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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	April 24, 2019
Safety Evaluator:	Christine Chamberlain, PharmD, BCPS, CDE Safety Evaluator, Division of Pharmacovigilance I (DPV-I)
Medical Officer:	Ivone Kim, MD, FAAP DPV-I
Team Leader:	Christian Cao, MPAS, PA-C, Safety Evaluator Team Leader, DPV-I
Division Director:	Cindy Kortepeter, PharmD, Division Director, DPV-I
Product Names:	Tresiba (insulin degludec injection) U-100 and U-200 FlexTouch Pens and U-100 multidose vial, Ryzodeg 70/30 (insulin degludec 70 units/ml and insulin aspart 30 units/ml) FlexTouch Pen
Pediatric Labeling Approval Date:	December 16, 2016
Application Type/Number:	NDA 203314 (Tresiba), NDA 203313 (Ryzodeg)
Applicant/Sponsor:	Novo Nordisk
OSE RCM #:	2019-346

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for insulin degludec and insulin degludec/insulin aspart injection in pediatric patients up to age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with insulin degludec and insulin degludec/insulin aspart injection in pediatric patients.

Insulin degludec (Tresiba, NDA 203314) and insulin degludec/insulin aspart (Ryzodeg, NDA 203313) injections were approved on September 25, 2015 to improve glycemic control in adults with diabetes mellitus. On December 16, 2016, the labels were updated with an approved pediatric indication to improve glycemic control in patients 1 year of age and older with diabetes mellitus. The following pediatric specific dosing and administration information for both insulin degludec pen and insulin degludec/insulin aspart pen was included in the label to minimize hypoglycemia risk: not recommended for pediatric patients requiring less than 5 units daily, for once daily dosing only, and to administer at the same time each day.

There were no new safety signals identified, no apparent increased severity or frequency of labeled adverse reactions and there were no deaths. We reviewed all serious FAERS reports with insulin degludec and insulin degludec/insulin aspart in the pediatric population (ages 0 to <18 years) during the period September 25, 2015 – January 23, 2019. We excluded duplicate reports, transplacental exposure reports, reports with alternative etiologies, reports of labeled adverse reactions, reports without an adverse event (product omission, diabetes management), and reports with limited information to adequately assess causality. The two reports with serious and unlabeled adverse events for insulin degludec included in this pediatric case series are single cases of elevated transaminases and a Langerhans cell histiocytosis. No specific pattern of adverse events was identified and assessment of causality for both cases was limited by lack of information provided in both narratives.

DPV did not identify any new pediatric safety concerns for insulin degludec and insulin degludec/insulin aspart during this review. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of insulin degludec and insulin degludec/insulin aspart.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for insulin degludec and insulin degludec/insulin aspart injection in pediatric patients up to age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with insulin degludec and insulin degludec/insulin aspart injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Insulin degludec (Tresiba, NDA 203314) and insulin degludec/insulin aspart (Ryzodeg, NDA 203313) injections were approved on September 25, 2015 to improve glycemic control in adults with diabetes mellitus. At the time of approval of Tresiba and Ryzodeg 70/30, Division of Metabolic and Endocrine Products (DMEP) waived the pediatric study requirements for type 1 diabetes mellitus (T1DM) in ages 0 to < 1 year and type 2 diabetes mellitus (T2DM) in ages 0 to < 10 years because the necessary studies would be impossible or highly impracticable due to the low number of children in this age range with diabetes mellitus. DMEP deferred pediatric studies for ages 1 to 17 years (inclusive) for this application because the products were ready for approval for use in adults and the pediatric studies had not been completed. Under the Pediatric Research Equity Act (PREA), a postmarketing requirement (PMR 2954-1) mandated "An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week safety extension."[1] Additionally, for Ryzodeg 70/30, PMR 2955-1 mandated "An open label, 16-week randomized controlled efficacy and safety trial comparing Ryzodeg 70/30 (insulin degludec and insulin aspart injection) administered once daily with a main meal and insulin aspart for additional meals to insulin detemir, in combination with mealtime insulin aspart at each meal, in pediatric patients with type 1 diabetes mellitus ages 1 to 17 years (inclusive)."[2]

Pediatric labeling was updated on December 16, 2016, with completion and analysis of the required pediatric studies.[3,4] Expansion of the indication to include patients 1 year of age and older with T1DM and T2DM is supported by evidence from adequate well-controlled studies and a pharmacokinetic study submitted by the sponsor in a prior approval supplemental new drug application for Tresiba (NDA 203314/S-003) and Ryzodeg (NDA 203313/S-002). Insulin degludec and insulin degludec/insulin aspart achieved glycemic lowering (change from baseline in HbA1c), which met the pre-specified non-inferiority margin.[5] Hypoglycemia was the most notable safety concern, which is an inherent risk with insulin administration. The DMEP medical reviewer identified a persistent pattern for a higher risk of hypoglycemia with insulin degludec and insulin degludec/insulin aspart when compared to insulin detemir. This increased risk was observed across multiple hypoglycemia definitions and across age subgroups (ages 2-5, 6-11, and 12-17 years); however, this imbalance was not statistically significant.[5] The following pediatric specific dosing for both insulin degludec and insulin degludec/insulin aspart was added to the label to minimize hypoglycemic risk: "In pediatric patients inject subcutaneously once daily at the same time every day" and a 20% dose reduction when converting from other insulins (See section 1.2 for Tresiba and Ryzodeg product labels). Insulin degludec/insulin apsart is

approved for once and twice daily dosing in adults; however, it is only approved for once daily dosing in pediatric patients because the two pediatric clinical trials only evaluated the once daily dosing.[6]

The pen device marketed in the U.S. (FlexTouch, 1-unit increment pen) is different from the penfill device (insulin cartridge with NovoPen Echo with ½ unit increments) used in the pediatric clinical trials and raised concern about the postmarketing potential for hypoglycemia in pediatric patients requiring lower doses of insulin. During the second review cycle of Tresiba and Ryzodeg 70/30 for the initial approval, the product presentation using the durable penfill devices was withdrawn by the sponsor for both applications because of concerns raised by the Division of Medication Error Prevention and Analysis (DMEPA) about the lack of external differentiation on the reusable delivery devices. These pens would be blank on the outside and differentiation of the insulin product can only occur after the pen cap is open to see the product inside.[5] In response to DMEPA's concerns, the sponsor proposed to market only the prefilled disposable pens, U-100 FlexTouch pens (for insulin degludec and insulin degludec/aspart), which can only be titrated by 1-unit increments, and the U-200 FlexTouch pens (for insulin degludec), which can only be titrated by 2-unit increments, in the pediatric population. This proposal satisfied DMEPA's concerns because it is an integrated cartridge, and the step to insert an insulin cartridge is eliminated compared to NovoPen Echo and thereby, eliminating the possibility of a use error associated with this step. The sponsor *did not* propose to manufacture a disposable pen delivering ½ unit insulin increments. Because of the incremental difference (inability to adjust by ½-unit increments) DMEP added the following label information to Limitations of Use: "Not recommended for pediatric patients requiring less than 5 units of [insulin degludec or insulin degludec/insulin aspart]."

On November 21, 2018, FDA approved insulin degludec (Tresiba) injection, 100 units/ml (U-100) 10 ml multi-dose vial to address the dosing safety concern in pediatric patients requiring less than 5 units daily. The label was updated with information in the Limitations of Use: "For pediatric patients requiring less than 5 units of TRESIBA each day, use a TRESIBA U-100 vial."[7]

This is the first pediatric postmarketing review and was stimulated by the December 16, 2016 pediatric labeling change for Ryzodeg and Tresiba.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Tresiba[8] and Ryzodeg[9] product labels contain the following information under HIGHLIGHTS and relevant pediatric labeling in DOSAGE AND ADMINISTRATION and USE IN SPECIFIC POPULATIONS:

1.2.1 Tresiba Product Labeling[8]

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------INDICATIONS AND USAGE----------
Limitations of Use:
Not recommended for treating diabetic ketoacidosis.
----------DOSAGE AND ADMINISTRATION----------

See Full Prescribing Information for important administration instructions.
Rotate injection sites to reduce the risk of lipodystrophy.
For pediatric patients requiring less than 5 units of TRESIBA each day, use a TRESIBA U-100 vial.
In adults, inject subcutaneously once daily at any time of day.
In pediatric patients inject subcutaneously once daily at the same time every day.
Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal.
The recommended days between dose increases are 3 to 4 days.
See Full Prescribing Information for recommended starting dose in insulin naïve patients and patients already on insulin therapy.

----------DOSAGE FORMS AND STRENGTHS----------

100 units/mL (U-100): 3 mL single-patient-use FlexTouch®.
200 units/mL (U-200): 3 mL single-patient-use FlexTouch®.
100 units/mL (U-100): 10 mL multiple-dose vial.

----------CONTRAINDICATIONS----------

During episodes of hypoglycemia.
Hypersensitivity to TRESIBA or one of its excipients.

----------WARNINGS AND PRECAUTIONS----------

Never share a TRESIBA FlexTouch pen between patients, even if the needle is changed.
Hyper-or hypoglycemia with changes in insulin regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring.
Hypoglycemia: May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness.
Hypoglycemia due to medication errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer TRESIBA into a syringe for administration as overdosage and severe hypoglycemia can result.
Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TRESIBA, monitor and treat if indicated.
Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.

----------ADVERSE REACTIONS----------

Adverse reactions commonly associated with TRESIBA are:
• hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain.

----------DRUG INTERACTIONS----------

Drugs that may increase the risk of hypoglycemia: antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.
Drugs that may decrease the blood glucose lowering effect: atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Drugs that may increase or decrease the blood glucose lowering effect:
Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine.
Drugs that may blunt the signs and symptoms of hypoglycemia: beta-blockers, clonidine, guanethidine, and reserpine.

DOSAGE AND ADMINISTRATION

Starting Dose in Patients Already on Insulin Therapy

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes Mellitus:

Start TRESIBA at 80% of the total daily long or intermediate-acting insulin unit dose to minimize the risk of hypoglycemia [see Warnings and Precautions]

USE IN SPECIFIC POPULATIONS

Pediatric Use

The safety and effectiveness of TRESIBA to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of TRESIBA have not been established in pediatric patients less than 1 year old.

The use of TRESIBA in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) and Clinical Studies. The use of TRESIBA in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus.

1.2.2 Ryzodeg Product Labeling[9]

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

These highlights do not include all the information needed to use RYZODEG 70/30 safely and effectively. See full prescribing information for RYZODEG 70/30.

RYZODEG® 70/30 (insulin degludec and insulin aspart injection), for subcutaneous use

Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

Limitations of Use:

Not recommended for treating diabetic ketoacidosis.

Not recommended for pediatric patients requiring less than 5 units.

----------DOSAGE AND ADMINISTRATION----------

DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions.

Rotate injection sites to reduce the risk of lipodystrophy.

Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal.

Administer subcutaneously once or twice daily with any main meal (s).

Administer a rapid- or short-acting insulin at other meals if needed.

Patients with type 1 diabetes will generally require a rapid-or short-acting insulin at meals when RYZODEG 70/30 is not administered.

Adjust the dose according to fasting blood glucose measurements.

The recommended time between dose increases is 3 to 4 days.

Converting from other insulin therapies may require adjustment of timing and dose of RYZODEG 70/30.

----------DOSAGE FORMS AND STRENGTHS----------

RYZODEG 70/30 100 units/mL (U-100) available in:

3 mL FlexTouch®.

----------CONTRAINDICATIONS----------

During episodes of hypoglycemia.

Hypersensitivity to RYZODEG 70/30 or one of its excipients.

Never share a RYZODEG 70/30 FlexTouch pen between patients, even if the needle is changed.

Hyper- or hypoglycemia with changes in insulin regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring.
Hypoglycemia: May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness.
Hypoglycemia due to medication errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. DO NOT transfer RYZODEG 70/30 into a syringe for administration as overdosage and severe hypoglycemia can result.
Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue RYZODEG 70/30, monitor and treat if indicated.
Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.

----------ADVERSE REACTIONS----------

Adverse reactions commonly associated with RYZODEG 70/30 are:
hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at (1-800-727-6500) or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs that affect glucose metabolism: Adjustment of insulin dosage may be needed; closely monitor blood glucose.
Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent.

DOSAGE AND ADMINISTRATION

General Dosing Instructions

In adults, inject RYZODEG 70/30 subcutaneously once or twice daily with any main meal and in pediatric patients once daily with any main meal.

Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Premix or Self-mix Insulin Alone or as Part of a Regimen of Multiple Daily Injections

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes
Start RYZODEG 70/30 at 80% of the total daily mixed insulin dose in order to minimize the risk of hypoglycemia [see Warnings and Precautions] and administer once daily with the main meal of the day. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Basal Insulin Alone or as Part of a Regimen of Multiple Daily Injections

Pediatric Patients 1 Year of Age and Older with Type 1 or Type 2 Diabetes
Start RYZODEG 70/30 at 80% of the long- or intermediate-acting insulin component of the daily regimen in order to minimize the risk of hypoglycemia [see Warnings and Precautions] and administer once daily with the main meal of the day. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

USE IN SPECIFIC POPULATIONS

Pediatric Use

The safety and effectiveness of RYZODEG 70/30 to improve glycemic control in type 1 and type 2 diabetes mellitus have been established in pediatric patients 1 year of age and older. The safety and effectiveness of RYZODEG 70/30 have not been established in pediatric patients less than 1 year old.

The use of RYZODEG 70/30 in pediatric patients 1 year of age and older with type 1 and type 2 diabetes mellitus is supported by evidence from an adequate and well-controlled study and a pharmacokinetic study (studies included pediatric patients 1 year of age and older with type 1 diabetes mellitus) [see Clinical Pharmacology and Clinical Studies]. The use of RYZODEG 70/30 in pediatric patients 1 year of age and older with type 2 diabetes mellitus is also supported by evidence from adequate and well-controlled studies in adults with type 2 diabetes mellitus [see Clinical Studies].

In pediatric patients 1 year of age and older with switching from other insulin therapies, start RYZODEG 70/30 at a reduced dose to minimize the risk of hypoglycemia [see Dosage and Administration].

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	March 6, 2019
Time Period of Search	September 25, 2015† - January 23, 2019
Search Type	FBIS Product Manufacturer Reporting Summary, FBIS Quick Query
Product Terms	Product Active Ingredient: insulin degludec; insulin aspart\insulin degludec
MedDRA Search Terms (Version 21.1)	All PT terms
Age (year)	0-17.99
NDA	203314, 203313
* See Appendix A for a description of the FAERS database. † U.S. Approval date for both Tresiba and Ryzodeg	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from September 25, 2015 – January 23, 2019 with insulin degludec or insulin degludec/insulin aspart. No additional reports of pediatric deaths were identified among reports not reporting an age.

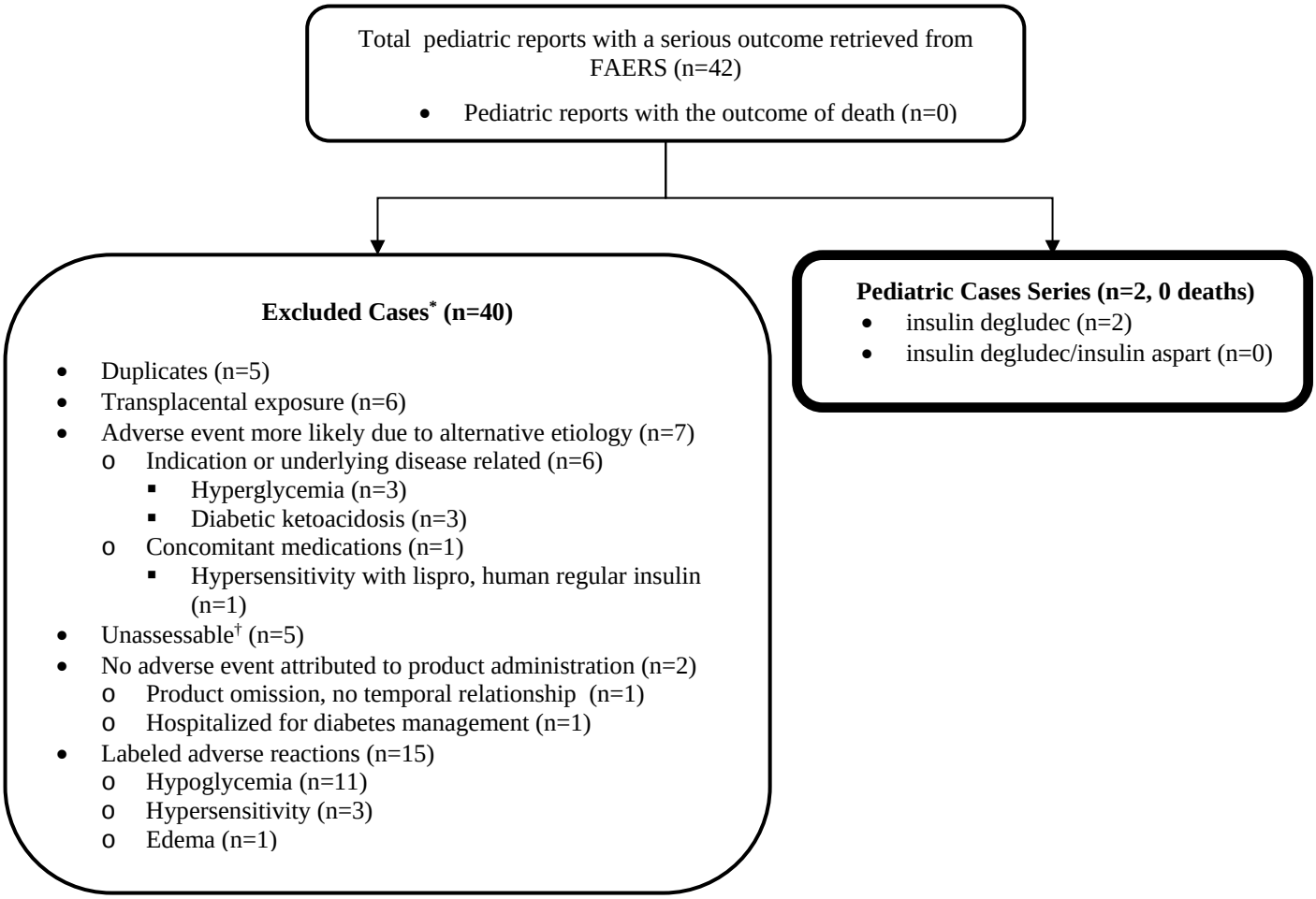
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from September 25, 2015 – January 23, 2019 with insulin degludec or insulin degludec/insulin aspart			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	3384 (2892)	951 (466)	64 (14)
Pediatrics (0 - <18 years)	76 (43)	**42 (9)**	0

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.1.2 Selection of Serious Pediatric Cases in FAERS

We reviewed 42 FAERS pediatric reports with a serious outcome (**See Table 2**). See **Figure 1** below for the selection of cases to be summarized in **Sections 3.2 and 3.3**.

Figure 1. Selection of Serious Pediatric FAERS Cases with Insulin Degludec or Insulin Degludec/Insulin Aspart



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.
† Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the two (2) serious pediatric cases for insulin degludec.

3.2 SUMMARY OF FATAL PEDIATRIC CASES (N=0)

We did not identify any fatal pediatric adverse event reports for insulin degludec or insulin degludec/insulin aspart.

3.3 SUMMARY OF ALL PEDIATRIC SERIOUS CASES (N=2)

We identified two serious FAERS cases with insulin degludec in the pediatric population reporting a non-fatal serious outcome. There were no reports with insulin degludec/insulin aspart reporting a non-fatal serious outcome.

FAERS Case 11888614 (Japan, 2016, Expedited, literature case)
A physician reported that a 5-year-old male patient experienced abnormal liver function tests, scrotal edema, and pruritic rash on his neck one, three, and six days respectively after starting insulin degludec (Tresiba) 4-6 units subcutaneously daily for T1DM. The patient was also taking insulin aspart (Novorapid Chu) for T1DM. The patient was hospitalized for treatment of diabetic ketoacidosis (DKA) one day prior to starting insulin degludec. Laboratory results on the day of admission were HbA1c 16.2%, white blood cell count 13,900, glucose 192 mg/dl, aspartate aminotransferase (AST) 19 IU/L, alanine aminotransferase (ALT) 18 IU/L, and total bilirubin 0.6 mg/dl. Twelve hours after initiating DKA treatment, the patient improved and was changed from regular insulin to insulin degludec and insulin aspart. On hospital day two, the patient developed a pruritic rash on his neck that improved after one day. Three days after starting insulin degludec, he developed scrotal edema. Six days after insulin degludec initiation, edema spread throughout the body and liver enzymes were elevated (AST 152 IU/L, ALT 108 IU/L); however, total bilirubin was within normal reference range at 0.4 mg/dl. Insulin degludec and insulin aspart were discontinued and intravenous regular insulin was resumed. The edema gradually reduced and resolved within five days. Liver enzymes improved (AST 39 IU/L, ALT 47 IU/L) after eight days. The patient started on insulin glulisine and insulin detemir and intravenous regular insulin was discontinued. The patient was hospitalized for 18 days and recovered from all events.

Reviewer Comments: The temporal association of the adverse events (elevated liver enzymes and generalized edema) and positive dechallenge upon discontinuation support a causal relationship with initiation of insulin degludec and insulin aspart. Insulin products are labeled for edema, which is mediated through sodium retention.[9] Product labels for Tresiba and Ryzodeg do not list elevated liver enzymes as an adverse event; however, elevated liver enzymes could have been a secondary complication of the edema related to congestion or hypoperfusion of the liver depending on the vascular condition at the time of the event. Furthermore, medical history to exclude hepatic disorders, details on hospital clinical course, and final diagnosis for the elevated liver enzymes is lacking in this report. Although the patient had leukocytosis, no infection was reported, and leukocytosis can occur with DKA in the absence of infection.[10] There is insufficient information to discern the etiology of the elevated liver enzymes or to directly attribute it to the use of insulin degludec.

FAERS Case 12720351 (Israel, 2016, Expedited)
A consumer reported that a 6-year-old female patient experienced a tumor in the right temple, diagnosed as Langerhans cell histiocytosis (LCH), an unspecified time after starting insulin degludec 13 units subcutaneously daily for T1DM. Concomitant medications included insulin aspart and human regular insulin. Two months prior to the date of the report, the patient experienced a "bump" on her right temple. MRI, skeleton screening, ultrasonography of the abdomen, blood tests and chest X-ray were performed; however, results of these tests were not reported. The patient underwent surgery for removal of the tumor that was partly extended into the skull. Biopsy of the tumor confirmed LCH and the patient was treated with cytarabine for 15 months to prevent recurrence. Insulin degludec, insulin aspart and human regular insulin treatment were continued (no change). The outcome of LCH was unknown.

Reviewer Comments: LCH is a rare disease of unknown etiology, arising from circulating myeloid dendritic cells.[11] The disease can occur in children and adults and involve multiple organs; however, bone involvement is the most common site, especially in children 5 to 10 years of age.[12] The medical literature has very few cases reporting T1DM or T2DM and LCH. A relationship between LCH and diabetes mellitus, insulin resistance, or insulin use has not been established.[13] A FAERS search on March 20, 2019 for LCH with insulin degludec or insulin degludec/insulin aspart use in adults did not retrieve any additional reports. This case lacks information on latency, family history, other exposures and outcome to assess for causal relationship between the LCH and use of insulin degludec.

4 DISCUSSION

There were no new safety signals identified, no apparent increased severity of labeled adverse reactions and there were no deaths.

We reviewed all serious FAERS reports with insulin degludec and insulin degludec/insulin aspart in the pediatric population (ages 0 to <18 years) during the period September 25, 2015 – January 23, 2019. We excluded duplicate reports, transplacental exposure reports, reports with alternative etiologies, reports of labeled adverse reactions, reports without an adverse event (product omission, diabetes management), and reports with limited information to adequately assess causality.

The two reports with serious and unlabeled adverse events for insulin degludec included in this pediatric case series are single cases of elevated transaminases and an LCH. No specific pattern of adverse events was identified and assessment of causality for both cases was limited by lack of information provided in both narratives.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for insulin degludec and insulin degludec/insulin aspart during this review.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of insulin degludec and insulin degludec/insulin aspart.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*	Indication
1	1/5/2016	11888614	3	JP-NOVOPROD-475228	Expedited (15-Day)	5	MALE	Japan	HO, OT	T1DM
2	9/7/2016	12720351	2	IL-NOVOPROD-508025	Expedited (15-Day)	6	FEMALE	Israel	HO, OT	T1DM

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant, T1DM=type 1 diabetes mellitus

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CHRISTINE E CHAMBERLAIN
04/24/2019 09:10:43 AM

IVONE E KIM
04/24/2019 09:14:56 AM

CHRISTIAN T CAO
04/24/2019 11:04:11 AM

CINDY M KORTEPETER
04/24/2019 12:32:15 PM