Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 29, 2023
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Product Names:	Victoza (liraglutide) Saxenda (liraglutide)
Pediatric Labeling Approval Dates:	June 17, 2019 (Victoza) December 4, 2020 (Saxenda)
Application Type/Number:	NDA 022341 (Victoza) NDA 206321 (Saxenda)
Applicant:	Novo Nordisk, Inc.
TTT Record ID:	2023-5022

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Victoza (liraglutide) and Saxenda (liraglutide) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) for Victoza and PREA for Saxenda. This review focuses on United States (U.S.) serious unlabeled adverse events associated with liraglutide in pediatric patients.

Victoza (liraglutide) is a glucagon-like peptide-1 (GLP-1) receptor agonist, initially approved in the U.S. on January 25, 2010. Victoza is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.

Saxenda (liraglutide) is a glucagon like peptide 1 (GLP-1) receptor agonist, initially approved in the U.S. on December 23, 2014. Saxenda is currently 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:
> • 30 kg/m^2 or greater (obese), or
> • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).
>
> Pediatric patients aged 12 years and older with:
> • body weight above 60 kg and
> • an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs.

This pediatric postmarketing safety review was stimulated by:

- The Victoza pediatric labeling change on June 17, 2019, which expanded the use of Victoza as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus in pediatric patients 10 years of age and older.

- The Saxenda pediatric labeling change on December 4, 2020, which expanded the use of Saxenda as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with body weight above 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs.

DPV reviewed all U.S. serious FAERS reports for liraglutide in the pediatric population less than 18 years of age from January 25, 2010, through June 1, 2023. Our evaluation did not identify any cases reporting unlabeled adverse event associated with liraglutide in the pediatric population. DPV detected no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to liraglutide.

DPV will continue to monitor all adverse events associated with the use of liraglutide.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Victoza (liraglutide) and Saxenda (liraglutide) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) for Victoza and PREA for Saxenda. This review focuses on United States (U.S.) serious unlabeled adverse events associated with liraglutide in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Victoza (liraglutide) is a glucagon-like peptide-1 (GLP-1) receptor agonist, initially approved in the U.S. on January 25, 2010. Victoza is currently indicated as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.

Saxenda (liraglutide) is a GLP-1 receptor agonist, initially approved in the U.S. on December 23, 2014. Saxenda is currently 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:
- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Pediatric patients aged 12 years and older with:
- body weight above 60 kg and
- an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cut-offs.

This pediatric postmarketing safety review was stimulated by:

- The Victoza pediatric labeling change on June 17, 2019, which expanded the use of Victoza as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus in pediatric patients 10 years of age and older.

- The Saxenda pediatric labeling change on December 4, 2020, which expanded the use of Saxenda as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in pediatric patients aged 12 years and older with body weight above 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs.

1.2 RELEVANT LABELED SAFETY INFORMATION FOR VICTOZA[1]

The Victoza labeling contains the following safety information excerpted from the Highlights of Prescribing Information of the labeling and the *Pediatric Use* subsection. For additional Victoza labeling information, please refer to the full prescribing information.

----------BOXED WARNING----------

WARNING: RISK OF THYROID C-CELL TUMORS

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

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

- VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- VICTOZA is contraindicated in patients with a serious hypersensitivity reaction to liraglutide or any of the excipients in VICTOZA.

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

- Thyroid C-cell Tumors: See Boxed Warning.
- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
- Never share a VICTOZA pen between patients, even if the needle is changed.
- Hypoglycemia: Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with VICTOZA regardless of insulin and/or metformin use. Reduction in the dose of insulin secretagogues or insulin may be necessary.
- Renal Impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of VICTOZA in patients with renal impairment.
- Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue VICTOZA and promptly seek medical advice.
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated.

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

- The most common adverse reactions, reported in ≥5% of patients treated with VICTOZA are: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation.

- Immunogenicity-related events, including urticaria, were more common among VICTOZA-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials.

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

8.4 Pediatric Use

The safety and effectiveness of VICTOZA as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older. Use of VICTOZA for this indication is supported by a 26-week placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with type 2 diabetes, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus. The risk of hypoglycemia was higher with VICTOZA in pediatric patients regardless of insulin and/or metformin use.

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

1.3 RELEVANT LABELED SAFETY INFORMATION FOR SAXENDA[2]

The Saxenda labeling contains the following safety information excerpted from the Highlights of Prescribing Information of the labeling and the *Pediatric Use* subsection. For additional Saxenda labeling information, please refer to the full prescribing information.

----------BOXED WARNING----------

WARNING: RISK OF THYROID C-CELL TUMORS

- Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether SAXENDA 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.
- SAXENDA is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors.

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

- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.
- Hypersensitivity to liraglutide or any excipients in SAXENDA.
- Pregnancy.

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

- Thyroid C-cell Tumors: See Boxed Warning.

- Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated.
- Hypoglycemia: Can occur in adults when SAXENDA is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin. The risk may be lowered by a reduction in the dose of concomitantly administered insulin secretagogues or insulin. In the pediatric clinical trial, patients did not have type 2 diabetes. Hypoglycemia occurred in SAXENDA-treated pediatric patients. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.
- Heart Rate Increase: Monitor heart rate at regular intervals.
- Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of SAXENDA in patients with renal impairment.
- Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue SAXENDA and other suspect medications and promptly seek medical advice.
- Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue SAXENDA if symptoms develop.

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

- Most common adverse reactions, reported in greater than or equal to 5% are: nausea, diarrhea, constipation, vomiting, injection site reactions, headache, hypoglycemia, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, upper abdominal pain, pyrexia, and gastroenteritis.

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

8.4 Pediatric Use

The safety and effectiveness of SAXENDA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management have been established in pediatric patients aged 12 years and older with body weight above 60 kg and an initial BMI corresponding to 30 kg/m^2 or greater for adults (obese) by international cut-offs (see Table 2). Use of SAXENDA for this indication is supported by a 56-week double-blind, placebo-controlled clinical trial in 251 pediatric patients aged 12 to 17 years, a pharmacokinetic study in pediatric patients, and studies in adults with obesity.

In the pediatric clinical trial, there was one death due to suicide in a SAXENDA-treated patient; one SAXENDA-treated patient had an event of pancreatitis; more episodes of hypoglycemia confirmed by self blood glucose monitoring occurred in SAXENDA-treated patients compared to placebo; and mean increases in resting heart rate of 3 to 7 bpm from baseline were observed with SAXENDA-treated patients.

The safety and effectiveness of SAXENDA have not been established in patients less than 12 years of age.

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	June 2, 2023
Time period of search	January 25, 2010† - June 1, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Liraglutide
MedDRA search terms (Version 26.0)	All PTs
* See Appendix A for a description of the FAERS database. † U.S. Approval Date for Victoza (liraglutide) Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities PT: Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

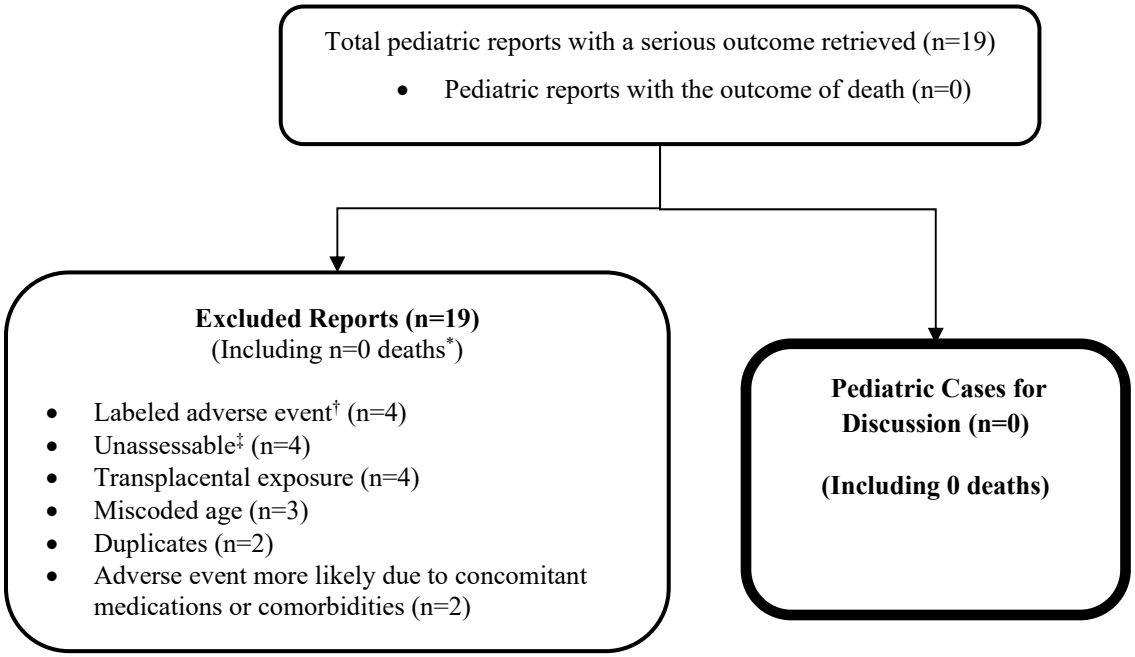
Table 2 presents the number of adult and pediatric FAERS reports from January 25, 2010, through June 1, 2023, with liraglutide.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 25, 2010, through June 1, 2023, with Liraglutide			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	22,850 (18,539)	9,366 (5,151)	698 (413)
Pediatrics (0 - <18 years)	65 (41)	43 (19)	1 (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, or other serious important medical events.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 19 U.S. serious pediatric reports from January 25, 2010, through June 1, 2023, with liraglutide. We reviewed all 19 reports and excluded these reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases with Liraglutide



* No U.S. FAERS reports described fatal outcomes.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The report 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 report cannot be supplemented or verified.

3.1.3 Summary of U.S. Fatal Pediatric Cases (n=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (n=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with liraglutide in pediatric patients less than 18 years of age from January 25, 2010, through June 1, 2023. Nineteen reports were identified; however, all 19 reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with liraglutide in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for liraglutide. DPV will continue to monitor all adverse events associated with the use of liraglutide.

6 REFERENCES

1. Victoza (liraglutide) [package insert]. Plainsboro, NJ. Novo Nordisk Inc. Revised June 2022.

2. Saxenda (liraglutide) [package insert]. Plainsboro, NJ. Novo Nordisk Inc. Revised June 2022.

7 APPENDICES

7.1 APPENDIX A. 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.

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/s/

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