Further, the components are (b) (4) within validated process (b) (4)
parameters in agreement with recommendations from suppliers (b) (4)

Also, the assembly processes are purely mechanical and do not change the chemical properties of the materials. Finally, the PDS290 IDegLira pen-injector is (b) (4)

Reviewer Comment - Updated May 12, 2016

The Agency recommended that the sponsor complete testing on the final finished device as manufacturing can impact the physicochemical properties of the material which can change the biological response to the final finished component. The sponsor provided a rationale that the manufacturing process will not impact the chemical properties of the materials. Additionally, their manufacturing processes are (b) (4)

Review Summary- Updated May 12, 2016

The CDRH biocompatibility reviewer has no further questions regarding the biocompatibility of the device.

CDRH Comments to CDER:

The Sponsor has provided dose accuracy results which demonstrate the device can deliver the medication after device conditioning is applied, per specifications which are compliant with ISO 11608-1:2012 Needle-based injection systems for medical use – Requirements and test methods. The device is capable of delivering doses (b) (4) to 50 increments. The priming dose is (b) (4) The specifications are (b) (4)
The Sponsor has not provided justification as to why the specification tolerances are acceptable other than they meet the standard. We defer the acceptability of the noted dose specifications to CDER.

CDRH Recommendation to CDER:

Review Summary: Overall review of the device constituent concludes that Novo Nordisk has designed a reasonably safe and effective pen injector delivery system based on the PDS 290 pen-injector system currently used for the FlexTouch. Therefore, approval is recommended for the prefilled pen injector for subcutaneous injection of Insulin degludec/liraglutide. Review assessed the design and development of the device constituent specifications, engineering risk analysis, performance studies and biocompatibility of the device constituent.

Digital Signature Concurrence Table	
Reviewer Sign-Off	<p>Sapana Patel -A</p> <p>Digitally signed by Sapana Patel -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sapana Patel -A, 0.9.2342.19200300.100.1.1=2001554957 Date: 2016.05.25 12:23:05 -04'00'</p>
Branch Chief Sign-Off	<p>Alan M. Stevens -S</p> <p>Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.06.02 15:14:50 -04'00'</p>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
06/02/2016

Clinical Inspection Summary

Date	5/25/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, GCPAB/DCCE/OSI Janice Pohlman, M.D., M.P.H., Team Leader, GCPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB/DCCE/OSI
To	Marisa Petruccelli, Regulatory Project Manager Tania Condarco, M.D., Medical Officer Lisa Yanoff, M.D., Medical Team Leader Division of Metabolism and Endocrinology Products
NDA	208583
Applicant	Novo Nordisk Inc.
Drug	Insulin degludec/liraglutide
NME	No
Therapeutic Classification	Hypoglycemic Agents
Proposed Indication	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Consultation Request Date	10/20/2015
Summary Goal Date	7/14/2016
Action Goal Date	9/14/2016
PDUFA Date	9/14/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 208583, six clinical investigator sites were inspected. These inspections did not reveal significant regulatory violations and no Form FDA 483s were issued. These inspections have been classified as No Action Indicated (NAI).

Based on results of these clinical investigator inspections, it appears that the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies appear to have been conducted adequately.

II. BACKGROUND

Insulin degludec/liraglutide is a combination of the long-acting basal human insulin analog, insulin degludec, and the glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide. Both insulin degludec and liraglutide are currently available and marketed as single products by this sponsor (Novo Nordisk). The clinical development program for the combination product

included five completed Phase 3 trials to evaluate the efficacy and safety of insulin degludec/liraglutide in subjects with type 2 diabetes mellitus. Two of these Phase 3 trials, NN9068-3697 (DUAL 1 trial) and NN9068-3912 (DUAL II trial) were selected by the review division for clinical site inspections.

Protocol NN9068-3697 was a randomized, parallel three-arm, open-label study in subjects with type 2 diabetes mellitus inadequately controlled with one or two oral antidiabetic medications (metformin or metformin + pioglitazone) comparing the efficacy and safety of the combination of insulin degludec/liraglutide with insulin degludec and liraglutide. Subjects were randomized 2:1:1 to insulin degludec/liraglutide, insulin degludec or liraglutide and continued their oral antidiabetic medications at pre-trial doses. Randomization was stratified based on previous treatment with metformin and metformin + pioglitazone and baseline HbA1c ($\leq 8.3\%$ and $> 8.3\%$). The primary efficacy endpoint was change in HbA1c after 26 weeks of treatment. Based on the non-inferiority and superiority criteria defined for this trial, the sponsor's analysis demonstrated that treatment with insulin degludec/liraglutide was non-inferior to insulin degludec and superior to liraglutide. Key secondary endpoints included mean change from baseline comparisons in fasting plasma glucose (FPG), post prandial plasma glucose (PPG) and body weight between the three treatment groups.

Protocol NN9068-3912 was a randomized, parallel two-arm, double-blind study in subjects with type 2 diabetes mellitus inadequately controlled with basal insulin and metformin with or without sulfonylureas or glinides comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec added on to metformin. Subjects were randomized 1:1 to once daily insulin degludec/liraglutide or once daily insulin degludec added on to metformin. The primary efficacy endpoint was change in HbA1c after 26 weeks of treatment. Based on the criteria defined for this trial, the sponsor's analysis found that treatment with insulin degludec/liraglutide was superior to insulin degludec. Key secondary endpoints included mean change from baseline in FPG and body weight.

Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site and/or site-specific efficacy effect size. Four of the six sites had no previous CDER inspections.

III. RESULTS (by site):

Site #, Name of CI, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #46394/759 Carl Meisner, M.D. DCT-Sugar Land LLC Dba Discovery Clinical Trials 2225 Williams Trace Blvd Suite 110 Sugar Land, TX	NN9068-3912: 7 subjects	12/2/2015 - 12/4/2015	NAI

Site #, Name of CI, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
Site #2327/826 Christopher Chappel, M.D. 222 Broadway, Ste. 302 Kissimmee, FL	NN9068-3697: 9 subjects	12/14/2015 - 12/17/2015	NAI
Site #15280/765 Ronald Chochinov, M.D. 3454 Loma Vista Road Ventura, CA	NN9068-3912: 10 subjects	12/14/2015 - 12/17/2015	NAI
Site #15229/896 Dennis Pangtay, M.D. 2021 N MacArthur Blvd Suite 350 Irving, TX	NN9068-3697: 10 subjects	12/3/2015 – 12/9/2015	NAI
Site #44623/942 Arles Perdomo, M.D. 330 SW 27th Avenue, Suite 304 Miami, FL	NN9068-3697: 29 subjects	12/02/2015 - 12/15/2015	NAI
Site #14818/760 Helena Rodbard, M.D. 3200 Tower Oaks Blvd Suite 250 Rockville, MD	NN9068-3912: 9 subjects	12/14/2015 - 12/15/2015	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Clinical Investigator: Carl Meisner, M.D.; Sugar Land TX; Site #46394/759

For Protocol NN9068-3912, eighteen subjects were consented and screened, seven subjects were randomized and five subjects completed the study. The two subjects who were discontinued from the study withdrew consent. An audit of the study records for all subjects who were screened was conducted. Signed informed consent documents were available for all subjects and indicated that informed consent was obtained prior to study participation. Other records reviewed included source documents (including subject diaries), inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, test article accountability, protocol deviations, and primary and secondary efficacy endpoints.

Review of records noted above generally revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection.

The field investigator did note protocol violations for two of the seven subjects randomized. Subject 759003 (two visits) and Subject 759007 (one visit) had high

fasting plasma glucose (FPG) values obtained from the central laboratory analysis that exceeded the threshold for having the subject return for an unscheduled visit to have FPG retested. If elevated values persisted, the subjects were to be withdrawn from the trial. These violations were identified by the Novo Nordisk monitor via Impact Reports approximately six months after the subjects had completed the study and were also included in site level data listing 1.62.10 (Important Protocol Deviations).

During the discussion of inspectional findings at the close of inspection, the clinical investigator stated that, given the subject's histories, these elevated FBP were not alarming and the subjects had no other clinical symptoms. He did, however, acknowledge that he should have followed the protocol.

Reviewer's comments: Although protocol violations were noted, these violations are considered minor and isolated. For subject 759003, FPG values were ~44 mg/dL and 22 mg/dL higher than the maximum value to repeat the lab. For subject 759007, the FPG value was 3 mg/dL higher than the maximum value to repeat the lab. The investigator noted that these subjects did not have any clinical symptoms. The sponsor's monitor noted these deviations on 10/8/2012, approximately six months after these subjects had completed the study. The monitor had requested that the site notify the IRB of the deviation. These protocol violations were included in the sponsor's submission (Listing 1.62.10). It is unlikely that these protocol violations would significantly subject safety or impact the efficacy results in this application.

The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

2. Clinical Investigator: Christopher Chappel, M.D.; Kissimmee FL; Site #2327/826

For Protocol NN9068-3697, fourteen subjects were consented and screened, nine subjects were randomized and seven subjects completed the study. The two subjects who were discontinued from the study withdrew consent. An audit of the study records for all subjects who were screened was conducted. Signed informed consent forms were present for all subjects who were screened to participate in the study prior to participation. Other records reviewed included source documents, CRFs, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, test article storage conditions (required refrigeration), protocol deviations, concomitant medications, and primary efficacy and safety endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

3. Clinical Investigator: Ronald Chochinov, M.D.; Ventura CA; Site #15280/765

For Protocol NN9068-3912, eighteen subjects were consented and screened, ten subjects were randomized and eight subjects completed the study. Two subjects discontinued the study, one withdrew consent and one experienced an SAE of major depression with psychotic features classified as unlikely related to study drug. This subject experienced two other SAEs that did not lead to discontinuation, acute renal failure and “possible” severe hypoglycemia; both were reported to the IRB and sponsor. Signed informed consent forms were present for all subjects who were screened to participate in the study prior to participation. An audit of the study records for the ten randomized subjects was conducted. Other records reviewed included source documents, CRFs, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, test article storage conditions (required refrigeration), protocol deviations, site monitoring logs, and primary efficacy and safety endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

4. Clinical Investigator: Dennis Pangtay, M.D.; Irving TX; Site #15229/896

For Protocol NN9068-3697, sixteen subjects were consented and screened, ten subjects were randomized and ten subjects completed the study. An audit of the study records for all subjects who were screened was conducted. Signed informed consent forms were present for all subjects who were screened to participate in the study prior to participation. Other records reviewed included source documents, subject diaries, CRFs, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, test article storage conditions (required refrigeration), protocol deviations, and primary efficacy and safety endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

5. Clinical Investigator: Arles Perdomo, M.D.; Miami FL; Site #44623/942

For Protocol NN9068-3697, forty-eight subjects were consented and screened (including three that were rescreened), twenty-nine subjects were randomized and twenty-nine subjects completed the study. An audit of the study records for all subjects who were screened was conducted. Signed informed consent forms were

present for all subjects who were screened to participate in the study prior to participation. Source documents were reviewed for sixteen subjects. Other records reviewed included subject diaries, CRFs, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, protocol deviations, and primary efficacy and safety endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

6. Clinical Investigator: Helena Rodbard, M.D.; Rockville MD; Site #14818/760
For Protocol NN9068-3912, twenty subjects were consented and screened, nine subjects were enrolled and 8 subjects completed the study. One subject was withdrawn from the study by the investigator due to noncompliance. An audit of the study records for all subjects who were screened was conducted. Signed informed consent forms were present for all subjects who were screened to participate in the study prior to participation. Other records reviewed included source documents, subject diaries, CRFs, inclusion/exclusion criteria, adverse event reports, IRB/sponsor/monitor communications, financial disclosure, test article accountability, test article storage conditions (required refrigeration), protocol deviations, site monitoring logs and primary efficacy and safety endpoints.

Review of records noted above revealed no significant discrepancies or regulatory violations. A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately and the data submitted by this site appear acceptable in support of the respective indication.

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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**

Drug Utilization Review

Date: April 27, 2016

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Drug names: Insulin Glargine and Lixisenatide
Insulin Degludec and Liraglutide

Application Type/Number: NDA 208673, NDA 208583

Applicant/sponsor: Sanofi-Aventis, Novo Nordisk

OSE RCM #: 2016-221

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EXECUTIVE SUMMARY

New drug applications (NDAs) for combination antidiabetic products containing a basal insulin and a GLP-1 agonist have been submitted by two sponsors for approval by the FDA. Currently, there are no FDA approved combination anti-diabetic products that also include insulin. In order to determine the proportion of patients who concurrently use a GLP-1 agonist with a basal insulin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology II (DEPI II) to provide the utilization patterns for GLP-1 agonists in combination with basal insulin from April 2010 through March 2015, annually. In support of DMEP's request, this review examined: 1) national cross-sectional outpatient retail data to assess the extent of use of GLP-1 agonists and 2) longitudinal healthcare plans claims data to assess the proportion of concurrent use of a GLP-1 agonist and basal insulin. In addition, this review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

The nationally estimated total number of unique patients who received dispensed prescriptions through the U.S. outpatient retail pharmacies for all GLP-1 agonists increased from approximately 535,000 patients in the 12-month period ending in March 2011 to 882,000 patients in the 12-month period ending in March 2015. The majority of patients were dispensed Victoza[®] and were adult patients aged 45 to 64 years in the 12-month period ending in March 2015. The patients who were dispensed GLP-1 agonists accounted for 5% of the total number of patients who received dispensed prescriptions for any OAD (oral anti-diabetic) and/or GLP-1 agonists in the 12-month period ending in March 2015.

For the concurrency analysis, patient data based on prescription claims for any OAD/GLP-1 agonists and basal insulin were obtained from a sample of the U.S. commercially insured population captured in the IMS Real World Data (RWD) Adjudicated Claims – US database. The number of patients who had prescription claims for any OAD and/or GLP-1 agonists and the patients on concurrent therapy with a GLP-1 agonist and basal insulin were obtained from this sample. The concurrency analysis are based on unprojected data and may not be nationally representative; therefore, the analysis focused on the proportion of patients rather than the absolute numbers in the sample. Among the patients who had a prescription claim for a GLP-1 agonist, the proportion of patients who had concurrent therapy with a GLP-1 agonist and a basal insulin increased from 17% of GLP-agonist patients in the 12-month period ending in March 2011 to 27% of GLP-agonist patients in the 12-month period ending in March 2015. However, the percentage of patients who were new to diabetes treatment and started on concurrent therapy with GLP-1 agonist and basal insulin was negligible ($\leq 0.1\%$) during the study period.

The sponsor conducted drug utilization analysis with three unrelated databases: (b) (4)

(b) (4) The sponsor's study has numerous limitations and assumptions among the three databases to conclude Lixilan can meet the insulin demands of (b) (4) % of the intended patient population. (b) (4) (b) (4) had a small sample size, the (b) (4)

(b) (4) data were not linked, and the use of (b) (4) data to determine accurate daily insulin dosing is difficult.

In summary, based on a sample population, it appears that about a quarter of commercially insured patients with prescription claims for GLP-1 agonist products concurrently had prescription claims for basal insulin. The sponsor's study concludes that their product will meet (b) (4) % of the insulin needs of their target population, however the studies used to reach that conclusion have limitations. Therefore, it is difficult to determine if a fixed dose combination product containing a basal insulin and GLP-1 agonist can meet the higher daily dose of insulin for many type 2 diabetic patients based on the studies provided.

1 INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) "increase glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, increases B-cell growth/replication, slows gastric emptying, and decreases food intake."¹ GLP-1 receptor agonists are indicated as "an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹ There are currently five GLP-1 receptor agonist being marketed:

GLP-1 Agonists ²		
Product Name	Formulations/Strengths	Approval Date
Byetta [®] (exenatide)	Injectable: 300mcg/1.2mL; 600mcg/2.4mL	April 28, 2005
Victoza [®] (liraglutide)*	Injectable: 18mg/3mL	January 25, 2010
Bydureon [®] (exenatide)	Injectable: 2mg/vial; 2mg (pen)	January 27, 2012
Tanzeum [®] (albiglutide)	Injectable: 30mg (pen); 50mg (pen)	April 15, 2014
Trulicity [®] (dulaglutide)	Injectable: 0.75mg/0.5mL; 1.5mg/0.5mL	September 18, 2014

*Saxenda[®] (liraglutide) is indicated for weight loss only and was NOT included in the study.

Currently, no combination antidiabetic product has been approved with one of the components being insulin. According to clinical treatment standards for type 2 diabetes, it is recommended that newly diagnosed patients are started on one oral antidiabetic product (i.e. metformin). If the patient fails to achieve hemoglobin A1c (HbA1c) level goals, step up therapy is warranted. Step up therapy would consist of adding an additional one or two antidiabetic products (sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP-4

¹ "Facts & Comparisons[®] EAnswers." *Facts & Comparisons[®] EAnswers*. Wolters Kluwer Health, Inc, Mar. 2015. Web. 23 Mar. 2016. <<http://online.factsandcomparisons.com/index.aspx>>.

² Drugs@FDA: FDA Approved Drug Products." *Drugs@FDA: FDA Approved Drug Products.*. Web. 23 Mar. 2016. <<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>>.

inhibitors), sodium/glucose co-transporter 2 (SGLT2 inhibitor), and/or GLP-1 agonists). If patients' HbA1c still remains uncontrolled, insulin therapy is the last step.³

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing new drug applications (NDA) submitted by Sanofi-Aventis (NDA 208673) and Novo Nordisk (NDA 208583) for approval. The two NDAs consist of combination products of a GLP-1 agonist and basal insulin. An advisory committee meeting is scheduled for May 24th and 25th to discuss the safety profiles of these NDAs and determine if these combination products have an unmet need. In support of DMEP's reviews of the NDAs and upcoming advisory committee meeting, this review from the Division of Epidemiology II (DEPI-II) provides: 1) national estimates of patients who were dispensed prescriptions for GLP-1 agonists from U.S. outpatient retail pharmacies, and 2) the proportion of patients who had concurrent prescription claims for a GLP-1 agonist and a basal insulin from a sample of U.S. commercially insured population for five 12-month time periods from April 2010 through March 2015. This review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

2 MATERIALS & METHODS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review. Full database descriptions are provided in Appendix 2 of the review.

2.1 NATIONAL CROSS-SECTIONAL UTILIZATION ANALYSES OF GLP-1 AGONISTS

2.1.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ database were used to determine the various settings of care to which GLP-1 agonists were sold to. During year 2015, the sale of GLP-1 agonists by number of bottles sold from manufacturers indicated that approximately 76% of total sales were distributed to the outpatient retail pharmacy settings, 18% to the mail-order/specialty pharmacies, and 6% to the non-retail pharmacy setting.⁴ As a result, outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty pharmacies and non-retail settings were not included in this review.

2.1.2 DATA SOURCES USED

The IMS, Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for an oral antidiabetic

³ "American Diabetes Association Standards of Medical Care in Diabetes D 2016." *Diabetes Care* 39.1 (2016): n. pag. Jan. 2016. Web. 23 Mar. 2016.

⁴IMS Health, IMS National Sales Perspectives™. 2015. Extracted March 2016. File: IMS DATA 2016-221 Lixilan AC.xlsx

(OAD) medication and/or a GLP-1 agonist from U.S. outpatient retail pharmacies. The nationally projected patient data for GLP-1 agonists were also stratified by molecule and patient age (0-17, 18-44, 45-64, 65 years and older) for five 12-month time periods from April 2010 through March 2015. Appendix 3 provides a list of selected OADs and GLP-1 agonists which were included in this analysis.

2.2 CONCURRENCY ANALYSIS OF GLP-1 AGONISTS AND BASAL INSULIN

In addition to the analysis of nationally estimated utilization trends of GLP-1 agonists in the outpatient retail setting, we examined a longitudinal patient-level database based on a sample of U.S. commercially insured patients to assess the concurrent use of GLP-1 agonists and basal insulins for five 12-month time periods from April 2010 through March 2015. These data were stratified by patient age groups (1-17, 18-44, 45-64, 65 years and older). These data particularly assessed: 1) the proportion of patients who filled a GLP-1 agonist and had a concurrent basal insulin therapy, and 2) the proportion of patients who were new to diabetes treatment and had a concurrent therapy of GLP-1 agonist and basal insulin as their first treatment.

2.2.1 DATA SOURCES USED

The IMS Health Real-World Data (RWD) Adjudicated Claims – US database (formerly known as “PharMetrics Plus”) was searched to obtain the number of commercially insured patients who had pharmacy prescription claims for any OAD and/or GLP-1 agonist from a sample of commercial health plans, as well as a sample of patients who had pharmacy prescription claims for basal insulin for five 12-month time periods from April 2010 through March 2015. The total number of patients in the database on any OAD and/or GLP-1 agonist for each examined time period served as a possible surrogate of treated Type 2 Diabetes patient population in the IMS RWD Adjudicated Claims – US database. From this sample of patients with OADs and/or GLP-1 agonist prescription claims, the number and proportion of patients on concurrent therapy of GLP-1 agonist and basal insulin were obtained for each examined time period. Appendix 3 provides a list of selected OADs, GLP-1 agonists, and basal insulins which were included in these analyses.

Patient-level summary information will be reported for five cohorts. Each cohort data time frame consists of a 1-year selection time period, a 1-year look-back period, and a 3-month washout period for allowable gaps in therapy. For each cohort, we require all patients to be continuously enrolled in their health plan throughout the corresponding data time frame in order to ensure a complete view of their claims history. Therefore, children less than one who are born between the look back periods are not captured.

The total number of patients on any OAD/GLP-1 agonist was defined as has having two or more prescription claims for any OAD/GLP-1 agonist. The more stringent definition of 2+ prescription claims were used for the total OAD/GLP-1 agonist patients to determine a conservative baseline population who were continuously on an OAD/GLP-1 agonist therapy. Patients with a prescription claim for GLP-1 agonist as well as a concurrent claim of basal insulin required a less stringent 1+ prescription claim during the look back period in order to allow for the capture of patients who received prescriptions for a GLP-1 agonist and basal insulin on the same day. Patients are

considered new if they have not received ANY OAD/GLP-1 agonist or basal insulin during the look back period.

Cohort Selection Time Frame
Year 1: April 1, 2010 – March 31, 2011
Year 2: April 1, 2011 – March 31, 2012
Year 3: April 1, 2012 – March 31, 2013
Year 4: April 1, 2013 – March 31, 2014
Year 5: April 1, 2014 – March 31, 2015

Concurrent use is defined as any prescription fill of GLP-1 agonist or basal insulin where, at the time of the fill, the patient is also on a continuous course of therapy of the other class (basal insulin or GLP-1 agonist). The following business rules will be used to determine if a patient is “on therapy” for the other class at the time of a given GLP-1 agonist or basal insulin fill.

- | |
|---|
| <ol style="list-style-type: none">1. Patient has a prescription for GLP-1 agonists
AND2. Patient has a fill for selected basal insulin during the reporting period and after the GLP-1 agonists fill
AND3. Patient has another fill of GLP-1 agonists after the basal insulin prescription (patient can change products within GLP-1 agonists, but as long as they are still filling within the class they will be considered “on therapy” of GLP-1 agonist at the time of the basal insulin fill)
AND4. The two GLP-1 agonists fills fall within an allowable “grace period” |
|---|

OR

- | |
|--|
| <ol style="list-style-type: none">1. Patient has a prescription for basal insulin
AND2. Patient has a fill for selected GLP-1 agonist during the reporting period and after the basal insulin fill
AND3. Patient has another fill of basal insulin after the GLP-1 agonist prescription (patient can change products within basal insulin, but as long as they are still |
|--|

filling within the class they will be considered “on therapy” of basal insulin at the time of the GLP-1 agonist fill)

AND

4. The two basal insulin fills fall within an allowable “grace period”

In addition, patients filling both a GLP-1 agonist and basal insulin on the same day will be considered to be using the classes concurrently. The “grace period” is the number of out-of-drug days allowed between the last day of supply for a given prescription and the fill date for the next prescription in the same class for the patient’s therapy to be considered continuous. The “grace period” will be 30 out-of-drug days.

The IMS RWD Adjudicated Claims – US database is a commercially insured health care claims database (not including Medicare and Medicaid claims) which captures commercially administered plans. The patient-level health plan claim analyses in this review were conducted using a sample of U.S. commercially insured population captured in this database. Healthcare plan pharmacy prescription claims were captured from outpatient retail and mail-order/specialty pharmacies. National estimates of these healthplan claim data are not available at the time of the analyses. Therefore, trending sample estimates of patient-level health plan claim data across time is not recommended because the number of contributed data may fluctuate over time and the true extent of use of these products is likely underestimated.

2.3 SPONSOR’S DRUG UTILIZATION STUDY OF LIXISENATIDE (GLP-1 AGONIST) AND INSULIN GLARGINE⁵

The sponsor submitted a drug utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product using the following databases: (b) (4)

The sponsor concluded that the combination lixisenatide/insulin glargine can meet the insulin requirements of a broad number of patients with type 2 diabetes. DMEP requested DEPI to provide comments on the data analysis of the study and the limitations of the databases used to come to their conclusion (section 3.3).

3 RESULTS

3.1 NATIONALLY ESTIMATED NUMBER OF PATIENTS RECEIVING OUTPATIENT RETAIL DISPENSED PRESCRIPTIONS FOR GLP-1 AGONISTS

Table 3.1 in Appendix 1 displays the nationally estimated number of unique patients who received dispensed prescriptions for any OAD and/or GLP-1 agonists from U.S. outpatient retail pharmacies for five 12-month time frames from April 2010 through March 2015. There were roughly 16-19 million total patients, annually, who received

⁵Sponsor Submission. Original New Drug Application: 208673. Submission Date: December 21, 2015, for NDA 208673

dispensed retail prescriptions for any OAD or GLP-1 agonists during the five year study period. Of these total patients who were dispensed any OAD and/or GLP-1 agonists, the proportion of patients who received a dispensed prescription for a GLP-1 agonist was small and slightly increased from 3% to 5%. In terms of absolute numbers, there was a 65% increase in the number of patients who received a dispensed prescription for a GLP-1 agonist from approximately 535,000 patients in the 12-month period ending in March 2011 to 882,000 patients in the 12-month period ending in March 2015.

For the most recent 12 month period from April 2014 through March 2015, Victoza[®] was the market leader, accounting for 68% of the total 882,000 GLP-1 patients, followed by Bydureon[®] with 20% and Byetta[®] with 12.5% of the total GLP-1 patients. Tanzeum[®] and Trulicity[®] were marketed in 2014 and accounted for 3% and 2%, respectively, of the total GLP-1 patients.

During the five-year study period, the majority of the patients receiving a dispensed prescription for a GLP-1 agonist were adult patients aged 18 years and older. In the recent 12-month period ending in March 2015, adult patients aged 45-64 years accounted for 58% of Victoza[®] patients, 62% of Bydureon[®] patients, 55.5% of Byetta[®] patients, 66% of Tanzeum[®] patients, and 65% of Trulicity[®] patients. The 65 years and older age group accounted for 29% of Victoza[®] patients, 24% of Bydureon[®] patients, and 33% of Byetta[®] patients, while the 18 to 44 years old age group accounted for 20% of Tanzeum[®] patients and 18% of Trulicity[®] patients.

3.2 CONCURRENCY ANALYSIS OF GLP-1 AGONISTS AND BASAL INSULIN (SAMPLE OF COMMERCIALY INSURED POPULATION)

Tables 3.2 and 3.3 in Appendix 1 provide the sample number of commercially insured patients who had prescription claims for an OAD and/or a GLP-1 agonist from April 2010 through March 2015. The number of unique patients with prescription claims for any OAD and/or GLP-1 agonist was used as the base population as a surrogate of treated type II diabetic patients in the sample dataset. During year one (April 2010 through March 2011), there were approximately 644,695 unique patients with pharmacy prescription claims for any OAD and/or GLP-1 agonists. By year five (April 2014 through March 2015) of the study period, the sample population in the dataset is 486,477 unique patients.

It is important to keep in mind the data are not projected and to focus on the percentage change between years rather than absolute patient counts. The number of total unique patients with prescription claims for any OAD and/or GLP-1 agonists **does not** reflect a decrease as is seen from year one to year five in table 3.2 and 3.3. Rather, there was a drop in enrolled patients available within data set. Therefore, trending these patient estimates is not recommended.

3.2.1 SAMPLE PATIENTS CURRENTLY ON A GLP-1 AGONIST THERAPY

Table 3.2 in Appendix 1 provides the sample and the proportion of patients on concurrent therapy with GLP-1 agonist and basal insulin. The percentage of patients who had prescription claims for a GLP-1 agonist was small and increased from approximately 7% in year one (April 2010 through March 2011) to 9.5% in year five (April 2014

through March 2015). Of these patients on GLP-1 agonists, the percentage of patients on concurrent therapy with basal insulin increased from 17% in year one to 27% in year five.

3.2.2 SAMPLE PATIENTS WHO WERE NEW TO DIABETES TREATMENT

Table 3.3 in **Appendix 1** provides the sample and the proportion of patients who were new to diabetes treatment and initiated on concurrent therapy with a GLP-1 agonist and basal insulin. The percentage of patients who were new to diabetes treatment and had prescription claims for any OAD and/or GLP-1 agonist remained steady (22-24%) throughout the study period. The percentage of patients who were new to diabetes treatment and initiated on concurrent therapy with a GLP-1 agonist and basal insulin was rare and accounted $\leq 0.1\%$ of patients throughout the five year study period.

3.3 ANALYSIS OF SPONSOR LIXISENATIDE (GLP-1 AGONIST) & INSULIN GLARGINE STUDY

The sponsor conducted drug utilization analyses incorporating several databases to estimate the percentage of patients who could potentially benefit/meet their daily insulin requirements from the fixed dose Lexilan product. (b) (4) was initially used by the sponsor to determine if Lexilan will meet the insulin requirements for the target population. This database is a prospective, cross-sectional survey of physicians conducted in a real-world clinical setting. The inclusion criteria using the (b) (4) database included patients identified as type 2 diabetic patients with an HbA1c value greater than 7%. From a total of (b) (4) physician surveys, (b) (4) patient records were collected and only (b) (4) records met the inclusion criteria for the analysis. The inclusion criteria contained patients who were on insulin glargine \pm (with or without) an OAD (oral antidiabetic) and had an HbA1c value $>7\%$. The sponsor determined from the (b) (4) patient records, Lexilan would not meet (b) (4) of the patients or (b) (4) % of sample population's insulin requirements.

One possible limitation of this study is the inclusion of patients who are only using insulin glargine. Restricting to only insulin glargine limits the inclusion criteria and excludes the sample population of type 2 diabetic patients who are using other basal insulins. In addition, it appears that the sponsor findings are based on a small sample size in the context of the prevalence of type 2 diabetes. These data are likely not nationally representative or reflective of the target population.

The second database that the sponsor used in their analysis was (b) (4), an electronic healthcare database. The only inclusion/exclusion criteria the sponsor established in the (b) (4) was that if a diabetic patient is controlled (b) (4) % or uncontrolled (b) (4) % as determined by HbA1c values less than or greater than 7. In addition, the methods used in the (b) (4) does not appear to differentiate between type 1 vs type 2 diabetic patients. Within (b) (4), the sponsor does not state the underlying number of patients in the 2014 dataset as a whole nor does the (b) (4) have similar inclusion/exclusion criteria as used in the (b) (4), the third dataset used in the sponsor's analysis.

Within the third database, (b) (4), the sponsor includes the first inclusion/exclusion criteria as number of patients on basal insulin +/-

OAD (oral antidiabetic) followed by number of patients who have an average daily dose of 60 units of basal insulin. The first inclusion/exclusion criteria of the number of patients on basal insulin +/- OAD separates type 2 vs. type 1 diabetic patients from the basal patient level. The sponsor is assuming that only type 2 patients would be concurrently taking basal insulin and an OAD while excluding patients with prescriptions for rapid acting insulin as a surrogate marker for type 1 diabetes patients. This inclusion criterion nets (b) (4) patients in the study sample.

The second inclusion/exclusion criteria of number of patients who have an average daily dose of 60 units of basal insulin is based on the calculation of the dose dispensed over the number of days the prescription is written for. It is difficult to determine daily insulin dose in this manner. This inclusion criterion narrows the sample patient population to (b) (4) patients and assumes patients are using basal insulin exactly as written. The (b) (4) should have incorporated the time between refills to determine exactly how long the initial basal insulin prescription lasted for a patient instead of days of supply, which is often determined at the pharmacy and may take into account billing restriction, i.e. a “30 day supply for a vial” to meet insurance requirements. However, prescriptions are typically written as “use as directed” with no other specific instructions. It is also unknown if daily insulin doses are changed or titrated after dispensing based on prescription claims data. Due to these limitations, prescription claims data alone are insufficient to accurately determine daily insulin dose.

After the inclusion/exclusion criteria was established for (b) (4) 2014 and (b) (4) 2015, the sponsor combines the included patient population of the two separate databases to make one assumption. The sponsor concludes that of the (b) (4) patients who use greater than 60 units of basal insulin per day, approximately (b) (4) % of them or (b) (4) are uncontrolled. The (b) (4) sample patients or (b) (4) % ((b) (4) patients/ (b) (4) patients) of the population are whom the sponsor cannot meet the greater than 60 units per day of basal insulin criteria under their current formulations for the Lexilan product.

The sponsor’s claim that Lexilan can meet the insulin requirements of (b) (4) % of the targeted patient population from the (b) (4) is based on many assumptions and on data with numerous limitations. The sponsor did not link the (b) (4) with the patient population in the (b) (4). Any comparisons of the two databases require the assumptions that the (b) (4) databases have similar patient populations and inclusion criteria. However, the inclusion criteria used for the two databases were not similar and (b) (4) database did not differentiate between type 1 and 2 type diabetic patients.

4 DISCUSSION

To assist DMEP in their review of NDAs for combination products containing a GLP-1 agonist and basal insulin, this review examines: 1) national cross-sectional outpatient retail data to assess the extent of use of GLP-1 agonists, and 2) longitudinal healthcare plans claims data to assess the proportion of concurrent use of a GLP-1 agonist and basal insulin. In addition, this review also comments on the sponsor’s submitted utilization

study of the proposed product Lixilan[®], a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

The findings from the national level cross-sectional patient database (IMS Total Patient Tracker) shown in Table 3.1 suggest that the nationally **projected** number of patients who received a dispensed prescription for a GLP-1 agonist have increased by 65% during the study period. However, in the context of patients who received any OAD or GLP-1 agonists, the proportion of patients on GLP-1 agonists was small and accounted for 3-5% of total patients per year of those who received dispensed retail prescriptions for any OAD or GLP-1 agonists from U.S. outpatient retail pharmacies. It is important to note that the data are only representative of outpatient utilization trends, data from mail-order/specialty or inpatient settings were not included. The estimates provided in Table 3.1 are national estimates, but no statistical tests were performed to determine statistically significant changes over time. All changes over time should be considered approximate and may be due to random error.

Utilization of GLP-1 agonists used concurrently with basal insulin were further assessed in a commercial healthcare plans database. The findings from the longitudinal patient-level database (IMS RWD Adjudicated Claims – US) showed that out of the total number of patients with prescription claims for GLP-1 agonists, the proportion of patients on concurrent therapy with a GLP-1 agonist and basal insulin increased from 17% to 27% of total patients during the study period. However, the percentage of patients who were new to diabetes treatment and started on concurrent therapy with GLP-1 agonist and basal insulin was negligible ($\leq 0.1\%$ of patients new to OAD/GLP-1 agonist therapy). Basal insulin doses were not determined because dosing instructions or “signa” are not available in claims data and there are limitations to using days supply and dispensed vial sizes in claims data to calculate accurate dosing for insulin products.

The IMS RWD Adjudicated Claims – US (Tables 3.2 and 3.3) provide a **sample** (unprojected) number of patients on a GLP-1 agonist as well those on a concurrent therapy with a GLP-1 agonist and basal insulin. When interpreting the IMS RWD Adjudicated Claims – US data, the numbers should not be trended because each reporting time period is distinct. Between each distinct 12 month time periods within the study, the pool of patients and healthcare plans contributing to the data sample may change over time. Since the data was not projected, it is imperative to focus on the proportion of patients throughout the study period.

Patient-level data captured in the IMS RWD Adjudicated Claims – US were obtained from a **sample** of healthcare claims from a commercially insured U.S. population, not including Medicare and Medicaid patients. Therefore, these analyses do not estimate the utilization of concurrent GLP-1 agonist and basal insulin therapy in cash payers, elderly, and the Medicare and Medicaid populations.

The sponsor estimates Lexilan can meet the insulin needs of approximately 80-90% of the targeted patient population. However, the methods and databases the sponsor used for the estimates have limitations. The sponsor used three disparate data sources that were not linked to the same patient populations. Assumptions were made to link the findings from one database to the other. The Adelphi Real World – Disease Specific Programs had a limited sample size that is not nationally representative, while the IMS Health Lab and

Health APLD Lifelink Patient level data were not linked. The IMS Lifelink data from the sponsor also only calculated days' supply of insulin based on 30 day supply of what was dispensed, not when the patient actually refilled the prescription. Dosing information on insulin based solely on claims data are insufficient due to limitations described above.

5 CONCLUSION

In support of FDA's review of NDAs for novel combination GLP-1 agonist and basal insulin products, this review examined both national level data on extent of GLP-1 agonists use as well as longitudinal patient-level data on the concurrent use of GLP-1 and basal insulin. In addition, this review also comments on the sponsor's submitted utilization study of the proposed product Lixilan, a fixed-dose insulin glargine and lixisenatide (a GLP-1 agonist) product.

Based on the FDA's analysis of longitudinal health plan claims data, about a quarter of the commercially insured patients in the sample population on GLP-1 agonists also had a concurrent prescription claim for basal insulin per year. The proportion of patients who were new to diabetes therapy and initiated on concurrent therapy with a GLP-1 agonist and basal insulin was negligible.

Based on the nationally projected cross-sectional outpatient retail data, patients on GLP-1 agonists have increased to nearly 900,000 patients in the most recent 12 month study period. The sponsor's study concludes that they will meet ^{(b) (4)} % of the insulin needs of their target population; however, the studies used to reach that conclusion contain many limitations. The ^{(b) (4)} had a small sample size, using pharmacy claims data to determine insulin dose is difficult, and the patients in the two disparate data sources, ^{(b) (4)} were not linked. Therefore, it is difficult to determine if a fixed dose combination product containing basal insulin and GLP-1 agonist can meet the higher daily dose of insulin for many type 2 diabetic patients.

APPENDIX 1: TABLES

Table 3.1

NATIONALLY ESTIMATED NUMBER OF PATIENTS WHO RECEIVED A DISPENSED PRESCRIPTION FOR GLP-1 AGONISTS STRATIFIED BY AGE FROM U.S. OUTPATIENT RETAIL PHARMACIES, APRIL 2010 - MARCH 2015, ANNUALLY

	Year 1		Year 2		Year 3		Year 4		Year 5	
	Apr. 2010 - Mar. 2011		Apr. 2011 - Mar. 2012		Apr. 2012 - Mar. 2013		Apr. 2013 - Mar. 2014		Apr. 2014 - Mar. 2015	
	Patient (n)	% Share								
TOTAL OAD & GLP-1 AGONISTS	15,720,189	100.0%	16,563,386	100.0%	16,628,789	100.0%	17,198,977	100.0%	18,557,716	100.0%
TOTAL GLP-1 AGONISTS	535,159	3.4%	616,165	3.7%	703,459	4.2%	768,935	4.5%	881,919	4.8%
VICTOZA	228,855	42.8%	348,563	56.6%	445,531	63.3%	539,874	70.2%	601,381	68.2%
0 - 17 years	547	0.2%	720	0.2%	683	0.2%	687	0.1%	633	0.1%
18 - 44 years	44,958	19.6%	65,196	18.7%	75,186	16.9%	84,679	15.7%	90,543	15.1%
45 - 64 years	146,164	63.9%	221,051	63.4%	271,833	61.0%	319,404	59.2%	348,576	58.0%
65+ years	39,850	17.4%	68,251	19.6%	106,505	23.9%	145,420	26.9%	172,581	28.7%
Unknown Age	48	< 0.1%	--	--	2	< 0.1%	1,176	0.2%	4,819	0.8%
BYDUREON	--	--	10,361	1.7%	97,882	13.9%	134,813	17.5%	175,920	19.9%
0 - 17 years	--	--	15	0.1%	140	0.1%	133	0.1%	183	0.1%
18 - 44 years	--	--	1,812	1.7%	16,404	16.8%	22,060	16.4%	27,475	15.6%
45 - 64 years	--	--	6,458	6.2%	61,909	63.2%	84,420	62.6%	108,443	61.6%
65+ years	--	--	2,076	20.0%	20,702	21.2%	30,352	22.5%	42,230	24.0%
Unknown Age	--	--	--	--	--	--	237	0.2%	1,316	0.7%
BYETTA	343,180	64.1%	286,864	46.6%	205,650	29.2%	136,842	17.8%	110,219	12.5%
0 - 17 years	720	0.2%	604	0.2%	360	0.2%	217	0.2%	191	0.2%
18 - 44 years	53,088	15.5%	42,688	14.9%	27,906	13.6%	17,080	12.5%	13,820	12.5%
45 - 64 years	211,189	61.5%	171,154	59.7%	119,118	57.9%	76,513	55.9%	61,177	55.5%
65+ years	83,649	24.4%	77,900	27.2%	62,273	30.3%	45,565	33.3%	36,747	33.3%
Unknown Age	122	< 0.1%	3	< 0.1%	--	--	231	0.2%	907	0.8%
TANZEUM	--	--	--	--	--	--	--	--	26,797	3.0%
0 - 17 years	--	--	--	--	--	--	--	--	13	< 0.1%
18 - 44 years	--	--	--	--	--	--	--	--	5,243	19.6%
45 - 64 years	--	--	--	--	--	--	--	--	17,794	66.4%
65+ years	--	--	--	--	--	--	--	--	3,708	13.8%
Unknown Age	--	--	--	--	--	--	--	--	219	0.8%
TRULICITY	--	--	--	--	--	--	--	--	15,625	1.8%
0 - 17 years	--	--	--	--	--	--	--	--	20	0.1%
18 - 44 years	--	--	--	--	--	--	--	--	2,850	18.2%
45 - 64 years	--	--	--	--	--	--	--	--	10,191	65.2%
65+ years	--	--	--	--	--	--	--	--	2,504	16.0%
Unknown Age	--	--	--	--	--	--	--	--	113	0.7%

**Please note due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across time periods.

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months)

IMS Health Vector One® Total Patient Tracker. Extracted Mar. 2016. File DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

Table 3.2

Patients with concurrent prescriptions for a GLP-1 agonist and basal insulin from a sample of the commercially insured * U.S. population, stratified by patient age, by reporting years, April 2010 through March 2015

	Year 1		Year 2		Year 3		Year 4		Year 5	
	April 2010 - March 2011		April 2011 - March 2012		April 2012 - March 2013		April 2013 - March 2014		April 2014 - March 2015	
	Patients (n)	% Share								
Total Number of Patients on OAD/GLP-1 Agonist	644,695	100.0%	664,629	100.0%	610,265	100.0%	578,363	100.0%	486,477	100.0%
Patients On A GLP-1 Agonist	45,647	7.1%	51,570	7.8%	55,343	9.1%	53,696	9.3%	46,216	9.5%
1-17 years	78	0.2%	68	0.1%	47	0.1%	25	0.0%	25	0.1%
18-44 years	7,286	16.0%	7,986	15.5%	8,266	14.9%	7,796	14.5%	6,945	15.0%
45-64 years	33,857	74.2%	38,333	74.3%	41,821	75.6%	41,045	76.4%	35,152	76.1%
65+ years	4,426	9.7%	5,183	10.1%	5,209	9.4%	4,830	9.0%	4,094	8.9%
Patients On Both GLP-1 Agonist & Basal Insulin	7,837	17.2%	9,799	19.0%	13,162	23.8%	13,807	25.7%	12,360	26.7%
1-17 years	4	0.1%	9	0.1%	6	0.0%	2	0.0%	6	0.0%
18-44 years	826	10.5%	1,050	10.7%	1,440	10.9%	1,515	11.0%	1,432	11.6%
45-64 years	6,054	77.2%	7,502	76.6%	10,264	78.0%	10,828	78.4%	9,606	77.7%
65+ years	953	12.2%	1,238	12.6%	1,452	11.0%	1,462	10.6%	1,316	10.6%

* Commercially insured excludes Medicare and Medicaid

Reporting Year - rolling 12 month period (i.e. April 2010 through March 2011 = reporting year 1)

Due to the study being unprojected, the data should not be trended between years. Inference may be made on percentage changes between years. Age groups may not be representative of the population.

Source IMS LifeLink PharMetrics Plus. Reporting Time April 2010 Through March 2015 Extracted March 2015. File DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

Table 3.3

Patients with concurrent prescriptions for a GLP-1 agonist and basal insulin from a sample of the commercially insured * U.S. population, stratified by patient age, by reporting years, April 2010 through March 2015

	Year 1		Year 2		Year 3		Year 4		Year 5	
	April 2010 - March 2011		April 2011 - March 2012		April 2012 - March 2013		April 2013 - March 2014		April 2014 - March 2015	
	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share	Patients (n)	% Share
Total Number of Patients on OAD/GLP-1 Agonist	644,695	100.0%	664,629	100.0%	610,265	100.0%	578,363	100.0%	486,477	100.0%
1-17 years	2,795	0.4%	2,716	0.4%	2,496	0.4%	2,564	0.4%	2,083	0.4%
18-44 years	89,949	14.0%	90,167	13.6%	86,267	14.1%	83,222	14.4%	74,572	15.3%
45-64 years	440,652	68.4%	455,106	68.5%	430,605	70.6%	414,367	71.6%	347,827	71.5%
65+ years	111,299	17.3%	116,640	17.5%	90,897	14.9%	78,210	13.5%	61,995	12.7%
Patients New To Any OAD/GLP-1 Agonist	147,679	22.9%	153,149	23.0%	135,148	22.1%	135,166	23.4%	114,694	23.6%
1-17 years	1,873	1.3%	1,803	1.2%	1,741	1.3%	1,712	1.3%	1,397	1.2%
18-44 years	39,191	26.5%	38,865	25.4%	37,142	27.5%	36,854	27.3%	33,042	28.8%
45-64 years	92,288	62.5%	96,380	62.9%	85,677	63.4%	86,316	63.9%	72,706	63.4%
65+ years	14,327	9.7%	16,101	10.5%	10,588	7.8%	10,284	7.6%	7,549	6.6%
Patients New To GLP-1 Agonist & Basal Insulin Concurrently	42	<0.1%	48	<0.1%	87	0.1%	76	0.1%	48	<0.1%
1-17 years	--	--	--	--	--	--	--	--	--	--
18-44 years	9	21.4%	13	27.1%	10	11.5%	17	22.4%	12	25.0%
45-64 years	29	69.0%	30	62.5%	70	80.5%	53	69.7%	32	66.7%
65+ years	4	9.5%	5	10.4%	7	8.0%	6	7.9%	4	8.3%

Reporting Year rolling 12 month period (i.e. April 2010 through March 2011 = reporting year 1)

** Commercially insured excludes Medicare and Medicaid*

Due to the study being unprojected, the data should not be trended between years. Inference may be made on percentage changes between years. Age groups may not be representative of the population.

Source IMS LifeLink PharMetrics Plus. Reporting Time April 2010 Through March 2015 Extracted March 2015. File DATA 2016-221 Combination GLP-1 Agonist & Insulin AC.xlsx

APPENDIX 2: DRUG UTILIZATION DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS Health Real-World Data (RWD) Adjudicated Claims – US

The IMS Health Real-World Data Adjudicated Claims - US Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9% of the United States commercially insured population based on year 2007 United States Census.

APPENDIX 3: LIST OF SELECTED ANTIDIABETIC DRUGS OF INTEREST AND GPI CODES

Class	Drugs Included	GPI Code(s)
Basal Insulin	Lantus, Toujeo, Levemir, Humulin N, Novolin N, Other Basal (Insulatard NPH, Relion N, Humulin L, Novolin L, Humulin U)	27104003* 27104006* 27104020* 2710403* 2710405*
GLP-1	Byetta, Bydureon, Bydureon Pen, Victoza, Trulicity, Tanzeum EXCLUDES: Saxenda	27170020* 27170050* 27170015* 27170010*
DPP-IV	Onglyza, KombiGlyze Januvia, Janumet, Janumet XR, Juvisync Tradjenta, Jentaduetto, Glyxambi Nesina, Oseni, Kazano	27550065*, 27992502607* 27550070*, 27992502700* 27992502707* 279930027* 27550050, 2799250240*, 2799650230 27550010* 279940021* 279925021*
Other OAD	Glyset, Miglitol, Precose, Acarbose Fortamet ER, Glucophage, Glucophage XR, Metformin HCl, Metformin HCl ER, Riomet, Prandin, Repaglinide, Starlix, Nateglinide, Acetohexamide, Amaryl, Glimepiride, Chlorpropamide, Diabinese, Diabeta, Dymelorm Glyburide, Glyburide Micro, Glycron, Glynase Prestab, Glipizide, Glipizide ER, Glipizide Cl, Glucotrol, Glucotrol XL, Orinase, Tolbutamide, Sk-Tolbutamide, Tolazamide, Tolinase, Rosiglitazone (Actos), Pioglitazone (Avandia)	2750* 2725*, 279990025* 2728* 2720* 2760* 279970* 279980* 279978* 279950*

	<p>Glipizide-Metformin, Glyburide-Metformin</p> <p>Pioglitazone HCl-Metformin, Rosiglitazone Maleate-Metformin</p> <p>Glimepiride-Rosiglitazone, Glimepiride-Pioglitazone</p> <p>Repaglinide-Metformin</p>	<p>2757402010*</p>
<p>SGLT2 Inhibitors</p>	<p>Invokana, Farxiga, Jardiance, Invokamet, Xigduo XR , Synjardy, Glyxambi</p>	<p>27700020*</p> <p>27700040*</p> <p>27700050*</p> <p>2799600220*</p> <p>2799600230*</p> <p>2799600240*</p> <p>2799650230*</p>

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LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 12, 2016

Requesting Office or Division: Division of Metabolism and Endocrinology (DMEP)

Application Type and Number: NDA 208583

Product Name and Strength: Xultophy (insulin degludec and liraglutide) injection, 300 units and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)

Product Type: Multi-ingredient Product and Combination Product

Rx or OTC: RX

Applicant/Sponsor Name: Novo Nordisk

Submission Date: September 14, 2015

OSE RCM #: 2015-2086

DMEPA Primary Reviewer: Ariane O. Conrad, PharmD, BCACP, CDE

DMEPA Team Leader: Yelena Maslov, PharmD

DMEPA Acting Associate Director: QuynhNhu Nguyen, MS

DMEPA Deputy Director: Lubna Merchant, M.S., PharmD

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA evaluate the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 208583 for Xultophy (insulin degludec and liraglutide) pen injector intended to treat type 2 diabetes.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
Other-Regulatory History	D
Labels and Labeling	E

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

For this product, DMEPA reviewed the human factors study design and results, and the proposed Prescribing Information (PI), Information for Use (IFU), and Medication Guide materials submitted by Novo Nordisk on September 21, 2015.

3.1 PRODUCT DESIGN

Insulin degludec and liraglutide is a multi-ingredient product that combines a long acting insulin with a glucagon-like peptide-1 (GLP-1) receptor analog into a single pen device. This product is intended for the treatment of patients with type 2 diabetes. Insulin degludec (under the proprietary name Tresiba) is currently approved to treat diabetes. Liraglutide (under the proprietary name Victoza) is currently approved for the treatment of type 2 diabetes. The product is to be available in a pen device using the same device platform currently marketed for Novolog.

In the process of reviewing this product, we identified the following unique aspect:

- It is a mixture of an insulin with a non-insulin active ingredient as a combination in a single container closure system. Importantly, unlike insulin-insulin mixtures, the two active ingredients in this proposed product are dosed using different units of measure (units vs. mg). See discussion in Section 3.3 of this review.
- Of concern is whether end users, particularly prescribers, will be aware that there are two components to be considered when initiating therapy, making dose

conversions, and switching therapy which may lead to drug duplications. This aspect of use was not evaluated in the submitted HF study. Therefore, the Agency requested that Novo Nordisk complete additional labeling comprehension studies to evaluate if prescribers understand this information.

Novo Nordisk submitted the proposed protocol for this label comprehension study on March 14, 2016. We are evaluating the protocol in a separate review¹.

3.2 HUMAN FACTORS STUDY

The HF study for insulin degludec and liraglutide was conducted with 174 representative users (16 physicians/physician assistants/nurse practitioners, 15 pharmacists, 15 nurses, and 64 adult diabetes patients, and 64 elderly diabetes patients). The study was designed to simulate use tasks and provide data to support that intended users can dispense, differentiate, prepare, and administer doses (refer to Appendix C). The study evaluated all the tasks necessary for the injection process (e.g., dialing and administering a dose). We previously reviewed the study protocol² and our comments have been implemented.

We have provided a summary of the study results and our evaluation in the following sections.

1. Product Differentiation:

For the product differentiation component of the study, all participants (including the 15 pharmacists) were presented with a variety of pen injector cartons and instructed to select the test product (i.e., Xultophy). After those selections were made, study participants (excluding the 15 pharmacists) were presented with a variety of pen injectors to determine if participants could select the Xultophy pen.

A. Carton Differentiation (n=174): Three patient participants selected the wrong pen-injector carton when presented with multiple comparator pens cartons (i.e., Novolog Mix 70/30, Levemir, and Novolog). Participants who selected the wrong carton failed the task due to incorrect perception of the task rather than poor differentiation among the products. Therefore, we consider these failures to be study artifacts.

B. Pen Differentiation (n=159): Five patient participants selected the wrong pen injector when presented with comparator pens (i.e., Novolog Mix 70/30, Levemir, Novolog, and Ryzodeg). Three of five participants selected the pen

¹ Conrad A. Human Factors Study Protocol Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April. OSE RCM # 2016-651.

² Vee S. Human Factors Study Protocol Review for Insulin Degludec and Liraglutide Injection (IND 109121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. OSE RCM # 2012-2754.

injector that corresponded with the incorrect carton selected in the previous task. The other two participants (both untrained and pen-naïve patients) selected the Ryzodeg pen because they recalled the navy blue color of the capped pen body, which Novo Nordisk uses for all of their insulin pen injectors. However, considering that both Xultophy and Ryzodeg contain insulin degludec, it is unlikely that patients will have both pens at home simultaneously. Thus, we did not identify any concern with these errors.

2. Product Handling, including visually checking the clarity of drug (n=159)

For the product handling component of the study, the study participants (excluding pharmacists) were presented with a carton of Xultophy pen injectors, the IFU, and other materials needed to simulate injection administration (e.g., injection cushion, needles, sharps container). Sixty-three of the 128 patient participants received training to use the Xultophy pen device. None of the healthcare practitioner participants received training.

A. Priming Errors

- i. Sixty-three participants (i.e., trained and untrained patients, nurses, and non-pharmacists healthcare providers) did not prime the pen injector for a total of 163 use errors. These participants stated that they did not realize or forgot that the pens need to be primed. Some participants reported that they typically do not prime pens at home. Thus, they applied same practice here.
- ii. Other priming errors included failure to tap the pen prior to priming (n=51) and not orienting the needle upward during priming (n=2).
- iii. In addition, one participant required clarification for the IFU when completing the priming task because the illustration used for the priming step was unclear but this did not result in an error.

Failure to prime or prime incorrectly may result in a small under dose which would be considered clinically insignificant based on consultation with the clinical team. However, Novo Nordisk indicated that they would further mitigate the potential for under dosing by increasing the prominence for the priming instructions in the IFU. While priming errors are not unique to this pen injector, we suggest including language and a picture clarifying that either a drop or a

stream may be noted during the priming step in addition to what the Sponsor proposed.

B. Dosing Errors

- i. Did not set dose correctly: Four patient participants did not set the assigned dose correctly prior to injecting one or more times for a total of seven errors.
 - One patient participant (pen-naïve, untrained) assumed that each number represented 10 units based on his assumptions regarding a “normal” dose of insulin. The subjective data and root cause analysis indicated that this error was a study artifact.
 - One patient participant (pen-experienced, untrained) thought that he had dialed the correct dose of “27” rather than “26”.
 - One participant (pen-naïve, trained) rushed through the task and failed to dial the dose before simulating the injection.
 - One participant (pen-experienced, untrained) misunderstood the task and dialed the dose that he would normally dial at home by listening to the pen clicks. Of note, he does not normally check the number in the dose window to verify that he has dialed the correct dose with his current pen.

Failure to dial the correct dose may result in a clinically relevant under dose or overdose of insulin degludec and liraglutide depending on the magnitude of the dose error and patient sensitivity to insulin. However, we understand that these dialing errors are not unique to this pen device. Novo Nordisk made modifications to the IFU and the pen to encourage use of the dose window to determine the dose dialed.

- ii. Split dose miscalculations: Participants were instructed to administer 40 units, but were required to split their dose by using the medication remaining in a current pen then completing the dose using a new pen. Three patient participants miscalculated the second portion of the dose when completing this task because they primed the pen injector then did not account for those 2 units when determining the dose to administer.
- iii. Priming when the intended dose is set: One participant (pen-naïve, trained) set the intended dose for injection on the pen injector, expelled

some medication for priming, and then administered the remainder without resetting the dose counter to the prescribed dose. This study participant did not understand that she was supposed to prime first then set the prescribed dose and she attributed this misunderstanding to deficits in her training. Although the participant attributed this error to lack of training, we note that training may not always occur. We note that the Applicant states that the IFU is maximized to address this error; however, we provide additional recommendation that highlight this information and may help mitigate this further.

C. Administration Errors

- i. Dose button not held down until dose counter back to “0”
 - Two participants (pen-experienced, untrained) pressed then released the dose button rather than hold the button to inject the full dose. They reported an assumption that pressing the button would administer the medication.
 - One participant (pen-naïve, untrained) also assumed that pressing the button would administer the dose and interpreted the click heard when the button was pressed to mean that the dose was delivered. We recommend that the IFU further emphasize that statement: “You may hear or feel a click when the 0 lines up with the dose pointer”, and the Sponsor should add that “This does not mean that the dose has been delivered.”

These failures could result in an under dose. The participants that did not press the dose button long enough to administer the full dose didn’t understand the functionality of the pen device and made incorrect assumptions about the release mechanism for the medication. Novo Nordisk determined that their current labeling should be adequate to minimize the risk of these errors. However, we provide some additional revisions to the IFU to help further mitigate error.

- ii. Dose administered prior to inserting into the cushion

Two participants (pen-experienced, trained and pen-naïve, untrained) inadvertently pressed the dose button without realizing it. Participant ENU1 believed that the method she used to hold the pen while attaching the needle caused her to

inadvertently press the button. The experienced pen user could not explain why she pressed the button just before inserting it into the cushion pad. We would expect that these errors would have limited clinical relevance since we would expect that patients would feel when the dose is administered after pressing the button; thus, these errors were study artifacts.

D. Not removing the Needle

- i. Five participants (untrained lay users and nurses) did not remove the inner needle cap prior to attempting to complete the injection. These errors were study artifacts. Additionally, three participants (untrained lay users) did not remove the needle after using the pen because they reported the re-use of the needle at home. These reuse errors are not unique to this pen device. However, we recommend modifications to IFU including additional language under Step 15 of the IFU to indicate that the needles should be removed after each use.

3. IFU Evaluation Exercise (n=69)

- A. The 63 trained participants and six of the untrained³ participants were asked to interpret two excerpts from the IFU after completing the hands-on tasks. They all demonstrated that they understood (1) that the dose prescribed will equal the number displayed in the dose counter and (2) how to set the prescribed dose using the dose selector and dose pointer.

3.3 LABELS AND LABELING

This review identified several deficiencies in the container label, carton labeling, patient instructions for use (IFU), and the prescribing information (PI) labeling. Although the human factor study results evaluating whether prescribers are able to appropriately prescribe and dose, make dose titrations, and convert patients to insulin degludec and liraglutide from other therapies is pending, we noted that some areas could be improved. We provide recommendations in sections 4.1 and 4.2 and recommend their implementation prior to approval of this NDA.

³ The IFU evaluation exercise only included 6 untrained participants, since they were the only ones in the untrained arm that interacted with the IFU.

Of note, we have some concern regarding the proposal to communicate the dose without using any units in the labeling, as studied in the HF study. However, it is unclear what terminology would be best to use for dosing this product. For example, the term “units” may be misleading since it only references the insulin component (insulin degludec) and does not impart the presence of two drugs. In addition, the use of both dosage units (units for insulin and mg for liraglutide) may create confusion for end users of the pen device, considering that this multi-ingredient product is dosed based on the insulin component alone. However, if the dosing on the pen device were to express both active ingredients, the cumbersome nature of the expression may actually create confusion for end users. Therefore, we considered the need for consistent terminology to determine that the use of the term “units” may be the least problematic strategy to use for dosing this multi-ingredient product.

4 CONCLUSION & RECOMMENDATIONS

The use errors noted in the HF study are not unique to this pen injector device. While we find the study results to be acceptable, we recommend additional modifications to the IFU to improve the prominence of important information in the proposed labeling to clarify information and mitigate for any confusion. Also, as previously noted, we will review the prescriber labeling comprehension study protocol and results in a different review memorandum.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. We will provide recommendations after reviewing the results of the labeling comprehension study that Novo Nordisk will conduct.

B. Instructions for Use (IFU)

1. Based on the results of the human factors study, we identified the following areas for improvement:
 - a. For Step 9, add language clarifying that the user may either see a drop or a stream when priming the pen. Consider also adding a pictorial to show that a stream of medicine may be noted as well.
 - b. Include the following statement in the beginning of step 10 “Make sure you prime your pen before setting your dose” to remind users to prime the pen.
 - c. Separate Step 13 into two separate steps because this information can be easily overlooked combined as one step. Therefore, we recommend moving the “keep the needle in your skin...” statement and associated

pictorial to a separate step immediately following the step with instructions to press and hold the dose button.

- For Step 13, consider modifying the statement [REDACTED] (b) (4) to read “You may hear or feel a click.” and follow with the statement “This does not mean that the dose has been delivered.”

d. Separate Step 15 into two distinct steps because the text and images for recapping the syringe are contradictory to the information provided in the first half of the step. Therefore, we recommend moving the “if you do not have a sharps container” instructions and associated pictorial to a separate step immediately following the step with instructions to remove the needle.

- e. Add a sub-bullet under Step 15 that warns users to remove the needle after each use.

4.2 RECOMMENDATIONS FOR NOVO NORDISK

We recommend the following be implemented prior to approval of this NDA:

C. Carton Labeling

1. On the primary display panel, consider adding line spaces between the proprietary name, established name, “For Single Patient Use Only” warning, and concentration statement since this information appears cluttered on the label. Since there is a large amount blank space available, this modification should improve readability.
2. Revise the statement [REDACTED] (b) (4) to “See prescribing information” for improved clarity.
3. Revise the statement [REDACTED] (b) (4) to “Must be refrigerated”.
4. Include the statements “Date of first opening ___/___/___ . Discard unused portion 21 days after first opening.” Since there will be multiple pens in each carton, we recommend including space for users to make note of the date for each pen in the box.

D. Professional Sample Label and Labeling

1. Increase the size and prominence of the “Sample. Not for Resale” statement on the drug sample’s label and the “Sample” statement on the drug sample container’s labeling so that it is clear that these are drug samples, per 21CFR 203.38(c).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xultophy that Novo Nordisk submitted on September 14, 2015.

Table 2. Relevant Product Information for Novo Nordisk				
Initial Approval Date	N/A			
Active Ingredient	insulin degludec and liraglutide			
Indication	Type 2 diabetes mellitus			
Route of Administration	Subcutaneous			
Dosage Form	Solution			
Strength	100 units insulin degludec and 3.6 mg liraglutide per mL			
Dose and Frequency	Individualized dose given once daily			
How Supplied	3 mL prefilled pens dispensed in boxes of (b) (4) 5 pens			
Storage	Prior to first use		After first use	
	Refrigerated 36°F to 46°F (2°C to 8°C)		Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
	Until expiration date		21 Days	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 25, 2016, we searched the L:drive using the terms, “degludec liraglutide”, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review⁴ of the proposed human factors study protocol and we confirmed that our previous recommendations were implemented or considered.

⁴ Vee S. Human Factors Study Protocol Review for Insulin Degludec and Liraglutide Injection (IND 109121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. RCM # 2012-2754.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

2.1 User groups

The participant sample included at least 15 representatives from each of the defined user groups, thereby matching industry convention and the FDA's current guidance on proper usability test sample sizing. The test included representatives from the following user groups:

- 128 patients: adult and elderly with T2DM who self-administer insulin and/or GLP-1 and/or Oral Anti-Diabetic medication. [Table 2](#) summarises the associated patient / caregiver⁴ sub-groups (pen-experienced / pen-naïve, trained / untrained).

Table 2 Summary of T2DM patient /caregiver sub-groups, each of which included at least 15 representatives

	Pen-experienced		Pen-naïve		Total
	Trained	Untrained	Trained	Untrained	
Adults (age 18-64)	16	15	16	17	64
Elderly (age 65+)	15	16	16	17	64
Total	31	31	32	34	128

- 46 HCPs who prescribe and/or dispense insulin and/or GLP-1 pen-injectors, and/or teach others how to perform injections, including:
 - 16 physicians, physician office staff (e.g., physician assistants and nurse practitioners)
 - 15 pharmacists
 - 15 nurses in general who inject patients during hospitalisation

2.2 Participant background

Section [3](#) provides a summary of the participants' background characteristics, and Section [22](#) provides detailed background information for each participant. None of the participants had participated in a usability test of any pen-injector within the past year.

2.3 Training

The training included a product orientation session during which trained participants (1) received 30 minutes of one-on-one, hands-on training by one of three independent Certified Diabetes Educators (CDEs), and (2) watched a training video with a 15-minute runtime. Subsequently, the CDE assessed each trainee's preparedness to use the PDS290 IDegLira pen-injector. They made the assessments by judging trainees' newly acquired skills and documenting their competency using the pre-defined training record (see Section [17](#)). Per the test plan, the CDE disqualified one participant following her training session (see Section [21.1](#) for the CDE's rationale). The trained participants then returned 2 – 36 hours later to participate in a test session lasting up to an hour and 15 minutes.

Approximately half of the patient participants (63 of 128) received training prior to participating in the usability test session, and the remaining patient participants (65 of 128) did not receive training. None of the 46 HCP participants received training. Withholding training from over half of the patient participants represented a "worst-case scenario" and enabled (b) (4) to assess the potential for use errors by untrained participants. Untrained participants first encountered the PDS290 IDegLira pen-injector during the Test Material Presentation Period.

During the usability test session, all participants (except pharmacists) had the option to read the IFU and/or to watch the ancillary instructional video on a laptop computer before and/or while performing the hands-on tasks. However, none of the participants were required to read the IFU and/or watch the ancillary instructional video during the hands-on tasks. The test administrator asked all trained participants to read and interpret two IFU excerpts after performing the hands-on tasks during the IFU Evaluation Exercise (see Section 5 for the IFU Evaluation Exercise results, and Section 19 for the script). (b) (4) used the same approach to evaluate untrained participants' understanding of the IFU if test personnel observed a use error, close call, or operational difficulty related to dosing terminology.

2.4 IFU Evaluation Exercise

(b) (4) assessed participants' understanding of select IFU content by asking all trained participants to read IFU excerpts after performing the hands-on tasks. After reading each excerpt, participants interpreted the content in their own words and answered specific questions related to the content. Refer to Section 5 for the IFU Evaluation Exercise results and Section 19 for the IFU Evaluation Exercise script and a list of the IFU excerpts that participants read and interpreted.

(b) (4) used the same approach to evaluate untrained participants' understanding of the IFU if test personnel observed a use error, close call, or operational difficulty related to the dosing terminology.

2.5 Test Material Presentation Period

Prior to administering the hands-on tasks, the test administrator gave each participant (except pharmacists) the opportunity to handle (e.g., pick up, practice injecting with) the PDS290 IDegLira pen-injector and test materials. The test administrator presented patient participants (adults and elderly) with a pharmacy bag containing a carton of Xultophy[®] pen-injectors, recognising that patients would retrieve their supplies from a pharmacy. The test administrator presented HCPs (except pharmacists) with a carton of Xultophy[®] pen-injectors, recognising that these individuals would not retrieve pen-injectors from a pharmacy.

During this period, all participants (except pharmacists) had access to the IFU (folded as it would come in the pen-injector carton, see Figure 1), a pen-injector carton, one pen-injector, an injection cushion, a box of needles, a sharps container, alcohol swabs, a pen and pad of paper, a phone, and a laptop computer loaded with the ancillary instructional video.²

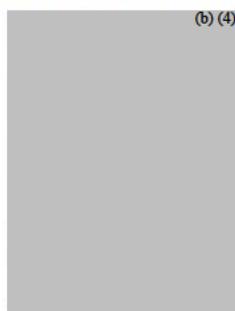


Figure 1 The IFU, folded as it would come in the pen-injector carton

2.6 Hands-on tasks

All participants performed the six hands-on tasks listed below, with the exception of pharmacists, who only performed Task 1 (carton retrieval). During all simulated injection tasks (Task 4 (dose reversal), Task 5 (normal injection), and Task 6 (end-of-content)) each participant, except pharmacists, used either the NovoFine[®] or NovoTwist[®] needle in a counterbalanced order pre-determined by the test personnel. For Task 1 (carton retrieval), the participant placed the Xultophy[®] pen-injector carton among the eight distractor products' cartons in the refrigerator (see Figure 2).



Figure 2 Xultophy[®] pen-injector carton and distractor products' cartons stored in a refrigerator

For Task 2 (pen-injector retrieval), the test personnel placed the Xultophy[®] pen-injector among the eight distractor pen-injectors in the open container (see [Figure 3](#)).



Figure 3 Xultophy[®] pen-injector and distractor products' pen-injectors stored in an open container

The test administrator presented the following specific task instructions to participants on an instruction card to initiate the task. Participants read the task instruction aloud, and then tried to perform the following tasks:

Task 1a (carton retrieval – patients):

Participants placed the Xultophy[®] pen-injector carton in the refrigerator. To evaluate a worst case scenario, the test administrator repositioned the cartons in the refrigerator prior to administering the differentiation tasks without informing the participant about doing so.

- Retrieve your new medication⁴ carton from the refrigerator. Take out one pen-injector, remove the pen cap, and confirm that you have chosen the right product.

Task 1b (carton retrieval – non-pharmacist HCPs):

Non-pharmacist HCPs placed the Xultophy[®] pen-injector carton in the refrigerator. To evaluate a worst case scenario, the test administrator repositioned the cartons in the refrigerator prior to administering the differentiation tasks without informing the participant about doing so.

- Retrieve the Xultophy[®] carton from the refrigerator. Take out one pen-injector, remove the pen cap, and confirm that you have chosen the right product.

Task 1c (carton retrieval – pharmacists):

Pharmacists did not see the Xultophy[®] carton and pen-injector before performing the tasks, representing a scenario in which a pharmacist interacts with Xultophy[®] for the first time.

- Retrieve the Xultophy[®] carton (insulin degludec/liraglutide [rDNA origin] injection) from the refrigerator and confirm that you have chosen the right product.

Task 2a (pen-injector retrieval – patients):

- Retrieve your pen-injector from the bin. Remove the pen cap and confirm that you have chosen the right product.

Task 2b (pen-injector retrieval – non-pharmacist HCPs):

- Retrieve the Xultophy[®] pen-injector from the bin. Remove the pen cap and confirm that you have chosen the right product.

Task 3 (check clarity of drug):

- Check that the medication in your Xultophy[®] pen is clear and colorless. Describe how you made this determination.

Task 4 (dose reversal):

- Deliver a dose of 20 using the Xultophy[®] pen-injector. *[To mimic dose reversal the test administrator asked participants to:]* Deliver a dose of 16 instead.

Task 5 (normal injection):

- Deliver a dose of 27 using the Xultophy[®] pen-injector.

Note, during this task, to simulate injecting another person as a caregiver, the patient participants injected into a cushion placed in an upright position (e.g., attached to a chair).

Task 6 (end-of-content):

- *[Test administrator provided a pen-injector containing a dose of approximately 6]* Deliver a dose of 40 using the Xultophy[®] pen-injector.

Scenario 1 is broken down into related user steps to be tested. The user steps are based on the user steps described in Section [4.3](#).

- Scenario 1: User does not receive the correct drug due to a mix-up (differentiation)
 - When dispensing e.g. at the pharmacy: *The HCP does not select the right drug*
 - Step 1: Pick the PDS290 IDegLira carton
 - Step 2: Cap removal (except pharmacists)
 - Step 3: Verify via label and cartridge holder that it is the correct pen-injector (*except pharmacists*)
 - When differentiating in the home environment: *The user does not receive/select the correct drug*
 - Step 1: Pick the PDS290 IDegLira carton/pen-injector
 - Step 2: Cap removal
 - Step 3: Verify via label and cartridge holder that it is the correct pen-injector

7.2 Scenario 2: The user does not administer the injection as intended (handling)

This scenario includes all the user steps related to the handling of the PDS290 pen injector. Scenario 2 is broken down into related user steps to be tested, (i.e. user steps that could result in a dosing error or needle stick injury). The user steps are based on the user steps described in Section 4.3 and are presented as follows:

- Scenario 2: The user does not administer the injection as intended (handling)
 - Step 2: Cap removal
 - Step 4: Check that the drug in the pen-injector is clear and colourless
 - Step 5: Needle mounting
 - Step 6: Checking the drug flow (priming)
 - Step 7: Setting the intended dose (reversing the dose setting, if necessary)
 - Step 8: Understand the End-of-content indication. This step only applies if the user is going to inject a dose larger than the remaining left in cartridge.
 - Step 9: Subcutaneous needle insert
 - Step 10: Injecting the dose, including leaving the needle in the skin after the dose counter has returned to 0 and counting slowly to 6
 - Step 11: Needle removal and disposal of used needle
 - Step 12: Cap mounting

C.2 Results

Table 3 Result of Analyses of Human Factors Validation

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
Scenario 1 Use error occurred in: • Task 1: Carton retrieval	User selected a pen-injector carton other than Xultophy® carton from the refrigerator.	<ul style="list-style-type: none"> • One participant (AXU8) explained that the open carton he previously placed in the refrigerator during the Test Material Presentation Period (the Xultophy® pen-injector carton) had pen-injectors containing a mix of two medications. • One participant (ENU11) explained that he chose the Levemir® FlexTouch® carton from the refrigerator because he recognised the medication 	3 out of 174 participants selected a pen-injector carton other than the Xultophy® carton from the refrigerator. 1 untrained, pen-experienced participant (AXU8) 1 trained, pen-experienced participant	3	<ul style="list-style-type: none"> • Test artefact – Simplified environment (b) (4) attributes three participants' use errors to test artefact (AXU8, EXT5, ENU11). Users are unlikely to have nine different insulin/GLP-1 products in their refrigerator. At the very least, the users will know which products are in their refrigerator. • Test artefact – Open NovoLog® Mix 70/30 FlexPen® carton. (b) (4) attributes 	Several mitigations are implemented in relation to carton retrieval: <ul style="list-style-type: none"> • Carton design - different presentation of pen-injector on carton, colour branding and text for differentiation purposes. • Pen-injector design - product colour on cartridge holder, container label, and dose button are used. • IFU section 1 includes the text "Before you start to prepare your injection, check the Xultophy Pen label before 	HF Validation	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?	
		name from a TV commercial, and the name was the most familiar to him. <ul style="list-style-type: none"> One participant (EXT5) explained that he selected the NovoLog® FlexTouch® carton because it was in the same location as the carton he placed in the refrigerator during the Test Material Presentation Period. Notably, the test administrator shuffled the cartons in the refrigerator without informing the participant after the participant had placed the carton in the refrigerator. 	(EXT5) 1 untrained, pen-naïve participant (ENU11)		one participant's use error to the NovoLog® Mix 70/30 FlexPen® carton having been previously opened (AXU8). As such, the Xultophy® and NovoLog® Mix 70/30 FlexPen® cartons were the only two cartons in the refrigerator that were previously opened. <ul style="list-style-type: none"> Medication composition. (b) (4) attributes one participant's use error to the fact that Xultophy® and NovoLog® Mix 70/30 FlexPen® are both combination medications (AXU8). Because both pen-injectors contain a mix of two medications, the participant assumed that the NovoLog® Mix 70/30 FlexPen® carton was the correct product. Test artefact – Limited exposure to packaging and medication name. (b) (4) attributes two participant's use error to test artefact resulting from limited exposure to the pen-injector packaging's appearance and medication name (AXU8, ENU11). Although the participants had time to interact with the product during the Test Material Presentation Period, they did not immediately recall the product appearance or name when asked to locate "[his/her] new medication" among 	<i>each use to make sure it is your Xultophy Pen.</i> <p>Additionally, in order for a product mix-up to occur in real life and before the user will be exposed to a potential harm, a series of unexpected events have to occur, for example:</p> <ul style="list-style-type: none"> The pharmacist or HCP chooses a wrong carton for the user and The user does not recognise receiving the wrong drug carton, or The user has more than one type of medication available (e.g., prescribed for his/her diabetes, or others with diabetes living in the same household) and Chooses the wrong carton/pen-injector and The user is unaware of/ignores the distinct design differences between different pen-injectors due to the product name, colouring, and labelling on the pen-injector when preparing the pen-injector for injection and during injection. <p>As described above, several mitigations must be neglected before a user in a real life setting selects and injects the wrong drug product.</p>			
					other pen-injector cartons in the refrigerator. (b) (4) expects that, in the real world, the user's HCP would provide a prescription to which the user can refer. Specifically, the user's HCP might mention the medication name during an appointment or telephone call, or might write down the medication name on a piece of paper for reference. Notably, per FDA's request, the task instruction did not include the medication name (i.e., Xultophy®). <ul style="list-style-type: none"> Prior exposure to Levemir® brand name. (b) (4) attributes the participant's use error to his prior exposure to the Levemir® product name (ENU11). The participant was reportedly familiar with Levemir® after having seen a television commercial for the product. Similar carton and appearance. (b) (4) attributes the participant's use error to the similar appearance of the Xultophy® and Levemir® FlexTouch® cartons' end panels (ENU11). Both end panels are the same size and shape (approximately 10.2 cm wide x 3.5 cm deep and rectangular), include a coloured bar on the left, and 		Novo Nordisk has tested the mitigations implemented and found that no further design optimisation of the carton would produce significant improvements, supported by root cause analysis. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.		

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
					present medication and pen-injector information using a similar format and position. Although each carton has a unique accent colour (i.e., pink or green), the cartons are mostly white, contributing to an overall similar appearance. <ul style="list-style-type: none"> • Test artefact – Planned test methodology - Rearranging of carton.s. (b) (4) attributes one participant's use error to the planned test methodology of the test administrator rearranging the medication cartons in the refrigerator prior to Task 1 (carton retrieval) (EXT5). As such, he did not intuit the need to inspect each carton individually; rather, he took the medication carton from the same location as the medication carton that he placed in the refrigerator during the Test Material Presentation Period. 			
Use error occurred in: • Task 2: Pen-injector retrieval	User selected a pen-injector other than Xultophy®	<ul style="list-style-type: none"> • One participant selected the Ryzodeg® FlexTouch® pen-injector and explained that she focused on the pen-injector's navy blue colour (ANU13). • One participant selected the Ryzodeg® FlexTouch® pen-injector and explained that he recalled the colour 	5 out of 159 participants selected a pen-injector other than the requested Xultophy® pen-injector from the open container. Notably, 3 of these participants selected the same product as the carton previously selected during Task 1 (carton retrieval) (AXU8,		<ul style="list-style-type: none"> • Test artefact – Simulated environment. (b) (4) attributes four participants' use errors to test artefact (ANU13, AXU8, ENU7, EXT5). Users are unlikely to have nine different insulin/GLP-1 products in their home. At the very least, the users will know which products they have in their home. 	Several mitigations are implemented in relation to pen retrieval: <ul style="list-style-type: none"> • Carton design - different presentation of pen-injector on carton, colour branding and text for differentiation purposes. • Pen-injector design - product colour on cartridge holder. 	HF Validation	No
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
		<p>scheme of the product with which he interacted during the Test Material Presentation Period to be navy blue with lighter blue accents (ENU7).</p> <ul style="list-style-type: none"> • One participant selected the NovoLog® Mix 70/30 FlexPen® pen-injector (AXU8). The participant explained that he selected the same medication he retrieved during Task 1 (carton retrieval). Moreover, he explained that he specifically looked for a pen-injector containing a mix of two medications. • One participant selected the NovoLog® FlexTouch® pen-injector (EXT5). The participant explained that he selected the same medication he retrieved during Task 1 (carton retrieval). • One participant selected the Levemir® FlexTouch® pen-injector (ENU11). The participant explained that he chose this pen-injector because it was the same medication he retrieved from the refrigerator during Task 1 (carton retrieval). 	<p>EXT5, ENU11). For example, a participant who selected the NovoLog® Mix 70/30 FlexPen® carton during Task 1 also selected the NovoLog® Mix 70/30 FlexPen® pen-injector during Task 2. Per the protocol, the test administrator did not inform the participants that they selected the incorrect product during Task 1 (carton retrieval).</p> <p>3 untrained, pen-naïve participants (ANU13, ENU7, ENU11)</p> <p>1 untrained, pen-experienced participant (AXU8)</p> <p>1 trained, pen-experienced participant (EXT5)</p>	5	<ul style="list-style-type: none"> • Test artefact – Limited exposure to packaging and medication name. (b) (4) attributes two participants' use errors to test artefact resulting from a limited exposure to the pen-injector's appearance and medication name (ANU13, ENU7). Although these participants had time to interact with the product during the Test Material Presentation Period, they did not immediately recall the product appearance or name when asked to locate "[his/her] new medication" among other pen-injectors in the container. (b) (4) expects that, in the real world, the user's HCP would provide a prescription to which the user can refer. Specifically, the user's HCP might mention the medication name during an appointment or telephone call, or might write down the medication name on a piece of paper for reference. Notably, per FDA's request the task instruction did not include the medication name (i.e., Xultophy®). • Similar pen-injector appearance. (b) (4) attributes two participants' use errors to the similar navy blue colouring of the Ryzodeg® 	<p>container label, and dose button are used.</p> <ul style="list-style-type: none"> • IFU section 1 includes the text "Before you start to prepare your injection, check the Xultophy Pen label before each use to make sure it is your Xultophy Pen." <p>Additionally, in order for a product mix-up to occur in real life and before the user will be exposed to a potential harm, a series of unexpected events have to occur, for example:</p> <ul style="list-style-type: none"> • The pharmacist or HCP chooses a wrong carton for the user and • The user does not recognise receiving the wrong drug carton or • The user has more than one type of medication available (e.g., prescribed for his/her diabetes, or others with diabetes living in the same household) and • Chooses the wrong carton/pen-injector and • The user is unaware of/ignores the distinct design 		

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
					<p>FlexTouch® pen-injector to the Xultophy® pen-injector (see Figure 1) (ANU13, ENU7). Notably, the participants relied on the product's navy blue colouring to identify the correct product.</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>Figure 1: The Xultophy® (top) and Ryzodeg® FlexTouch® (bottom) pen-injectors' shown side by side</p> <ul style="list-style-type: none"> • Previous task performance. (b) (4) attributes three participants' use errors to their performance in the previous task, Task 1 (carton retrieval) (AXU8, EXT5, ENU11). During Task 1, the participants incorrectly selected the NovoLog® Mix 70/30 FlexPen® carton (AXU8), NovoLog® FlexTouch® (EXT5) or Levemir® FlexTouch® (ENU11) carton rather than the Xultophy® carton. Per the test plan, the test administrator did not notify the participants of their previous use error. As such, the participants assumed they should select the same product as during Task 1. 	<p>differences between different pen-injectors due to the product name, colouring, and labelling on the pen-injector when preparing the pen-injector for injection and during injection.</p> <p>As described above, several mitigations must be neglected before a user in a real life setting selects and injects the wrong drug product.</p> <p>Novo Nordisk has tested the mitigations implemented and found that no further design optimisation of the carton would produce significant improvements, supported by root cause analysis. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Scenario 2 Use error	Did not tap pen-injector	• Some participants did not realise that they need to	51 out of the 137 participants who primed the pen-injector one or		• Reliance on user. The pen-injector's design relies on the user	Several mitigations were implemented for the IFU and ancillary instructional video in	HF Validation	No
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
<p>occurred in:</p> <ul style="list-style-type: none"> • Task 4: Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC) 	before priming:	<p>tap the pen-injector after attaching a needle and before priming the pen-injector (ANT16, ANU14, ENT07, ENU04, ENU16, ENU17, NuX07, ANT16, ANU02, AXU11, ANT02, ANT16, ENT07).</p> <ul style="list-style-type: none"> • Some participants simply forgot to tap the pen-injector before priming it (ANT03, ANT10, ANT14, ANU10, ENT05, ENT12, ENT14, AXT14, EXT01, EXT03, EXT15, H16, NuN02, ANT03, ANT10, ANT12, ANU10, ANU14, ENU12). • Some participants do not normally tap the pen-injector they currently use before priming it (AXT07, AXT11, AXT12, AXU03, AXU05, EXT04, EXT10, EXU03, EXU05, EXU16, H03, H09, H13, NuX08, ENT11, EXT14, EXU13, AXT11, EXU12, EXU13). 	<p>more times during the test session did not tap to dislodge air bubbles in the medication before priming.</p> <p>14 trained, pen-naïve participants (ANT2, ANT3, ANT7, ANT9, ANT10, ANT12, ANT14, ANT16, ENT5, ENT7, ENT11, ENT12, ENT13, ENT14)</p> <p>11 trained, pen-experienced participants (AXT7, AXT11, AXT12, AXT14, EXT1, EXT3, EXT4, EXT7, EXT10, EXT14, EXT15)</p>	163	<p>to either consult the IFU or independently realise that s/he must tap the pen-injector after attaching a needle and before priming the pen-injector (ANT16, ANU14, ENT07, ENU04, ENU16, ENU17, NuX07, ANT16, ANU02, AXU11, ANT02, ANT16, ENT07).</p> <ul style="list-style-type: none"> • Forgetfulness. Some participants reportedly forgot to tap the pen-injector (ANT03, ANT10, ANT14, ANU10, ENT05, ENT12, ENT14, AXT14, EXT01, EXT03, EXT15, H16, NuN02, ANT03, ANT10, ANT12, ANU10, ANU14, ENU12). • Habit. Some pen-experienced participants do not normally tap their current pen-injectors when priming. As such, they were not aware of the need to tap the pen-injector (AXT07, AXT11, AXT12, AXU03, AXU05, EXT04, EXT10, EXU03, EXU05, EXU16, H03, H09, H13, NuX08, ENT11, EXT14, EXU13, AXT11, EXU12, EXU13). 	<p>relation to tapping the pen-injector before each injection:</p> <ul style="list-style-type: none"> • IFU section 2: "<i>Priming your Xultophy Pen</i>" is a stand-alone section describing the importance of priming and illustrates tapping the pen-injector <ul style="list-style-type: none"> • <i>Step 8 "Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top"</i> • Figure illustrating how to hold and tap the pen-injector <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
			10 untrained, pen-naïve participants (ANU2, ANU4, ANU10, ANU14, ENU4, ENU12, ENU14, ENU16, ENU17, NuN2)					
			10 untrained, pen-experienced participants (AXU3, AXU5, AXU11, EXU3, EXU5, EXU12, EXU13, EXU16, NuX7, NuX8)					
			6 untrained HCPs (H2, H3, H9, H13, H14, H16)					
Use error	Did not prime	• Some participants did	63 out of 159 participants did not prime the pen-		• Reliance on user. The pen-	Several mitigations were implemented for the pen-injector.	HF	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
occurred in: • Task 4: Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC)	pen-injector	not realise that they needed to prime the pen-injector after attaching a Needle (ANT12, ANU01, ANU13, ENU01, ENU06, ENU10, ENU11, AXU01, AXU06, AXU12, EXU04, EXU12, EXU13, H01, H05, H06, NuN03, NuN04, NuN06, NuX05, NuX09, ANU01, ANU12, ANU13, ENU07, ENU16, AXU01, EXU04, EXU11, H08, H12, ENT15). • Some participants simply forgot to prime the pen-injector (ANU03, ANU09, ANU12, ENT13, ENU02, ENU07, AXU14, AXU15, EXU09, NuN05, NuX02, ANT11, ANU03, ANU09, ENU01, ENU02, ENU10, ENU11, AXU14, AXU15, EXU09, ENT13). • Some participants do not prime the pen-injector they currently use (AXT06, AXU01, AXU07, AXU10, EXU02, EXU08, EXU10, EXU11, EXU14, H07, H11, H15, NuX01, NuX, 04, AXU02, AXU06, AXU07, AXU10, AXU12, EXU02, EXU05, EXU08, EXU10, EXU14, H03) AXT03, AXT10,	injector one or more times before injecting a dose. 25 untrained, pen-experienced participants (AXU1, AXU2, AXU3, AXU6, AXU7, AXU10, AXU12, AXU14, AXU15, EXU2, EXU4, EXU5, EXU6, EXU8, EXU9, EXU10, EXU11, EXU12, EXU13, EXU14, NuX1, NuX2, NuX4, NuX5, NuX9)	163	injector's design relies on the user to either consult the IFU or independently realise that s/he must prime the pen-injector after attaching a needle (ANT12, ANU01, ANU13, ENU01, ENU06, ENU10, ENU11, AXU01, AXU06, AXU12, EXU04, EXU12, EXU13, H01, H05, H06, NuN03, NuN04, NuN06, NuX05, NuX09, ANU01, ANU12, ANU13, ENU07, ENU16, AXU01, EXU04, EXU11, H08, H12, ENT15). • Habit. Some pen-experienced participants do not normally prime their current pen-injectors. As such, they were not aware of the need to prime the pen-injector (ANU03, ANU09, ANU12, ENT13, ENU02, ENU07, AXU14, AXU15, EXU09, NuN05, NuX02, ANT11, ANU03, ANU09, ENU01, ENU02, ENU10, ENU11, AXU14, AXU15, EXU09, ENT13). • Forgetfulness. Some participants reportedly forgot to prime the pen-injector (AXT06, AXU01, AXU07, AXU10, EXU02, EXU08, EXU10, EXU11, EXU14, H07, H11, H15, NuX01, NuX, 04, AXU02, AXU06, AXU07, AXU10,	IFU and ancillary instructional video in relation to priming the pen-injector before each injection: • Mitigations implemented for the pen: • The first numerical dose (2) shown on the dose counter is used for priming and this link is featured in the IFU with text and an illustrative figure. • IFU section 2 "Priming your Xultophy Pen" describes the importance of priming the pen: • The section is designed as a stand-alone section with a prominent position in the IFU. • Turn the dose selector to (b) (4) accompanied by a figure illustrating (b) has been selected) • Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer. A drop of Xultophy should be seen at the needle tip	Validation	

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
		AXT12, AXT13).	ANU3, ANU9, ANU12, ANU13, ENU1, ENU2, ENU6, ENU7, ENU10, ENU11, ENU16, NuN3, NuN4, NuN5, NuN6) 11 untrained HCPs (H1, H2, H3, H5, H6, H7, H8, H9, H11, H12, H15)		AXU12, EXU02, EXU05, EXU08, EXU10, EXU14, H03). AXT03, AXT10, AXT12, AXT13).	<ul style="list-style-type: none"> Figure illustrating how to perform the priming and with an inset figure of a primed pen. <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error occurred in: • Task 4: Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC)	Dose not set correctly	<ul style="list-style-type: none"> One participant assumed each of the dose counter's numbers represented ten units (i.e., "1" represented 10 units, "2" represented 20 units, etc.) based on an assumption on the perception he had of a "normal" dose; he did not have any actual experience dialling a pen-injector (ANU12). One participant explained that he thought he 	5 out of 159 participants did not set the intended dose prior to injecting one or more times. 2 trained, pen-experienced participants (EXT9, EXT11) 1 untrained, pen-	7	<ul style="list-style-type: none"> Even numbered dose presentation. (b) (4) attributes one participant's use error to the scale drum's presentation of only even-numbered doses (EXU5). The scale drum presents even-numbered doses using numerals, whereas it presents odd-numbered doses using hash marks. Because the hash marks are relatively small, the participant might have overlooked the hash mark. 	The device user interface of the PD5290 IDegLira pen-injector has been designed with the following mitigations implemented for the pen: <ul style="list-style-type: none"> When a dose is dialled, the dose counter always indicates the dose selected (i.e., the full dose number is shown in the dose window). Dose number is large for easy readability. Dose counter print is dark grey on white background for 	HF Validation	No
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
		had set a dose of "27" rather than "26" (EXU5). <ul style="list-style-type: none"> One participant explained that she rushed to perform the simulated injection and forgot to dial the dose (ENT12). One participant thought he should set the dose he normally injects using his pen-injector (i.e., 6 mL) (AXU1). He explained that he sets a dose by listening and counting the clicks the pen-injector emits when he turns the dose selector; he normally does not check which number the dose counter displays. He did not realise he needed to set a different dose for each simulated injection task and attributed his mistake to his routine of dialling his normal injection dose. 	experienced participant (AXU3)		<ul style="list-style-type: none"> Incorrect mental model of pen-injector. (b) (4) attributes one participant's use error to his incorrect mental model of the pen-injector's mechanical function (ANU12). The participant initially assumed each of the dose counter's numbers represented 10 units; he did not have any actual experience dialling a pen-injector. That said, this instance seems to represent a rare case for which (b) (4) considers the use error to be idiopathic and unlikely to occur frequently. Rushing. (b) (4) attributes one participant's use error to the fact that she was reportedly rushing to complete the task (ENT12). Negative transfer. (b) (4) attributes 6/8 participants' use errors to negative transfer (ANU9, AXU1). One participant based this assumption on his previous experience using syringes, which demarcate using increments of 10 (ANU9). The other participant did not set the target dose; rather, he set his normal injection dose without checking the dose counter number (AXU1). 	better readability. In addition, several mitigations were also implemented for the IFU and ancillary instructional video in relation to the setting the dose correctly: <ul style="list-style-type: none"> By design, a prominent stand-alone section in bold text: Section 3 "Selecting your dose" is positioned in the IFU to distinguish this important step. IFU section 3: "Selecting your dose" describes with a figure and text how to set the dose correctly. "Step 10: Turn the dose selector to select the dose you need to inject. The dose pointer should line up with your dose. If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose. The even numbers are printed on the dial. The odd numbers are shown as lines." Figure illustrating how to set a correct dose (even or odd number). <p>Novo Nordisk has tested the</p>		

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
						mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable		
Use error occurred in: • Task 6: End of content (EOC)	Miscalculated size of second part of an injection	<ul style="list-style-type: none"> One participant primed but did not inject any medication with the EOC pen-injector and injected a dose of 38 using a new pen-injector (EXT9). During the post-test interview, the participant explained that she recalled having injected a dose of 2 using the EOC pen-injector, which led her to believe she needed to inject a dose of 38 using the new pen-injector. One participant primed and then injected a dose of 4 using the EOC pen-injector and injected a dose of 34 using a new pen-injector (EXT11). During the post-test interview, the participant explained that she did not deduct the priming dose of 2 from the dose of 6 remaining in the EOC pen-injector. As such, she thought she injected a dose of 6 using the EOC pen-injector, and then 	3 out of 159 participants miscalculated the size of the second part of an injection when splitting a dose between an end-of-content pen-injector and a new pen-injector	3	<ul style="list-style-type: none"> Multi-purpose dose selector. (b) (4) attributes three participants' use errors to the fact that users can use the dose selector for purposes other than selecting a dose (AXU3, EXT9, EXT11). Users use the dose selector for several purposes: (1) to prime the pen-injector, (2) to check the remaining medication amount, and (3) to set the dose. These participants seemed to confuse the amount of medication they injected using the EOC pen-injector with the amount of medication they used to prime the pen-injector. As such, they likely remembered turning the dose selector but did not remember the specific reason for doing so. 	<p>The following mitigations are implemented for the IFU and ancillary instructional video in relation to identifying how much drug is left in the pen-injector and thus how to determine a dose:</p> <p>Mitigations implemented for the pen:</p> <ul style="list-style-type: none"> The pen-injector cannot set a dose higher than what is left in the pen-injector. If the remaining dose left in the pen-injector is less than 50, the dose counter will stop at the remaining dose. The residual scale on the cartridge holder indicates the approximate volume of drug left in the pen-injector. <p>IFU section 3: "Selecting your dose" describes the following in figures and text:</p> <ul style="list-style-type: none"> "The Xultophy Pen scale will show you how much Xultophy is left in your Pen." 	HF Validation	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
		she injected a dose of 34 using a new pen-injector.				<ul style="list-style-type: none"> To see how much Xultophy is left in your Pen: Turn the dose selector until it stops. The dose counter will line up with the dose that is left in your Pen. If the dose counter shows 50, there is a dose of at least 50 left in your Pen. If the dose counter shows less than 50, the number shown in the dose counter is the total (b) (4) left in your Pen. Figure illustrating how to approximate the remaining drug volume by using the residual scale on the cartridge holder. <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error occurred in: • Task 4: Dose Reversal • Task 6: End of content	Dose setting is altered	<ul style="list-style-type: none"> One participant explained that she was unsure if she had administered the beginning of the dose into the cushion (AXT16). She could not explain why she depressed the dose button just before inserting the 	2 out of 159 participants set a dose and inadvertently depressed the dose button (thereby releasing medication) before inserting the needle into the cushion. These participants did not notice that they altered		<ul style="list-style-type: none"> Blunder. (b) (4) attributes one participant's use error to blunder (AXT16). The participant currently uses two pen-injectors (SoloSTAR® and KwikPen®), suggesting that she knows how to administer a dose and simply blundered during the 	<p>The device user interface of the PDS290 IDegLira pen-injector has been designed with the following mitigations implemented for the pen:</p> <ul style="list-style-type: none"> When a dose is dialled, the dose counter always indicates the dose selected (i.e., the full 	HF Validation	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
(EOC)		<p>needle into the cushion.</p> <ul style="list-style-type: none"> One participant explained that she held the dose selector while attaching the needle, which might have led her to twist the dose selector and press the dose button inadvertently (ENU1). 	<p>the set dose.</p> <p>1 trained, pen-experienced participant (AXT16)</p> <p>1 untrained, pen-naive participant (ENU1)</p>	2	<p>task.</p> <ul style="list-style-type: none"> Natural pen-injector grip. (b) (4) attributes one participant's use error to the fact that it is natural to grip an item at its base (ENU1). The participant held the pen-injector's dose selector while attaching the needle and, as such, the participant altered the dose while twisting the needle onto the pen-injector. 	<p>dose number is shown in the dose window).</p> <ul style="list-style-type: none"> Dose number is large for easy readability. Dose counter print is dark grey on white background for better readability. <p>Several mitigations are also implemented for the IFU and ancillary instructional video in relation to the setting the dose correctly:</p> <ul style="list-style-type: none"> IFU section 3: "Selecting your dose" describes in figures and text how to set the dose correctly. <ul style="list-style-type: none"> Step 10: Turn the dose selector to select the dose you need to inject. The dose pointer should line up with your dose. If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose. The even numbers are printed on the dial. The odd numbers are shown as lines. Figure illustrating how to set a correct dose (even or odd number). IFU section 4: "Giving your 		
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
						<p>injection" emphasises that the user must be able to see the set dose.</p> <ul style="list-style-type: none"> Step 12: "Insert the needle into your skin. Make sure you can see the dose counter. Do not cover it with your fingers; this can stop your injection." <p>Novo Nordisk has implemented and tested the above mitigations and found that further mitigations would not produce significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error occurred in: • Task 4: Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC)	Needle not oriented upward during priming	<ul style="list-style-type: none"> Both participants explained that they did not want to spray the medication on the table or around the room (ANU7, H13). One participant also explained that he typically holds pen-injectors at a 45° angle with the needle upward when priming at work (H13). 	<p>2 out of 159 participants did not orient the needle upward while priming the pen-injector.</p> <p>1 untrained, pen-naive participant (ANU7)</p> <p>1 untrained HCP (H13)</p>	4	<ul style="list-style-type: none"> Test artefact – Perceived courtesy. (b) (4) attributes two participants' use errors to test artefact (ANU7, H13). The participants did not consider spraying medication on the table or across the room to be appropriate during the study. Rather, these participants considered their approach to be courteous. 	<p>Several mitigations were implemented for the IFU and ancillary instructional video in relation to priming the pen-injector before each injection:</p> <p>IFU section 2: "Priming your Xultophy Pen" is a stand-alone section describing the importance of priming and how the pen-injector should be oriented during the priming.</p> <ul style="list-style-type: none"> Step 9: Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". 	HF Validation	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
						<p>The "0" must line up with the dose pointer.</p> <ul style="list-style-type: none"> Figure illustrating how to perform the priming and with an inset figure of a primed pen. <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error occurred in: • Task 4: Dose Reversal	Dose button not held down until dose counter returns to "0"	<ul style="list-style-type: none"> Two participants explained that they assumed they had to press and release the dose button rather than press and hold the dose button to inject the full dose (EXU5, EXU10). One participant explained that she assumed pressing the dose button once would release all the medication immediately (ANU13). She interpreted the click she heard after pressing the dose button to mean the pen-injector had delivered the medication. 	<p>3 out of 159 participants did not hold down the dose button until the dose counter returned to "0" when injecting.</p> <p>2 untrained, pen-experienced participants (EXU5, EXU10)</p> <p>1 untrained, pen-naïve participants (ANU13)</p>	5	<ul style="list-style-type: none"> Dose button behaviour. (b) (4) attributes three participants' use errors to not realising that the pen-injector requires them to press and hold the dose button to administer the entire dose (EXU5, EXU10, ANU13). These participants released the dose button shortly after pressing it. The participants appeared to expect that the dose button had a momentary function, similar to that of an elevator call button or ball-point pen. As such, they expected the button's function to be accomplished with a momentary button press, not recognising that the pen-injector's dynamics called for it to be held down until the pen-injector made a final clicking 	<p>Several mitigations are implemented in relation to holding down the dose button until the dose counter returns to "0".</p> <p>Mitigations implemented for the pen.</p> <ul style="list-style-type: none"> The dose counter shows "0" to indicate when the user can stop pressing the dose button. Supportive click that indicates when the dose counter shows "0". <p>IFU section 4: "Giving your injection" describes the following in figures and text:</p> <ul style="list-style-type: none"> "Make sure you can see the dose counter. Do not cover it 	HF Validation	No
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
					<p>noise.</p> <ul style="list-style-type: none"> Pen-injector's audible feedback. (b) (4) attributes one participant's use errors to the pen-injector's audible feedback when the user presses the dose button (ANU13). The participant inquired that she had injected the full dose because she interpreted the dose counter's clicks to mean that she had completed the injection. 	<p>with your fingers, this can stop the injection."</p> <ul style="list-style-type: none"> "Press and hold down the dose button until the dose counter shows "0". The "0" must line up with the dose pointer. You may then hear or feel a click. "Keep the needle in your skin after the dose counter has returned to "0" and count slowly to 6." Figure showing how to press down the dose button until the dose counter shows "0". <p>Furthermore, the "Giving your injection" section of the IFU emphasises the importance of holding down the dose button until the dose counter returned to "0".</p> <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not provide significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error occurred in: • Task 4:	Does not remove outer or inner needle cap prior to	<ul style="list-style-type: none"> Two participants thought that the needles were not real because they were performing simulated 	5 out of 159 participants did not remove the inner needle cap before injecting.		<ul style="list-style-type: none"> Test artefact – Simulated injection. (b) (4) attributes two participants' use error to test artefact resulting from the 	<p>The following mitigations are implemented for the IFU and ancillary instructional video in relation dose to the removal of</p>	HF Validation	No

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC)	injecting	injections (ENU1, H12). • One participant thought she was using a safety needle that would pierce through a thin membrane on the protective needle cap, rather than require manual removal of two needle caps (ENU2). • One participant explained that she was in a hurry when she performed the task, which led her to forget to remove the inner needle cap (NuN3). Notably, during the subsequent two injection tasks the participant stated that she realised she forgot to remove the inner needle cap and removed both the needle caps prior to injecting. • One participant explained that she did not pay sufficient attention while performing the task, suggesting that she forgot to remove the inner needle cap (NuX2). Notably, during the subsequent two injection tasks the participant stated that she realised she forgot to remove the inner needle cap and removed both needle caps prior to injecting.	3 untrained, pen-naive participants (ENU1, ENU2, NuN3) 1 untrained, pen-experienced participant (NuX2) 1 untrained HCP (H12)	12	simulated injection (ENU1, H12). The participants assumed that they would not use real needles during the usability test and, as such, they did not expect to see a needle when injecting. • Inner needle cap appearance. (b) (4) attributes one participant's use error to the inner needle cap's appearance (ENU2). The inner needle cap's resemblance to a safety needle led the participant to mistake the inner needle cap for a safety cover the needle would pierce through during an injection. • Rushing. (b) (4) attributes one participant's use error to the fact that she was reportedly rushing to complete the task (NuN3). • Overconfidence. (b) (4) attributes one participant's use errors to overconfidence (NuN3). The participant did not read the IFU at all during the first injection task and exuded overconfidence due to her nursing experience. • Forgetfulness. (b) (4) attributes one participant's use error to forgetfulness (NuX2). The participant realised independently during the second simulated injection task that she did not remove the inner needle cap during	the inner and outer needle caps: Mitigations implemented for IFU: • A figure illustrating the different parts of the needle including the outer and inner needle caps • IFU section 1 " <i>Preparing your Xultophy Pen</i> " describes in figures and text emphasised in bold how to remove the inner and outer needle caps stepwise before injection • " <i>Pull off the outer needle cap. Do not throw it away.</i> " • " <i>Pull off the inner needle cap and throw it away</i> " In a real life setting, this use error would be unlikely to occur since patients would realise that the needle did not pierce their skin due to the lack of tactile sensation from the needle entering their skin. Therefore, it is assessed that the risk of not removing the inner and/or outer needle cap(s) has been reduced to as low as reasonably practicable and further mitigations would not provide significant improvements.		
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
					the first task, suggesting that she forgot to do so.			
Use error occurred in: • Task 4: Dose Reversal • Task 5: Normal Injection • Task 6: End of content (EOC)	Did not remove needle after use.	• Two participants only remove their current pen-injector's needle after every third injection (i.e. once per day) (AXU7, AXU12). They explained that they do not consider this approach to be unsafe because they are sole users of their pen-injector. As such, these participants did not remove the used needle from the pen-injector after injecting. • One participant removes his current pen-injector's needle only after the pen-injector is empty (AXU15). As such, this participant did not remove the used needle from the pen-injector after injecting.	Three out of 159 participants did not remove the used needle from the pen-injector after injecting. Rather, they replaced the pen-injector's cap and stored the pen-injector with the needle attached. 3 untrained, pen-experienced participants (AXU7, AXU12, AXU15)	7	• Habit. (b) (4) attributes three participants' use errors to habit (AXU7, AXU12, AXU15). The participants typically do not remove the pen-injector's needle after every injection.	Several mitigations are implemented for the needles, IFU, and ancillary instructional video in relation to proper needle use: Mitigations implemented for the needle: • Needles are clearly marked as single use devices. IFU section 1: " <i>Preparing your Xultophy Pen</i> " highlights the importance of using a new needle. • " <i>Always use a new needle for each injection to help ensure sterility and prevent blocked needles.</i> " • " <i>Select a new needle. Pull off the paper tab from the outer needle cap.</i> " IFU section 2: " <i>Priming your Xultophy Pen</i> " describes the importance of priming the Xultophy pen-injector prior to each injection to ensure flow through the needle. IFU section 4: " <i>Giving your injection</i> " describes how the needle must always be removed	HF Validation	No

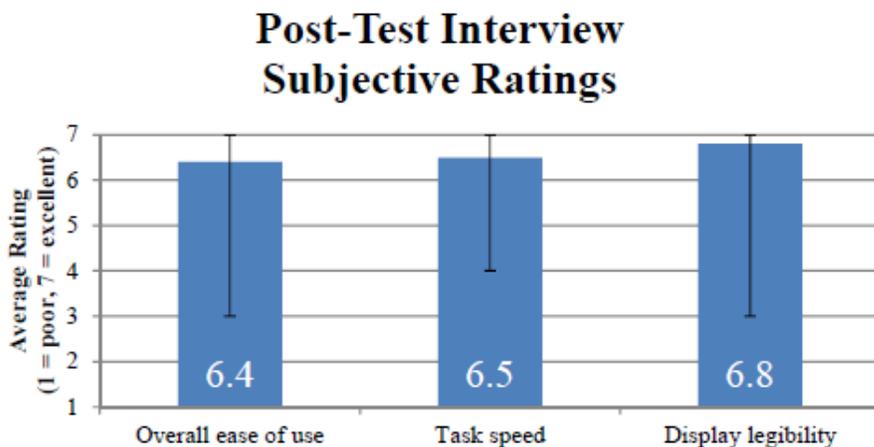
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
						<p>after use.</p> <ul style="list-style-type: none"> • <i>Step 15: "Carefully remove the needle from the Pen and throw it away.</i> • <i>Do not recap the needle. Recapping the needle can lead to needle stick injury.</i> • <i>If you do not have a sharps container, carefully slip the needle into the outer needle cap. Safely remove the needle and throw it away as soon as you can.</i> • <i>Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen."</i> <p>IFU section 5: "After your injection" describes how the used needle should be discarded following current FDA guidelines.</p> <p>Novo Nordisk has tested the mitigations implemented and found that further mitigations would not produce significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		
Use error	Performs priming when	<ul style="list-style-type: none"> • One participant 	1 out of 159 participants dialled the pen-injector to		<ul style="list-style-type: none"> • Multi-purpose dose selector. 	Several mitigations were implemented for the IFU and the	HF	No
Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
<p>occurred in:</p> <ul style="list-style-type: none"> • Task 4: Dose Reversal 	intended dose is set and does not reset dose	<p>explained that she did not think the pen-injector would decrement the dose counter during priming (ENT8). She explained that she did not recall the nurse trainer emphasising setting a priming dose of 2 during training and, as such, she did not remember that she needed to prime the pen-injector using a dose of 2 and then set the full dose amount.</p>	<p>the correct dose, expelled some of the fluid to prime, and then injected the remaining dose without resetting the dose counter to the target dose, resulting in an underdose.</p> <p>1 trained, pen-naïve participant (ENT8)</p>	1	<p>(b) (4) attributes one participant's use error to the fact that users can use the dose selector for purposes other than selecting a dose (ENT8). Users use the dose selector for several purposes: (1) to prime the pen-injector, (2) to check the remaining medication amount, and (3) to set the dose. This participant seemed to think that the pen-injector would detect that she wanted to prime, rather than deliver a dose, likely due to the fact that users turn the dose selector to dial both the priming and injection doses.</p>	<p>ancillary instructional video in relation to priming the pen-injector and setting the dose:</p> <ul style="list-style-type: none"> • By design, two prominent, stand-alone sections in bold text: Section 2: "Priming your Xultophy Pen" and Section 3 "Selecting your dose" are positioned in the IFU to distinguish the two important steps: priming the pen-injector and then selecting the dose. • Specifically, IFU section 2 "Priming your Xultophy Pen" describes the priming process with simple detail. <ul style="list-style-type: none"> • <i>Step 7: "Turn the dose selector to (b) (4) (accompanied by a figure illustrating (b) (4) has been selected).</i> • <i>Step 8 "Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top" (accompanied by a figure illustrating the tapping process).</i> • <i>Step 9 "Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the</i> 	Validation	

Study Tasks	Use errors – Observation of user	Use Errors – Subjective feedback from user	Participants committing the user error (ID)	Number of error	Possible root causes	Mitigation Strategy prior to UT94	Evaluation of mitigation strategy	Re-design needed ?
						<p><i>dose pointer.</i>"</p> <ul style="list-style-type: none"> • Figure illustrating how to perform the priming and with an inset figure of a primed pen. • IFU section 3: "<i>Selecting your dose</i>" describes in figures and text how to set the dose correctly. <ul style="list-style-type: none"> • <i>Step 10: "Turn the dose selector to select the dose you need to inject. The dose pointer should line up with your dose.</i> • <i>If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.</i> • <i>The even numbers are printed on the dial.</i> • <i>The odd numbers are shown as lines."</i> • Figure illustrating how to set a correct dose (even or odd number). <p>Novo Nordisk has implemented and tested the above mitigations and found that further mitigations would not produce significant improvements. Therefore, it is assessed that the risk is reduced to as low as reasonably practicable.</p>		

Post-Task Interview and Subjective Assessment

During the post-test interview, the test administrator asked each participant (except pharmacists) to rate each aforementioned characteristic. In total, 156 participants rated each characteristic. Ratings were not collected from three non-pharmacist participants due to time constraints (ANT2, AXT15, EXT5).

[Figure 17](#) presents the average rating for each criterion. The ratings are ordered from left to right in ascending order (i.e., lowest average rating to highest average rating).



IFU Evaluation Exercise

^{(b) (4)} assessed the 63 trained participants' and six of the untrained participants' understanding of the IFU by asking them to read and interpret two IFU excerpts after performing the hands-on tasks. After reading each excerpt, participants summarised the content in their own words and answered specific questions related to the content. See Section [19](#) for the two IFU excerpts and follow-up questions.

All 69 participants who participated in the IFU Evaluation correctly interpreted the IFU excerpts and, therefore, understood:

- The dose equals the number shown in the dose counter
- How to use the dose selector and dose pointer to set the pen-injector to the target dose

APPENDIX D. REGULATORY HISTORY

During the review process, clinical team questioned the safety and clinical impact of each product component and expressed concern regarding Novo Nordisk's ability to provide data to support the safe use of this product if allowed onto the market. The clinical team is also concerned about the clinical benefit versus risk associated with the use of a multi-ingredient product that contains liraglutide at doses that have been determined to be below the clinically effective dose while still causing side effects. Novo Nordisk provided several submissions in relation to this review:

- On November 21, 2012, Novo Nordisk submitted the Human Factors Usability Test Protocol for insulin degludec and liraglutide for review under IND 109121.
- On February 1, 2013, as part of the Type C meeting written responses provided to Novo Nordisk, DMEPA provided recommendations on the HF protocol against the use of the terminology "dose step" for dosing in the labeling. They were advised to express the dose of medication in degludec unis/liraglutide milligrams since the medication should be ordered as "insulin degludec and liraglutide". In addition, DMEPA provided recommendations for other identified deficiencies in the protocol.
- On July 23, 2014, as part of the Type C meeting written responses provided to Novo Nordisk, DMEPA provided more recommendations on the HF protocol regarding the dose terminology and HF protocol submitted for review.
- On September 14, 2015, Novo Nordisk submitted the Human Factors Summative Usability Test results for insulin degludec and liraglutide for review under NDA 208583.
- On February 16, 2016, in the agenda for the Mid-Cycle Communication meeting scheduled for February 18, DMEPA recommended that Novo Nordisk submit data to support prescribers' ability to appropriately prescribe and dose the medications since this information was not provided in the original submission.
- On February 18, 2016, DMEPA sent an IR to Novo Nordisk regarding the HF study results to request reorganization of the results to aid in our review.
- During the February 18 meeting, Novo Nordisk agreed to develop a protocol for a labeling comprehension study for prescribers and submit to FDA for review prior to conducting the study. In addition, they agreed to reformat the study results for our review.
- On February 26, 2016, Novo Nordisk submitted the reorganized results of the HF study results for review.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARIANE O CONRAD
04/18/2016

QUYNHNHU T NGUYEN
04/18/2016

LUBNA A MERCHANT on behalf of YELENA L MASLOV
04/18/2016

LUBNA A MERCHANT
04/18/2016

LABELING COMPREHENSION STUDY PROTOCOL REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 12, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology (DMEP)
Application Type and Number:	NDA 208583
Product Name and Strength:	Xultophy (insulin degludec and liraglutide) injection, 300 units insulin degludec and 10.8 mg liraglutide per 3 mL pen (100 units insulin degludec and 3.6 mg liraglutide per mL)
Product Type:	Multi-ingredient Product and Combination Product
Rx or OTC:	RX
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	March 14, 2016
OSE RCM #:	2016-651
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Acting Associate Director for Human Factors	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review evaluates the protocol for labeling comprehension study for Xultophy (insulin degludec and liraglutide) Injection that the Novo Nordisk submitted on March 14, 2016. The Agency requested this information during the mid-cycle meeting with Novo Nordisk on February 18, 2016 to help evaluate whether prescribers will be able to appropriately prescribe and dose Xultophy, make dose titrations and convert patients to Xultophy from other therapies since this product has unique risks due to combination of insulin with a GLP-1 agonist.¹

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Labeling Comprehension Study Protocol	C
Labeling	D

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We agree with the proposed methodology in terms of objectives, participants, and simulated use environment (See Appendix C for these details).

However, we do not agree with the proposed materials provided and moderator script in terms of providing only Dosage and Administration Section of PI and directing participants to read specific relevant sections of the Dosage and Administration Section in order to be able to prescribe the product correctly as it introduces bias to the study. Specifically, the study proposes to direct prescribers to Dosage and Administration Section and Table 1 of Dosage and Administration Section that contains information regarding composition of the product. After directing prescribers to the relevant Section or Table, the moderator provides a case-based scenario or asks questions regarding the number of units of insulin degludec and milligrams of liraglutide contained in the product. This exercise does not mimic actual use where prescribers

¹ Conrad, A. Label and Labeling and Human Factors Results Review for Xultophy (insulin degludec and liraglutide) NDA 208583. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); RCM # 2015-2086.

would be expected to read the PI and interpret the information on their own without specific directives. Thus, in Section 4.1 we provide recommendations to address this issue.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the comprehension labeling protocol and we agree with the proposed methodology in terms of objectives, participants, and simulated use environment. However, we disagree with the proposed methodology in terms of proposed moderator script. Thus, we provide recommendations in section 4.1 below to ensure the comprehension labeling protocol represents real world environment.

4.1 RECOMMENDATIONS FOR THE NOVO NORDISK

We recommend Novo Nordisk implements the following changes in the protocol prior to initiation of the labeling comprehension study. The Applicant does not need to submit the revised protocol to the Agency provided they understand and agree with following recommendations:

1. Materials Provided and Moderator Script

- a. We recommend that you provide the entire PI instead of only supplying the Dosage and Administration Section to simulate real use of the document and we recommend that you do not specifically direct participants to read the Dosing and Administration Section during the case-based scenarios. For example, you state “Use the Dosage and Administration section of the Physician Insert to determine a starting dose of Xultophy...” for Task 1 and “Explain in your own words how to titrate... based on Dosage and Administration Section of Physician Insert” for Task 8. Providing participants with only Dosage and Administration Section of the PI and directing participants to read it to prescribe the correct dose of the product does not mimic actual use and may not inform the review of the product in terms of whether prescribers can find and comprehend the information in the labeling.
- b. We recommend you do not direct participants to read Table 1 in Dosage and Administration Section to help determine the amount of active ingredients in specific doses of the product. For example, you state “Use Table 1 in Dosage and Administration Section of the Physician Insert to determine the number of units of insulin Degludec and milligrams of Liraglutide in Xultophy dose of 10” in Task 2. In actual use, prescribers would have to find this information in the PI by themselves. Therefore, we encourage you to revise the scenarios to delete these types of directives.
- c. We recommend that you do not direct participants to read the PI. The PI should be available for use at the physician’s discretion. Also, make sure to collect data

- regarding the number of participants that refer to the PI and those that do not use the PI for dosing instructions. In addition, collect the number of correct and incorrect responses during the tasks and separate that data based on participant use of the PI to facilitate comparison of prescribing performance.
- d. We recommend that you add a use scenario to assess the prescribers' comprehension regarding the dose limitation of this product and identify when the product is not appropriate for patients that need higher doses of insulin degludec. For example, include a patient scenario where the patient is currently taking 80 units of insulin degludec daily and ask participants to initiate Xultophy.
 - e. Please ensure that participants complete each test scenario.
 - f. Provide any subjective feedback provided by participants regarding the tasks.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xultophy that Novo Nordisk submitted on September 14, 2015 and March 14, 2016.

Table 2. Relevant Product Information for Xultophy			
Initial Approval Date	N/A		
Active Ingredient	Insulin degludec and Liraglutide		
Indication	Type 2 diabetes mellitus		
Route of Administration	Subcutaneous		
Dosage Form	Injection		
Strength	100 units and 3.6 mg per mL		
Dose and Frequency	Individualized dosing once daily		
How Supplied	3 mL prefilled pen containing 300 units insulin degludec and 10.8 mg liraglutide		
Storage	Prior to first use	After first use	
	Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
	Until expiration date	21 Days	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 30, 2016, we searched the L:drive and AIMS using the terms “degludec liraglutide” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous review², and we confirmed that our previous recommendations were implemented.

² Vee, S. Human Factors Study Protocol Review for Insulin Degludec and Liraglutide Injection (IND 109121). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Jan 30. RCM # 2012-2754.

APPENDIX C. LABELING COMPREHENSION STUDY PROTOCOL

C.1 Study Design

2 Test Objective

The objective of the labeling comprehension test is to assess if prescribers are able to understand and interpret the draft PI – Dosage and Administration section to appropriately:

- Prescribe and dose IDegLira
- Make dose titrations
- Convert patients to IDegLira from other therapies

3 Test Participants

3.1 Test participant sample

This test will include the user group who will prescribe and dose IDegLira, make dose titrations and convert patients to IDegLira from other therapies, namely prescribing HCPs. Novo Nordisk consider the HCP user group to include the following subgroups:

- Diabetes Specialists (i.e. Endocrinologists)
- Primary Care Physicians (non-specialists)
- Physician Assistants
- Nurse Practitioners

Each sub-group will include 5 participants.

4.2 Test Environment

In this test, an environment similar to an HCP's office will be simulated.

Administer Labeling Comprehension - Knowledge Tasks

Scenario 1 - Initiation of Xultophy® for a Type 2 diabetic patient currently treated with oral anti-diabetic agents

The scenario will start by introducing the participant to Patient Profile A, Mr. Clark.

Patient Profile A:

Mr. Clark is 65 years old and diagnosed with type 2 diabetes. He is currently treated with oral anti-diabetic agents – Metformin.

Task 1

After the introduction, the participant will be informed that Mr. Clark shall be initiated onto Xultophy®.

I would like you to imagine that you have decided to initiate Mr. Clark onto Xultophy®.

The participant is asked to read out loud Task card 1 and perform the task as written.

Task card 1:

Use the Dosage and Administration section of the Physician Insert to determine a starting dose of Xultophy® for Mr. Clark and write the starting dose on the card provided.

When the task has been performed the moderator will ask the participant the following questions:

Questions:

- *What starting dose have you determined?*
- *What did you base your decision on? Please point out the text you used.*

If the participant defines another starting dose than recommended in the draft PI the moderator will ask the following question:

- *Please clarify why this is the appropriate starting dose for Mr. Clark?*

The moderator will thank the participant for completing the task and move on to the next task.

Task 2

The participant is asked to read out loud Task card 2 and perform the task as written.

Task card 2:

Use Table 1 in the Dosage and Administration section of the Physician Insert to determine the units of insulin degludec and milligrams of liraglutide in a Xultophy® dose of 10.

When the participant is ready the moderator will ask the following questions:

Questions:

- *How many units of insulin degludec does a dose of 10 contain?*
- *How many milligrams of liraglutide does a dose of 10 contain?*

If the participant defines other units and milligrams than listed in table 1 in the draft PI the moderator will ask the following questions:

- *What information in the insert did you use to determine those numbers?*
- *Please clarify why?*

The moderator will thank the participant for completing the task and move on to the next scenario.

Scenario 2 – Conversion to Xultophy[®] for a Type 2 diabetic patient currently treated with GLP-1 receptor agonists

The scenario will start by introducing the participant to Patient Profile B, Mrs. Lee.

Patient Profile B:

Mrs. Lee is 53 years old and diagnosed with type 2 diabetes. She is currently treated with injectable GLP-1 medication once daily, in the morning.

Task 3

After the introduction, the participant will be informed that Mrs. Lee shall be initiated onto Xultophy[®].

I would like you to imagine that you have decided to initiate Mrs. Lee onto Xultophy[®].

The participant is asked to read out loud Task card 3 and perform the task as written.

Task card 3:

Use the Dosage and Administration section of the Physician Insert to determine a starting dose of Xultophy[®] for Mrs. Lee and write the starting dose on the card provided.

When the task has been performed the moderator will ask the participant the following questions:

Questions:

- *What starting dose have you determined?*
- *What did you base your decision on? Please point out the text you used.*

If the participant defines another starting dose than recommended in the draft PI the moderator will ask the following question:

- *Please clarify why this is the appropriate starting dose for Mrs. Lee?*

The moderator will thank the participant for completing the task and move on to the next task.

Task 4

The participant is asked to read out loud Task card 4 and perform the task as written.

Task card 4:

Use Table 1 in the Dosage and Administration section of the Physician Insert to determine the units of insulin degludec and milligrams of liraglutide in a Xultophy[®] dose of 16.

When the participant is ready the moderator will ask the following questions:

Questions:

- *How many units of insulin degludec does a dose of 16 contain?*
- *How many milligrams of liraglutide does a dose of 16 contain?*

If the participant defines other units and milligrams than listed in table 1 in the draft PI the moderator will ask the following questions:

- *What information in the insert did you use to determine those numbers?*
- *Please clarify why?*

The moderator will thank the participant for completing the task and move on to the next task.

Task 5

The participant is asked to read out loud Task card 5 and perform the task as written.

Task card 5:

Use the Dosage and Administration section of the Physician Insert to determine if you are required to change anything in Mrs. Lee's current diabetes treatment and write it as a note to the patient on the card provided.

When the task has been performed the moderator will ask the participant the following questions:

Questions:

- *What is your decision?*
- *What did you base your decision on? Please point out the text you used.*

If the participant does not discontinue the current treatment as recommended in the draft PI the moderator will ask the following question:

- *Please clarify why you made this decision?*

The moderator will thank the participant for completing the task and move on to the next scenario.

Scenario 3 – Conversion to Xultophy[®] for a Type 2 diabetic patient currently treated with basal insulin

The scenario will start by introducing the participant to Patient Profile C, Mr. Smith.

Patient Profile C:

Mr. Smith is 48 years old and diagnosed with type 2 diabetes. He is currently treated with basal insulin once daily. Mr. Smith injects 20 units of insulin in the evening.

Task 6

After the introduction, the participant will be informed that Mr. Smith shall be initiated onto Xultophy[®].

I would like you to imagine that you have decided to initiate Mr. Smith onto Xultophy[®].

The participant is asked to read out loud Task card 6 and perform the task as written.

Task card 6:

Use the Dosage and Administration section of the Physician Insert to determine a starting dose of Xultophy[®] for Mr. Smith and write the starting dose on the card provided.

When the task has been performed the moderator will ask the participant the following questions:

Questions:

- *What starting dose have you determined?*
- *What did you base your decision on? Please point out the text you used.*

If the participant defines another starting dose than recommended in the draft PI the moderator will ask the following question:

- *Please clarify why this is the appropriate starting dose for Mr. Smith?*

The moderator will thank the participant for completing the task and move on to the next task.

Task 7

The participant is asked to read out loud Task card 7 and perform the task as written.

Task card 7:

Use the Dosage and Administration section of the Physician Insert to determine if you are required to change anything in Mr. Smith's current diabetes treatment and write it as a note to the patient on the card provided.

When the task has been performed the moderator will ask the participant the following questions:

Questions:

- *What is your decision?*
- *What did you base your decision on? Please point out the text you used.*

If the participant does not discontinue the current treatment as recommended in the draft PI the moderator will ask the following question:

- *Please clarify why you made this decision?*

The moderator will thank the participant for completing the task and move on to the next task.

Scenario 4 - Titration of Xultophy[®] for type 2 diabetic patient

Task 8

The participant is asked to read out loud Task card 8 and perform the task as written.

Task Card 8:

Explain in your own words how to titrate a type 2 diabetic patient on Xultophy[®] based on the Dosage and Administration section of the Physician Insert.

When the participant is ready the moderator will ask the following questions:

Questions:

- *Please explain in your own words how to titrate a patient on Xultophy[®].*
- *What did you base your decision on? Please point out the text you used.*

If the participant does not describe titration as recommended in the draft PI the moderator will ask the following question:

- *Please clarify why you made this decision?*

The moderator will thank the participant for completing the task and wrap up the session.

APPENDIX D. DOSAGE AND ADMINISTRATION SECTION FROM PRESCRIBING INFORMATION

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following information from the Xultophy PI submitted by Novo Nordisk on March 14, 2016.

Dosage and Administration Section of PI

2 DOSAGE AND ADMINISTRATION

(b) (4)



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immediately following this page

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ARIANE O CONRAD
04/15/2016

QUYNHNHU T NGUYEN
04/15/2016

LUBNA A MERCHANT on behalf of YELENA L MASLOV
04/15/2016

LUBNA A MERCHANT
04/15/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

DATE: February 25, 2016

TO: Suong Tran , OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
WO21 RM2518
Suong.Tran@fda.hhs.gov

Anika Lalmansingh, OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
WO75, RM4631
anika.lalmansingh@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: LT Viky Verna, Combination Product Branch Lead, REGO/DMQ/
OC/CDRH, WO-66, Room 3435

Viky

Verna -A

Digitally signed by Viky Verna -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Viky Verna -A,
0.9.2342.19200300.100.1.1=2000
495623
Date: 2016.03.01 12:23:26 -05'00'

From: Christopher J Brown, P.E., REGO/DMQ/ OC/CDRH
WO-66, Room 3428

Applicant: Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark
FEI# 3000151819

Application # NDA 208583

Consult # ICC1600071 addresses firms response to deficiencies from ICC1500522

Product Name: IDegLira pen-injector for use with Insulin degludec and liraglutide

Inspection Needed: No - **Recommendation Date:** 11/30/2015

Documentation Review: No Additional Information Required

Final Recommendation: **APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208583.

PRODUCT DESCRIPTION

PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 ml cartridge with drug, see Figure 1. According to the firm the drug is not in contact with the device. The device is intended to function with a standard needle thread 1 or a needle with a bayonet coupling. The intended use is as a pen-injection delivery system for use with Insulin degludec and liraglutide. The drug is intended to improve glycemic control in adults with type 2 diabetes mellitus. Physical characteristics:

- Length and thickness: Approximately 138 mm without cap and 156 mm with cap. Thickness is approximately Ø19 mm
- Dose button displacement: Approximately 2 mm, non-rotating dial during injection
- [redacted] (b) (4)
- Components: [redacted] (b) (4) 1 cartridge
- [redacted] (b) (4)
- End-of-dose click

According to the firm, the PDS290 IDegLira pen-injector was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Needle-based injection systems for medical use - requirements and test methods – Part 1: Needle-based injection systems).

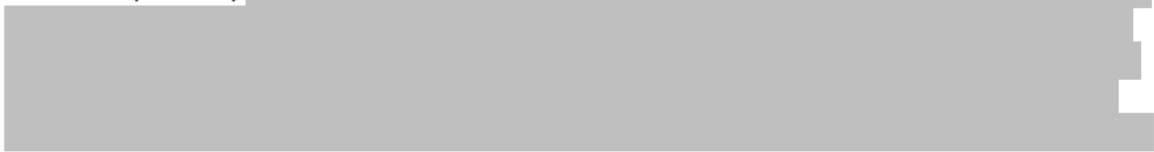


Figure 1. Image PDS290 IDegLira pen-injector

The pen mechanism can be considered as two interacting systems:

- Dose system
- Dial system

During dose setting, the dial mechanism consisting of dial [redacted] (b) (4) rotates sequentially [redacted] (b) (4)



To deliver a set dose, the dose button [redacted] (b) (4) is pushed by the user. [redacted] (b) (4)



(b) (4)



(b) (4)



Figure 2. Exploded View of Injector Pen

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this page

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of NDA 208583 and has the following recommendations:

The application for IDegLira pen-injector for use with Insulin degludec and liraglutide NDA 208583 is approvable from the perspective of the applicable Quality System Requirements:

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
- (2) There were no facility inspections for compliance with applicable Quality System

Requirements needed for approvability determination.

Christopher J. Brown -S
2016.03.03 18:10:11 -05'00'

Christopher J Brown, P.E.

Prepared: CJBrown: 11/30/2015, 02/25/2016
Reviewed: VVerna 12/3/2015; 12/7/15; 3/1/2016

CTS No.: ICC1500522
NDA 208583

Review Cycle Meeting Attendance:
November 02, 2015

Inspectional Guidance

Firm to be inspected:

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

FEI Number: 3000151819

CDRH recommends that the next routine inspection of the firm listed above covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Christopher J Brown, P.E.

Mechanical Engineer,

Respiratory, ENT, General Hospital and Ophthalmic (REGO)

Division of Manufacturing Quality (DMQ)

Office of Compliance, WO66 RM 3428

Phone: 301-796-0380

Secondary Contacts (if Primary is unavailable and a timely answer is required)

LT Viky Verna,

Combination Product Branch Lead,

REGO, DMQ

Office of Compliance, WO66 RM 3435

Phone: 301-796- 5770

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

ANIKA A LALMANSINGH

03/05/2016

Uploading on behalf of Christopher J Brown



Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum of NDA - Initiated in Vivo Bioequivalence Inspection Assignment

Date: January 21, 2016
From: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
To: ORAHQDFFIIIOBBIMO@fda.hhs.gov
Subject: Premarket Original BIMO Inspection Assignment

Preannounce: No

Compliance Program: 7348.001
PAC Code: 48001A
Priority: High
Operation Code: 11 (Foreign Inspection)
31 (Sample Collection)
41 (Sample Analysis)

Application Number: NDA 208583
Product Name: Insulin degludec/liraglutide (Xultophy)

Sponsor: Novo Nordisk Inc.
POC: Rick Spring
Address: 800 Scudders Mill Rd., Plainsboro, NJ 08536
Telephone No.: 609-987-5046
Fax No.: 609-580-2355
Email Address: rspr@novonordisk.com

Study/Protocol Number: NN9068-4026

Inspection Due Date: 5/10/2016
EIR Due Date: 6/10/2016

Center Participation: No
Joint Regulatory Agency Participation: No

Establishment(s) for inspection	FEI Number	FACTS Number
PROFIL Institute für stoffwechselforschung GmbH POC: Dr. med. Christoph Kapitza Address: Hellersbergstraße 9,	Refer to ORA	11603460

D-41460 Neuss, Germany Telephone No.: +49 2131 4018-157 Email: christoph.kapitza@profil.com		
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Note	<p>Please contact Dr. Arindam Dasgupta prior to the beginning of the inspection at Arindam.dasgupta@fda.hhs.gov or (301) 796-3326 to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.</p> <p>Please follow the compliance program with emphasis on the specific instructions in the memorandum.</p> <p>If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately.</p> <p>At the end of the inspection, send an e-mail to Arindam.dasgupta@fda.hhs.gov and CDER OSIS BEQ (CDER-OSIS-BEQ@fda.hhs.gov) with any inspection findings. If a form FDA-483 is issued, send to CDER OSIS BEQ or fax it to the OSIS Project Specialist at (301) 847-8748. Forward the EIR and exhibits to CDER OSIS BEQ or</p> <p>Ms. Dinah Miller Project Specialist FDA/CDER/OTS/OSIS WO51 RM5333 HFD-45 10903 New Hampshire Ave. Silver Spring, MD 20993-0002</p> <p>Important: Forward any post-inspection correspondence from the establishment to Arindam.dasgupta@fda.hhs.gov and CDER OSIS BEQ as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.</p>
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BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct the inspection of the clinical portion of the following clinical bioequivalence (BE) study. Background material is available in ECMS under the ORA folder.

Do not reveal the study to be inspected, drug names, or the study investigator to the site prior to the start of the inspections. The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of completed sections A, B, and C of this memo to the OSIS POC.

Study #1: NN9068-4026
Study Title: A trial to demonstrate bioequivalence between two insulin degludec/liraglutide formulations, B5 and V2, in healthy subjects
Investigator: Dr. med. Christoph Kapitza
of Subjects: 50 (32 M/18 F)

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Refer to Table 1 for an example. Please do spot checks to verify that the lot number(s) listed in the table match the reserve samples in the clinical site storage.

Table 1

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	Aspirin + Dipyridamole Capsules	Fast	XXXX	USFDA	Dec 24-Dec 31, 2014	At Site	300 for test, 200 for reference	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX	Third Party	two kits	XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX	Not retained	two bottle for test, two bottles for reference	XXXX and XXX

SECTION A - BLINDING CODES

RANDOMIZATION OR BLINDING: Because this is a randomized and blinded bioequivalence study, it is necessary to break the blind and use the treatment codes to verify and confirm that the subjects were dosed according to the treatment randomization schedule. Please verify the following during the inspection:

- Collect a complete copy of the study randomization schedule and blinding code for the site and the dosing logs from the firm/clinical investigator. Unseal the blinding code and note the date and your initials on the envelope. Exhibit a photocopy of the complete randomization schedule and blinding code in the EIR, and include a photocopy with the reserve samples sent to DPA. If the blinding code was already unsealed, determine the reasons why. If a sealed blinding code is not available, please notify the DBGLPC POC immediately.
- Unblind the treatment codes (e.g., test or reference article) on the Case Report Forms, and use the treatment codes to verify that 100% of the subjects were dosed according to the study randomization schedule. Please scratch off the label covers on the CRF, if needed, to reveal the codes. Document the date and time that you unblind the treatment codes, if applicable.
- Collect a written statement or affidavit to confirm that the blinding code remained in the possession of the clinical site prior to dosing the initial subject and until the FDA inspection, and that the subjects remained blinded throughout the study. In the event the study related documentation is stored at an alternate site, verify by affidavit that the alternate site is independent of the applicant, packager and manufacturer.

SECTION B - RESERVE SAMPLES

Reserve samples must be collected for study NN9068-4026. In addition, verify that the lot numbers on the reserve sample containers match those in the study report.

Because these bioequivalence studies are subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and

retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the OSIS POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION C - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

- Confirm that informed consent was obtained for all subjects enrolled in the study.
- Audit the study records for all subjects enrolled in Study NN9068-4026.
- Compare the study report submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records,

inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to commencement of the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to CDER OSIS BEQ, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC and CDER OSIS BEQ as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER OSIS BEQ, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

OSIS POC: Arindam Dasgupta, Ph.D.
Deputy Division Director
Office of Study Integrity and Surveillance (OSIS)
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

The endorsed EIR should be sent to the following:

If electronic: **CDER OSIS BEQ**

If paper:

Ms. Dinah Miller
Project Specialist
FDA/CDER/OTS/OSIS

WO51 RM5333 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Email cc:

ORAHQ/OMPTO/DMPTI/BIMO/Bukowczyk/Arline/Montemurro/Colon
OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Kadavil/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Cho
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: CGC 12/30/2015, 1/14/16, 1/21/2015 (revisions)
Edit: CB 1/13/2016

ECMS (OSIS): Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/PROFIL Institute für stoffwechselforschung GmbH, Neuss, Germany/NDA 208583_Insulin degludec/liraglutide

ECMS (ORA):

Cabinets/ORA/OMPTO/BIMO/FY'16/CDER/DMPTI/11603460_NDA 208583

OSI file #: BE7029 (NDA 208583)

FACTS: 11603460

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/s/

CHING-JEY G CHANG
01/21/2016

CHARLES R BONAPACE
01/21/2016

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/21/2015

TO: Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

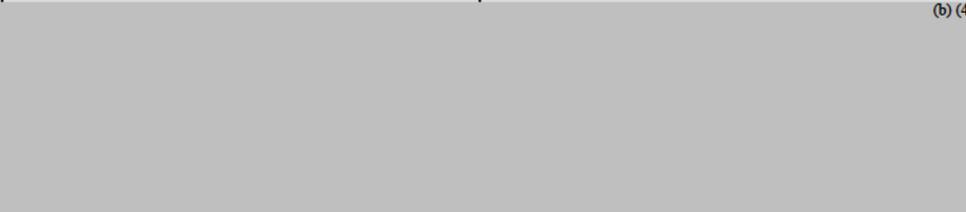
RE: NDA 208583

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	 (b) (4)	
Analytical		

Nicola M.
Nicol -S

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DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001347
020, cn=Nicola M. Nicol -S
Date: 2015.12.22 11:36:00 -05'00'

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/s/

NICOLA M FENTY-STEWART
12/22/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208583	NDA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Xultophy Established/Proper Name: insulin degludec and liraglutide [rDNA origin] injection Dosage Form: solution for injection Strengths: 100U insulin degludec, 3.6 mg liraglutide/mL		
Applicant: Novo Nordisk Inc. Agent for Applicant (if applicable):		
Date of Application: September 12, 2015 Date of Receipt: September 14, 2015		
PDUFA Goal Date: September 14, 2016	Action Goal Date (if different):	
Filing Date: November 13, 2015	Date of Filing Meeting: October 28, 2015	
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input checked="" type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 109121 insulin degludec/liraglutide
IND 076496 insulin degludec
IND 061040 liraglutide

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.				
Are the established/proper and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			X	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2)	YES	NO	NA	Comment

(NDAs/NDA Efficacy Supplements only)																				
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:		<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 		<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 		<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>		Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3542a patent forms in M1																
If yes , # years requested:																				

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
Pediatrics	YES	NO	NA	Comment
<u>PREA</u>				
Does the application trigger PREA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>				

²

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Will be submitted separately
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	In module 1.16
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Will request it in 74 day letter
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 9, 2010	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): June 16, 2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): N/A	<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 2, 2015

BACKGROUND:

NDA 208583 insulin degludec and liraglutide is a fixed dose combination product in a pre-filled pen. Liraglutide was approved under NDA 22341 on January 25, 2010. Insulin degludec approved under NDA 203314 Tresiba on September 25, 2015. This fixed dose combination product came in as an NME, but is now just a new combination, but will still be reviewed under The Program.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Marisa Petruccelli	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Lisa Yanoff		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy			
Clinical	Reviewer:	Tania Condarco	Y
	TL:	Lisa Yanoff	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sang Chung	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Anna Kettermann	Y
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Dave Carlson	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
	RBPM:	Anika Lalmansingh	
• Drug Substance	Reviewer:	N/A	
• Drug Product	Reviewer:	Xavier Ysern	
• Process	Reviewer:	Peter Krommenhoek	
• Microbiology	Reviewer:	Peggy Kriger	
• Facility	Reviewer:	Peter Krommenhoek	
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
Safety	RPM	Elisabeth Hanan	
	TL	Jenn Pippins	
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Aman Sarai	
	TL:	Marcia Britt Williams	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Mishale Mistry	Y
	TL:	Yelena Maslov	
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	Y
	TL:	Naomi Redd	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro	Y
	TL:	Janice Pohlman	
Other reviewers/disciplines			
• OCP	Reviewer	Patricia Love	Y
	TL	Bindi Nikhar	
• CDRH	Reviewer	Ryan McGowan	Y
	TL	Alan Stevens	
• DEPI	Reviewer:	Yandong Qiang	Y
	TL:	Patricia Bright	
• DPV	Reviewer:	Debra Ryan	Y
		Ali Niak	Y
	TL:	Christian Cao	Y
Other attendees	Christopher Brown, CDRH Compliance		Y
	Terrolyn Thomas, OSE		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments: Tania Condarco pointed out language in the labeling regarding ‘flexibility in timing’ that may be something to discuss during the review. Lisa Yanoff raised the issue of how we should review safety data with adjusted statistical analyses with respect to Simpson’s paradox.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: OSI has selected three sites for each of the two pivotal Phase 3 trials: 3697 and 3912.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: Jean-Marc Guettier will discuss with the Office whether this application should have an AC meeting. Though both components of this product are approved, this type of fixed-ratio product is new, and there are questions about:</p> <ol style="list-style-type: none"> the risk-benefit balance of a fixed dose product where one component is not providing benefit until a certain dose, but is still exposing subjects to risk in the meantime. the logic in starting a patient on two products when they could get control under just one. 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? BE study (Trial 4026) is pivotal bridging study for Phase 3 trial and intended commercial formulation. 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Anna Kettermann said that there would be two comments for the applicant in the 74 day letter regarding the MMRM models and SAS codes provided and the collection and inclusion of post-rescue data.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: A consult to DPMH for PLLR may not be necessary; to be determined after applicant provides supporting information for PLLR section.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Because both components of this product are approved, CMC will not re-review the substances. CMC will defer to Clin Pharm on whether the commercial formulation is acceptable. The CMC review won't include the device evaluation, but will include the CDRH facilities memo. Once this memo is received, OPQ will arrange for inspections per CDRH Facilities' recommendations. Any technical discussion of the device, or discussion of the manufacturing process, will occur between CDRH and CDRH Facilities. CMC will confirm with Pharm/Tox toxicology evaluations for two leachables. CMC confirmed with the CDRH device reviewer that the CDRH review will include evaluation of dose accuracy.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CMC will have comments for the 74 day letter.</p> <p>CDRH and CDRH Facilities will have comments for the letter. CDRH was unable to locate stability information for the device constituent parts.</p>	
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO 	
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments: OPQ and CDRH are identifying facilities for inspection.</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Not Applicable
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: N/A</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Review issues for 74-day letter

<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Jean-Marc Guettier, M.D. Division Director, DMEP</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): February 10, 2016</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
11/13/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: NDA 208583

Application Type: New NDA

Name of Drug/Dosage Form: insulin degludec and liraglutide injection

Applicant: Novo Nordisk

Receipt Date: September 14, 2015

Goal Date: September 14, 2016

1. Regulatory History and Applicant's Main Proposals

NDA 208583 was submitted for insulin degludec and liraglutide (IDegLira) on September 14, 2015. This is a Type 4 new combination. Insulin degludec is approved under Tresiba NDA 203314 and liraglutide is approved under Victoza NDA 022341. IDegLira is a fixed ratio combination product in a pre-filled pen. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Additional information to support the PLLR changes is needed. A request will be included in the 74-day letter.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by Friday, December 18, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *A waiver will most likely be granted for the 1/2 page requirement.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *The CONTRAINDICATIONS heading is not perfectly centered*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *remove white space after DOSAGE FORMS AND STRENGTHS heading*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES

Selected Requirements of Prescribing Information

21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: The applicant should ensure that ALL citations follow this format. For example, the reference on 612 (see Pregnancy, Data, Animal Data, Liraglutide) should be [see Use in Specific Populations (8.1)].

- N/A** 33. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 35. In the BW, all text should be **bolded**.

Comment:

- YES** 36. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

Comment:

- NO** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment: *The applicant inserted the word 'additional' into the verbatim statement, and changed 'not always possible' to 'generally not possible.' These changes seem minor enough to exclude from the 74-day letter; the review team may change them during labeling negotiations.*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
11/02/2015