

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203313Orig1s000

203314Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: August 31, 2015

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Division of Risk Management

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Subject: Review to determine if a REMS is necessary

Drug Names: Tresiba (Insulin degludec)
Ryzodeg (Insulin degludec/Insulin aspart 70/30)

Therapeutic Class: Insulin degludec: long-acting insulin analog
IDegAsp 70/30: fixed ratio combination of long and short acting insulin analogs

Dosage and Route: Individualized dose administered subcutaneously once daily using a fixed or flexible dosing interval

Division: Division of Metabolic Endocrine products (DMEP)

Application Type/Number: NDA 203313 & 203314

Submission Date: March 26, 2015

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2015-714 & 723
2015-717 & 726

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1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if risk evaluation and mitigation strategies (REMS) are necessary for Tresiba [(Insulin Degludec (IDeg)] and Ryzodeg [(Insulin Degludec/Insulin Aspart)(IDegAsp)]. The applicant, Novo Nordisk, submitted New Drug Applications (NDAs) 203314 (IDeg) and 203313 (IDegAsp) for their proposed indication to improve glycemic control in adults with diabetes mellitus.

During the first review cycle of the NDAs submitted on September 29, 2011, an increased cardiovascular (CV) safety signal was identified. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of new molecular entities Tresiba [(Insulin Degludec (IDeg)] and Ryzodeg [(Insulin Degludec/Insulin Aspart)]. The Advisory Committee agreed that there was an increase in CV risk observed in most of the clinical trials. A Complete Response letter was issued to Novo Nordisk on February 8, 2013. Novo Nordisk conducted a cardiovascular outcomes trial and included it in the resubmission to FDA on March 26, 2015.

Novo Nordisk submitted a risk management plan in the original application with identified risks of hypoglycemia and immunogenicity-related events (allergic reactions). A potential risk associated with IDeg and IDegAsp was identified in the risk management plan as medication errors due to mix-up between IDegAsp and bolus insulin. Novo Nordisk's submission included a pharmacovigilance plan, which proposed to manage these events through routine pharmacovigilance and product labeling (package insert, patient information, and carton & container). Novo Nordisk did not submit a REMS for this application.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Novo Nordisk's Clinical Modules [sections 2.5, 2.7.3 and 2.7.4 (original NDA) and sections 2.5 and 2.7.4 (resubmission)] for Tresiba & Ryzodeg
- Risk Management Plan submitted September 29, 2011 for Tresiba and Ryzodeg
- Tresiba [(Insulin Degludec (IDeg)] draft label, August 7, 2015
- Ryzodeg [(Insulin Degludec/Insulin Aspart (IDegAsp)] draft label, August 7, 2015
- Draft Clinical Review for IDeg by Dr. Jean Marc Guettier (January 26, 2013 & February 1, 2013)
- Draft Clinical Review by Dr. Karim A. Calis (December 18, 2012)
- Draft Clinical Review by Dr. Tania Condarco (version July 30, 2015)

3 REGULATORY HISTORY

Listed below are the pertinent regulatory history milestones for this NDA:

- October 5, 2007 – IND 76496 submitted for IDeg
- April 21, 2008 – IND 73198 submitted for IDegAsp

- September 29, 2011 – NDA applications received
- November 8, 2012 – (Endocrinologic & Metabolic Drug Advisory Committee Meeting)
- December 7, 2012 Regulatory Briefing
- February 8, 2013 – Complete Response Letter Issued
- March 26, 2015 – Class 2 Resubmissions Received (Part 1-3)
- June 17, 2015 Midcycle Meeting
- **PDUFA (Action) date – September 26, 2015**

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT

Diabetes remains the 7th leading cause of death in the United States (US) in 2010. Diabetes is a serious, highly prevalent life-threatening condition which impacts 9.3% of the U.S. population (~29 million people). Of those 29 million people, ~1.25 million people have type 1 diabetes.¹ Diabetes leads to macrovascular and microvascular morbidity and mortality and reduces life expectancy.² According to the Center for Disease Control, as of 2011, diabetes rates in men (6.9%) were slightly higher than women (5.9%). Close to 7.6% of those diagnosed with diabetes are Caucasians, 9% Asian Americans, 12.8% Hispanics, 13.2% African Americans, and 15.9% American Indians/Alaskan natives.³

It is estimated that approximately 26% of US adults diagnosed with diabetes use insulin alone or insulin in combination with other oral anti-diabetic agents to treat their diabetes. In Type 1 diabetes (T1DM), insulin is administered exogenously several times per day to cover fasting and post-prandial hyperglycemia. In subjects with Type 2 diabetes (T2DM), insulin is used when diet, exercise, and non-insulin anti-diabetic drugs are no longer sufficient to provide adequate glycemic control.⁴

Several comorbid conditions and complications are associated with diabetes. In 2011, about 282,000 emergency room visits for adults aged 18 years or older had hypoglycemia as the reason for the visit and diabetes as secondary reason. Hypertension, dyslipidemia, cardiovascular death, heart attacks, and stroke were higher in patients with diabetes compared to those with no diabetes.⁵

¹ <http://www.diabetes.org/diabetes-basics/statistics> accessed 8/2/15

² Insulin Degludec/Insulin Aspart March 26, 2015 Clinical Overview Section 2.5

³ <http://www.cdc.gov/diabetes/statistics/prev/national/figbyrace.htm> accessed 7.14.15

⁴ Draft clinical review by Dr. Jean-Marc Guettier (January 26, 2013)

⁵ <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf> accessed 8.3.15

Current treatment options for T1DM are insulin and pramlintide. For T2DM, approved products include: biguanides, sulfonylureas, meglitinides, insulins, thiazolidinediones, incretins, α -glucosidase inhibitors, dipeptidyl peptidase IV inhibitors, and dopamine agonists. Despite the available treatment options, the majority of patients will fail to meet the recommended levels of glycemic control required to reduce long-term microvascular and macrovascular complications. Also, strict treatment regimens have an impact on patient's lifestyle contributing to lack of adherence and suboptimal glycemic control. IDeg and IDegAsp will be the first type of insulin that will allow low day-to-day variability of glucose-lowering action as it will contain both a long-acting and a rapid-acting insulin with a once daily administration schedule.

IDeg/IDegAsp: Insulin degludec (IDeg) is an ultra-long acting basal insulin produced using yeast (*Saccharomyces cerevisiae*), recombinant DNA technology and chemical modification. Insulin degludec differs from human insulin by omission of a threonine ^{(b) (4)} at the amino terminal B-chain (B30) and by attachment of the 16 carbon fatty acid, hexadecanedioic acid, to the epsilon-amino group of the lysine residue at position 29 of the B-chain through a gamma-glutamic acid spacer. IDegAsp is a co-formulation consisting of 70% IDeg and 30% the rapid-acting bolus insulin analogue aspart (IAsp).

4.2 CLINICAL DEVELOPMENT PROGRAM

No new efficacy studies for IDeg and IDegAsp were submitted in the resubmission to FDA on March 26, 2015. Included in the March 26, 2015, resubmission was a safety update which included accumulated safety information obtained up to September 30, 2014 for completed and ongoing trials. As of this date, the clinical development program for IDeg included 17 confirmatory trials and for IDegAsp 11 confirmatory trials.

4.2.1 Efficacy^{4,6,7,8,9}

Analysis of the efficacy data was taken from the original NDA submission submitted to FDA on September 29, 2011, with a data cut-off date of January 31, 2011, and was reviewed by Drs. Jean-Marc Guettier and Karim Anton Calis. The summary below provides a high level overview of the efficacy studies.

Please refer to the above reviewers' full reviews for complete description and analysis of the efficacy data submitted in the September 29, 2011 NDA. The following is a summary of the key findings from labeling discussions for insulin degludec (IDeg) and insulin degludec/insulin aspart 70/30 (IDegAsp) as of **August 19, 2015**.

Key Efficacy Findings:

⁶ Draft clinical review by Dr. Jean-Marc Guettier (February 1, 2013)

⁷ Draft clinical review by Dr. Karim Anton Callis (December 18, 2012)

⁸ Tresiba (Insulin Degludec) draft label, August 19, 2015

⁹ Ryzodeg (Insulin Degludec/Insulin Aspart) draft label, August 19, 2015

Tresiba [Insulin Degludec (IDeg)]: Two phase 2 trials explored the efficacy and safety of different IDeg dose strengths and schedules in Type 1 DM (Trial 1835) and Type 2 DM (Trial 1836). Eleven phase 3, randomized, open-label, parallel-group, active comparator, multicenter, and multinational trials evaluated the efficacy and safety of different degludec dose strengths and administration schedules in Type 1 DM (i.e., Trials 3583, 3585, and 3770) and Type 2 DM (Trials 3582, 3579, 3672, 3586, 3580, 3668, 3718, 3724). IDeg was used in combination with metformin in Trials 3586, 3668 and 3580; with pioglitazone (TZD) in Trials 3582, 3580 and 3668; with DPP-4 inhibitors (i.e., sitagliptin) in Trials 3579 and 3672, and with α -glucosidase inhibitors (i.e., acarbose or miglitol) in Trial 3586. Trial 3668 provided additional information on the use of IDeg as monotherapy in a small subset of subjects with T2DM.¹⁰

The primary objective in all of the confirmatory trials was to confirm the efficacy of IDeg in controlling long-term glycemia used either alone or in combination with bolus insulin, with or without oral anti-diabetics, in subjects with either T1DM or T2DM. The study aimed for a predefined fasting plasma glucose (FPG) of <5 mmol/L (90 mg/dL) in order to achieve an HbA1c < 7%.¹⁰ In all the trials except trial 3580, efficacy was established by comparing glucose control in IDeg treated subjects to that observed in the comparator arm which in all but 2 trials used glargine as the comparator. Reduction in HbA1c was similar between IDeg and comparator products ranging from 1.1-1.6% with IDeg and 1.2-1.4% with comparator products.¹⁰ After 52 weeks of treatment, 39.8% of IDeg treated subjects reached HbA1c <7.0% compared to 42.7% with insulin glargine (IGlar) and subjects reaching HbA1c <7% without severe hypoglycaemia were 38.4% for IDeg and 42.3% with IGlar.¹¹ The results of exploratory trials were in line with the results of the therapeutic confirmatory trials: In Trial 1835, the observed mean reduction in HbA1c was 0.6% after 16 weeks of IDeg treatment, and in Trial 1836, the mean reduction in HbA1c was approximately, 1.3% with IDeg OAD.

Secondary objectives were to support the primary efficacy findings by comparing degludec to comparators with respect to the proportion of subjects reaching HbA1c targets, fasting plasma glucose, glucose profiles, interstitial glucose profiles, and patient reported outcomes.

The key withdrawal criteria were the following: pregnancy, severe hypoglycemia, protocol deviation, and lack of effect which entails, after week 12, the patient does not have a reduction in HbA1c and has a pre-breakfast SMPG reading >13.3 mmol/L (>240 mg/dL) on three consecutive days despite appropriate dose adjustments. An FPG should be obtained, and if this FPG exceeds 13.3 mmol/L (>240 mg/dL) and no treatable cause for the hyperglycemia has been diagnosed, the subject must be withdrawn.¹¹

¹⁰ Insulin Degludec September 29, 2011 Clinical Overview 2.5

¹¹ Insulin Degludec September 29, 2011 Summary of Clinical Efficacy 2.7.3

The baseline demographics and disease characteristics of the intention-to-treat (ITT) population were balanced between the two treatment arms. More patients with type 2 diabetes were exposed to degludec compared to patients with type 1 DM. The trials included a slightly higher proportion of men (56%) than women with an equal distribution between the treatment arms. The mean age at baseline was 43 years in T1DM and 58 years in T2DM. A substantial number of geriatric subjects (>65 years) were enrolled; hence in the T1DM trials, 107 subjects (7%) were >65 years and 14 subjects (0.9%) were >75, and in the T2DM trials, 969 subjects (24%) were >65 years and 123 subjects (3%) were >75 years. Caucasians accounted for 75% of the trial population, while Asians, Hispanics/Latinos, and African-Americans accounted for 18%, 10%, and 6%, respectively.¹⁰

A total of 4275 patients were randomized to confirmatory trials with IDeg. Eleven hundred and two patients were in the T1DM trials and 3173 patients in T2DM trials. The treatment period was 26-52 weeks in duration in the confirmatory trials and 6-16 weeks in the exploratory trials. Degludec could be started in insulin naïve T2DM patients at 10 units once daily and for most patients with Type 2 diabetes taking basal, basal-bolus, premix or self-mixed insulin therapy, changing the basal insulin to IDeg can be done unit-to-unit based on the previous basal insulin dose with individual dosage adjustments. For most patients with type 1 diabetes, changing the basal insulin to IDeg can be done unit-to-unit based on the previous basal insulin dose with individual dosage adjustments. For patients transferring from twice-daily basal insulin or having HbA_{1c} <8.0% at the time of transfer, the dose of IDeg should be determined on an individual basis. Dose reduction should be considered with subsequent individual dosage adjustment based on the glycemic response.

Ryzodeg [Insulin Degludec /Insulin Aspart 70/30 (IDegAsp)]: Two, phase 2 trials explored the efficacy and safety of different fixed ratio combinations of IDegAsp and of different administration schedules in T2DM (Trial 1791 & 1792). Five pivotal, randomized, open-label, parallel-group, active comparator controlled multi-center, multi-national trials evaluated the efficacy and safety of IDegAsp with respect to glucose control in T1DM (Trial 3594) and T2DM (i.e., Trials 3590, 3593, 3592, and 3597 (T2DM)). In Trial 3594, insulin detemir was used as the comparator while in trial 3593 and 3590, insulin glargine was used as the comparator. In trial 3592 and 3597, the comparator was biphasic insulin aspart. The primary and secondary objectives were identical to the IDeg confirmatory trials.

The key withdrawal criteria were the following: pregnancy, severe hypoglycemia, protocol deviation, patients randomized in error, significant change in systemic treatment that could interfere with glucose metabolism, donation of blood, or lack of effect as described above.¹²

The baseline demographics and disease characteristics of the intention-to-treat (ITT) population were balanced between the two treatment arms. The trials included a slightly

¹² Insulin Degludec/Insulin Aspart September 29, 2011 Summary of Clinical Efficacy 2.7.3

higher proportion of men (54%) than women as seen in the IDeg trial with an equal distribution between the treatment arms. The mean age at baseline was 41 years in T1DM and 58 years in T2DM. In the T1DM trials, a small portion of geriatric patients were enrolled. Twenty-five patients (4.6%) > 65 years and 6 patients (1.1%) > 75 years. In the T2DM trials, 486 subjects > 65 years and 60 patients (3.2%) > 75 years. Caucasians accounted for 56% of the trial population, while Asians, Hispanics/Latinos, and African-Americans accounted for 38%, 5%, and 4%, respectively.¹³

A total of 1360 patients were randomized to confirmatory trials with IDegAsp. Three hundred sixty-two patients in T1DM trials and 998 patients in T2DM trials. The treatment period was 26-52 weeks in duration in the confirmatory trials and 16 weeks in the exploratory trials. IDegAsp could be started in insulin-naïve T2DM patients at 10 units once daily. For patients with T1DM or T2DM on once daily insulin therapy, the once-daily premix insulin therapy can be converted unit-to-unit to once-daily or twice daily IDegAsp. For patients switching from once-daily basal insulin therapy to twice-daily IDegAsp, the dose can be converted unit-to-unit at the same total daily insulin dose. For patients switching from once-daily basal insulin to once-daily IDegAsp, the dose should be reduced due to the rapid-acting insulin component, with subsequent individual dosage adjustment based on the glycemic response. For those T1DM or T2DM patients on a more than once daily insulin therapy, patients switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to twice daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose and for those patients switching from basal/bolus or self-mixed insulin therapy to IDegAsp, the dose will need to be converted based on their individual needs.¹²

The clinical studies conducted with IDeg and IDegAsp showed a reduction in HbA1c to be statistically significant or non-inferior.

DEVOTE Trial: The FDA identified a signal of cardiovascular risk (CV risk) associated with IDeg in the phase 3 programs for IDeg and IDegAsp based on analysis of MACE. DEVOTE, a dedicated CVOT was designed specifically to assess the CV safety of IDeg and to rule out or rule in the CV signal generated from the phase 3 meta-analyses. The primary endpoint in DEVOTE was time to first Major Adverse Cardiac Event (MACE) (CV death, non-fatal MI and non-fatal stroke). The trial is currently ongoing. The trial was fully enrolled (7638 subjects) on November 30, 2014. DEVOTE was designed as a head to head comparison of IDeg vs IGlax and was randomised 1:1. A total of 3818 patients were randomized to IDeg and 3820 subjects to IGlax. The median duration of treatment was 6.4 months.^{2,14}

4.2.2 Safety^{7,8,9,15}

Analysis of the safety data was taken from the original NDA submission submitted to FDA on September 29, 2011 and was reviewed by Dr. Karim Anton Calis. Analysis of

¹³ Insulin Degludec/Insulin Aspart September 29, 2011 Clinical Overview 2.5

¹⁴ Insulin Degludec March 26, 2015 Summary of Clinical Safety 2.7.4

the safety update provided in the resubmission was performed by Dr. Tania Condarco. At the time of this writing, Dr. Condarco was still completing analysis of the safety update. The summary below provides a high level overview of the safety data pooled for the IDeg and IDegAsp program and an overview of the cardiovascular outcomes trial (CVOT). A full review of this study has not been done as this trial is still ongoing.

Please refer to the review of Dr. Karim Anton Calis for complete description and analysis of the safety data submitted in the September 29, 2011 NDA and Dr. Tania Condarco's review of the safety update in the resubmission. The following is a summary of the key findings from their reviews and of labeling discussions for insulin degludec (IDeg) and insulin degludec/insulin aspart 70/30 (IDegAsp) as of **August 19, 2015**.

Key Safety Findings:

Overall, a total of 10,773 patients were exposed to any form of IDeg (i.e., IDeg, IDegAsp, and IDeg+IDegAsp).

The safety events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0 or Version 13.1 for classification of adverse event data in the original NDA and 17 in the safety update. In both T1DM and T2DM, the most frequently reported AEs in therapeutic confirmatory trials were nasopharyngitis, headache and upper respiratory tract infection.²

The serious adverse events most commonly reported in the T1DM population included hypoglycemia, hypoglycemic unconsciousness and seizures, hypoglycemia coma, and diabetic ketoacidosis. For the T2DM population, hypoglycemia, cardiac disorders, and infections were the serious adverse events most commonly reported.

The adverse event of concern was hypoglycemia. In the T1DM trials with IDegAsp, 15/362 in the IDegAsp arm versus 9/180 in the comparator arm had hypoglycemia, and in the T2DM trials, 3/998 from the IDegAsp arm and 7/857 in the comparator arm had hypoglycemia.²

In subjects with T1DM, a total of 19 subjects (1.7%) treated with IDeg withdrew due to reasons related to hypoglycemia compared to 4 subjects (0.9%) treated with comparator products. In subjects with T2DM, a total of 11 subjects (0.4%) treated with IDeg withdrew due to hypoglycemia-related causes compared to 6 subjects (0.5%) treated with comparators.¹⁶

In the IDeg group, the most frequent adverse events that led to patient withdrawal from the study was hypoglycemia (8 events), weight increased (7 events), and myocardial infarction (6 events). In the IDeg program, 2.3% of patients discontinued treatment on IDeg and 1.3% of patients discontinued treatment while on comparator. Of the AEs leading to withdrawal, 17 events in the IDeg group and 6 events in comparators group was reported as MACE. In the IDegAsp program, the percentage of subjects discontinuing study drug due to AEs were 1.8% for IDegAsp and 1.5% for comparators.

¹⁵ Draft clinical review by Dr. Tania Condarco (July 30, 2015)

¹⁶ Insulin Degludec September 29, 2011 Summary of Clinical Safety 2.7.4

The percentage of subjects reporting AEs leading to dose reduction were 4.4% for IDeg and 3.3% for comparators. The most frequent AEs leading to dose reduction were events of hypoglycemia.

In the IDegAsp program, the rate of discontinuation due to adverse events for patients with T1DM and T2DM was higher in the overall IDeg program versus the comparators. Nervous system disorders, metabolism and nutrition disorders, and general disorders and administration had the highest rate of discontinuation in T1DM patients while for T2DM patients, discontinuation of study drug was mainly due to neoplasms and cardiac disorders.

Deaths: All the deaths in the IDeg program occurred in the Phase 3 trials. A total of 26 (0.4%) deaths in IDeg and 12 (0.4%) deaths in the comparator arm were reported in all completed IDeg trials. Overall, the proportion of deaths in the IDeg versus the comparator was similar in both the T1DM and T2DM patients.

In total, 6 deaths were reported in IDegAsp clinical trials. Five of the deaths occurred in the confirmatory trials. Two of the deaths in IDegAsp patients were noted to be due to interstitial lung disease.⁴

The applicant proposed to communicate all safety events through labeling and therefore did not submit a REMS.

The adverse event of hypoglycemia will be addressed in labeling under the Warnings & Precautions section.

4.3 ASSESSMENT OF RISK: BENEFIT PROFILE

Despite the available treatment options, the majority of patients will fail to meet the recommended levels of glycemic control required to reduce long-term microvascular and macrovascular complications. Also, strict treatment regimens will have an impact on the patient's lifestyle contributing to lack of adherence and suboptimal glycemic control. IDeg and IDegAsp will be the first type of insulin that will allow low day-to-day variability of glucose-lowering action as it will contain both a long-acting and a rapid-acting insulin and once daily administration with a less strict dosing schedule. The indication for IDeg and IDegAsp is to improve glycemic control in adults with diabetes mellitus.

Current available treatment options for T1DM are insulin and an amylin analogue (pramlintide). For T2DM, a biguanide such as metformin, sulfonylurea (glimepiride, glyburide or glipizide), meglitinide (repaglinide), insulin (glaragine or detemir), thiazolidinedione (rosiglitazone or pioglitazone), glucagon-like peptide-1 (GLP-1) receptor agonist or incretin mimetic (exenatide, albiglutide, dulaglutide, or liraglutide), a-glucosidase inhibitor (acarbose or miglitol), and dipeptidyl peptidase IV inhibitor (linagliptin, saxagliptin, and sitagliptin) are used. Less frequently used treatments are a dopamine agonist such as bromocriptine mesylate or a bile acid sequestrant like colesevelam.⁴

Of the currently available or approved treatments, a thiazolidinedione (rosiglitazone) and three GLP-1 receptor agonists (liraglutide, albiglutide, and dulaglutide) contain a communication plan REMS. The goal of the REMS for rosiglitazone is to provide

training to likely prescribers about the cardiovascular risk associated with this drug, while the goal of the REMS for the GLP-1 receptor agonists is to mitigate the potential risk of medullary thyroid carcinoma and the risk of pancreatitis.

Four classes of drugs contain a Boxed Warning: biguanide (metformin), thiazolidinedione (rosiglitazone & pioglitazone), amylin analogue (pramlintide), and GLP-1 receptor agonists (exenatide, albiglutide, dulaglutide, and liraglutide). A Boxed Warning is used to describe the risk of lactic acidosis with taking metformin, congestive heart failure for rosiglitazone & pioglitazone, severe hypoglycemia for pramlintide and thyroid c-cell tumors for the GLP-1 receptor agonists noted above.

The most common adverse event with any of these drugs are gastrointestinal issues which is seen in the biguanide, sulfonylurea, meglitinide, amylin analogue, and α -glucosidase inhibitor classes. Weight gain is more commonly seen in the sulfonylurea, insulin and thiazolidinedione classes as well as IDeg and IDegAsp, while headache is more commonly seen in the dipeptidyl peptidase IV inhibitor and sulfonylurea classes. Injection site reactions, lipodystrophy, pruritus, rash, and edema are common amongst all of the insulins.

The most serious adverse event with IDeg and IDegAsp is hypoglycemia. None of these agents, except for pramlintide, have hypoglycemia as a Boxed Warning. Similar to IDeg and IDegAsp, hypoglycemia is described in the Warnings & Precautions section for the sulfonylureas. The Division determined this event could be adequately addressed in the Warnings & Precautions section of the label for IDeg and IDegAsp. Medication errors related to accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported with IDeg and IDegAsp. To avoid medication errors with these products, per labeling, patients should be instructed to check the insulin label before each injection.

A REMS is not necessary to ensure the benefits outweigh the risks of IDeg and IDegAsp for the following reasons:

- IDeg and IDegAsp has shown statistical significance or non-inferiority in clinical studies with regards to HbA1c reduction,
 - issues regarding hypoglycemia will be addressed in the Warnings and Precautions section of the label as reflected in labeling similar to other drugs used to treat diabetes mellitus,
- and
- IDeg and IDegAsp will be managed by prescribers who are familiar with the disease and adverse events seen with drugs used for the treatment of diabetic mellitus.

5 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

PMR's and PMC's have not been finalized at the time of this writing.

6 CONCLUSION

DRISK and DMEP concur that at this time a REMS for IDeg and IDegAsp is not necessary to ensure that the benefits outweigh the risks for the proposed indication to improve glycemic control in adults with diabetes mellitus. The risks associated with IDeg and IDegAsp are similar to other currently approved basal insulin products which did not require a REMS, and the risks will be communicated through professional labeling and routine pharmacovigilance. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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