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:	May 7, 2024
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Product Name:	Gattex (teduglutide)
Pediatric Labeling Approval Date:	May 16, 2019
Application Type/Number:	NDA 203441
Applicant:	Takeda Pharmaceuticals USA, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gattex (teduglutide) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with teduglutide in pediatric patients.

Gattex (teduglutide) is a glucagon-like peptide-2 (GLP-2) analog that was initially approved in the U.S. on December 21, 2012, for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.[1]

On May 16, 2019, FDA expanded the teduglutide indication to include treatment of adults and pediatric patients aged 1 year and older with SBS who are dependent on parenteral support. The safety and effectiveness of teduglutide in patients aged less than 1 year have not been established.[2]

This pediatric postmarketing safety review was stimulated by pediatric labeling on May 16, 2019, that expanded the indication for use in patients 1 year of age and older. FDA has not previously presented a pediatric postmarketing pharmacovigilance review for teduglutide to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with teduglutide in pediatric patients less than 17 years of age from December 21, 2012 – December 17, 2023, and identified 347 reports; however, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with teduglutide in pediatric patients less than 17 years of age.

DPV did not identify any new pediatric safety concerns for teduglutide at this time and will continue routine pharmacovigilance monitoring for teduglutide.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Gattex (teduglutide) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with teduglutide in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Gattex (teduglutide) is a glucagon-like peptide-2 (GLP-2) analog that was initially approved in the U.S. on December 21, 2012, for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.[1]

On May 16, 2019, FDA expanded the teduglutide indication to include treatment of adults and pediatric patients aged 1 year and older with SBS who are dependent on parenteral support. The safety and effectiveness of teduglutide in patients aged less than 1 year have not been established.[2]

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1.2 RELEVANT LABELED SAFETY INFORMATION

The Gattex labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Gattex labeling information, please refer to the full prescribing information.[1]

> ----------CONTRAINDICATIONS----------
> None. (4)
>
> ----------WARNINGS AND PRECAUTIONS ----------
> - Acceleration of Neoplastic Growth: In adults and pediatric patients, colonoscopy is recommended after 1 year of treatment. Perform subsequent colonoscopies no less frequently than every 5 years. In case of intestinal malignancy, discontinue GATTEX. The decision to continue GATTEX in patients with non-gastrointestinal malignancy should be made based on benefit-risk considerations. (5.1)
> - Intestinal Obstruction: In patients who develop intestinal or stomal obstruction, temporarily discontinue GATTEX pending further clinical evaluation and management. (5.2)
> - Biliary and Pancreatic Disease: Obtain bilirubin, alkaline phosphatase, lipase, amylase every 6 months. If clinically meaningful changes are seen, further evaluation is recommended including imaging, and reassess continued GATTEX treatment. (5.3)
> - Fluid Overload, Including Congestive Heart Failure: If fluid overload occurs, adjust parenteral support, and reassess continued GATTEX treatment. (5.4)
> - Potential for Increased Absorption of Oral Medications: Monitor patients on concomitant oral medications (e.g., benzodiazepines) for adverse reactions related to the concomitant drug; dosage reduction of the other drug may be required. (5.5, 7.1)
>
> ----------ADVERSE REACTIONS ----------
> Most common adverse reactions (≥10%) are: abdominal pain, nausea, upper respiratory tract infection, abdominal distension, injection site reaction, vomiting, fluid overload, and hypersensitivity. (6.1)

8.4 Pediatric Use
The safety and effectiveness in pediatric patients less than 1 year of age have not been established.

The safety and effectiveness of GATTEX have been established in pediatric patients 1 year to less than 17 years of age who are dependent on parenteral support for the treatment of SBS. Use of GATTEX in this population is supported by evidence from adequate and well-controlled studies in adults, with additional efficacy, safety, pharmacokinetic and pharmacodynamic data in pediatric patients 1 year to less than 17 years of age [see Dosage and Administration (2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]. These data were derived from two studies of 24-week (Study 5) and 12week (NCT01952080) duration in which 41 pediatric patients were treated with GATTEX in the following groups: 1 infant (1 year to less than 2 years), 37 children (2 years to less than 12 years) and 3 adolescents (12 years to less than 17 years).

In these 2 studies and the corresponding extension studies (Study 6 and NCT02949362), 29 pediatric patients were administered GATTEX prospectively for up to 94 weeks [see Clinical Studies (14.2)]. Adverse reactions in pediatric patients were similar to those seen in adults [see Adverse Reactions (6.1)].

Juvenile Animal Toxicity Data
In a juvenile toxicity study, teduglutide was administered to juvenile minipigs at subcutaneous doses of 0.5, 2.5 and 12.5 mg/kg twice daily (1, 5, and 25 mg/kg/day) from post-natal day 7 and continuing for 90 days). Exposures (AUC) at these doses were at least 12-, 25-, and 170-fold the pediatric clinical exposure for ages 1 year to 11 years at 0.05 mg/kg, respectively, and 10-, 21-, and 141-fold the pediatric clinical exposure for ages 12 years to 17 years at 0.05 mg/kg, respectively.

In juvenile minipigs, subcutaneous teduglutide caused intestinotrophic effects, gall bladder mucosal hyperplasia, bile duct mucosal hyperplasia, and injection site reactions, similar to those observed in adult animals.

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	December 18, 2023
Time period of search	December 21, 2012 † - December 17, 2023
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: Teduglutide, teduglutide\water
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Initial teduglutide U.S. approval date. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

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 December 21, 2012 – December 17, 2023, with teduglutide.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From December 21, 2012 – December 17, 2023, With Teduglutide			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	5200 (3481)	4649 (3013)	449 (363)
Pediatrics (0 - < 17 years)	831 (376)	793 (347)	20 (9)

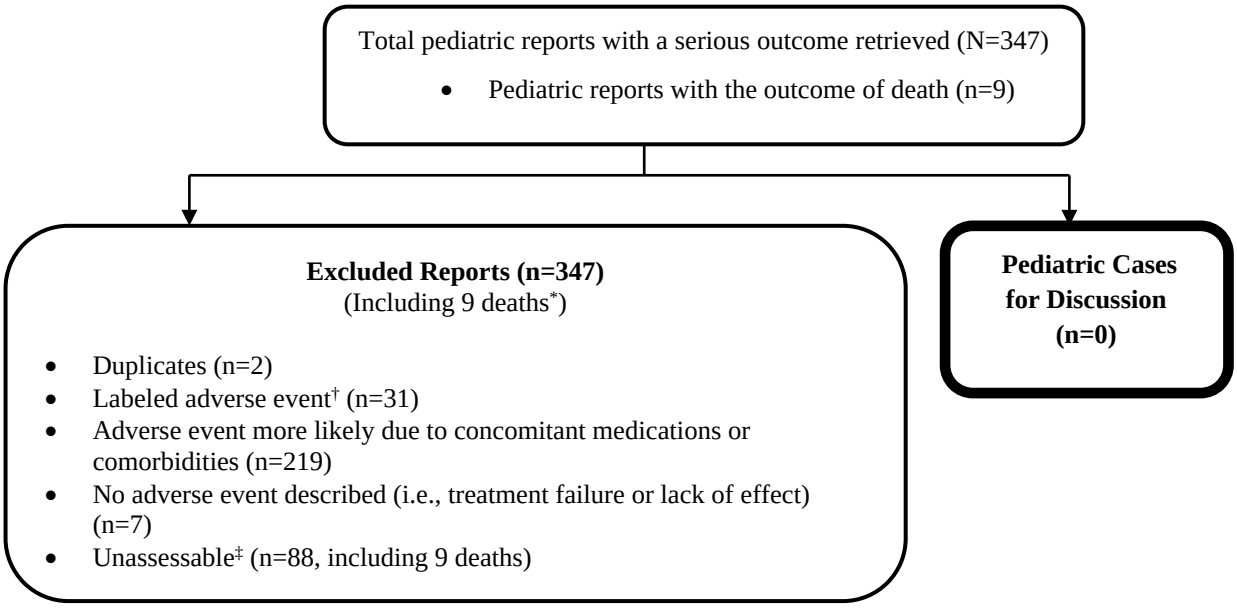
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 347 U.S. serious pediatric reports from December 21, 2012 – December 17, 2023. DPV reviewed all U.S. FAERS pediatric reports with a serious outcome and excluded all 347 reports from the case series for the reasons listed in **Figure 1**.

Figure 1. Selection of U.S. Serious Pediatric Cases With Teduglutide



* Nine excluded U.S. FAERS reports described fatal outcomes. We assessed causality for all nine reports as unassessable with teduglutide. Four cases reported patients with prolonged complicated clinical courses but provided insufficient information to determine temporality of events with teduglutide, involvement of concomitant medications and comorbidities, or cause of death. The remaining five cases included no information about the patient's clinical course to allow for a causality assessment with teduglutide.

† 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), 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 teduglutide in pediatric patients less than 17 years of age from December 21, 2012 – December 17, 2023, and identified 347 reports; however, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with teduglutide in pediatric patients less than 17 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for teduglutide at this time and will continue routine pharmacovigilance monitoring for teduglutide.

6 REFERENCES

1. Gattex (teduglutide). [Prescribing information]. Bedminster, NJ; NPS Pharmaceuticals: December, 2012.
2. Gattex (teduglutide). [Prescribing information]. Lexington, MA; Takeda Pharmaceutical U.S.A., Inc.: February, 2024.

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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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