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 Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 24, 2023
Reviewer:	Ivone Kim, MD, Medical Officer Division of Pharmacovigilance I
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Product Names:	Welchol (colesevelam hydrochloride) tablets Welchol (colesevelam hydrochloride) for oral suspension Welchol (colesevelam hydrochloride) chewable bars
Pediatric Labeling Approval Dates:	April 3, 2019 October 20, 2021
Application Type/Numbers:	NDA 210895, 021176, 022362
Applicant:	Cosette
TTT Record ID:	2023-6226

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Welchol (colesevelam hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with colesevelam in pediatric patients.

Welchol (colesevelam hydrochloride) is a bile acid sequestrant currently indicated as an adjunct to diet and exercise to:

- Reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia
- Reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familiar hypercholesterolemia (HeFH), unable to reach LDL-C target levels despite an adequate trial of diet and lifestyle modification
- Improve glycemic control in adults with type 2 diabetes mellitus

There are four dosage forms for Welchol including capsule (NDA 021141), tablet (NDA 021176), suspension (NDA 022362), and chewable bar (NDA 210895). Notably, NDA 021141 was never manufactured or distributed, and NDAs 210895 and 022362 (1.875 g only) have been withdrawn from marketing.

This pediatric postmarketing safety review was prompted by the following pediatric labelings:

- Pediatric labeling on April 3, 2019, at initial approval for NDA 210895 that included use in pediatric patients aged 10 years and older for the reduction of LDL-C levels in boys and postmenarchal girls with HeFH
- Pediatric labeling on October 20, 2021, for NDA 021176 and NDA 022362 that included information about studies that failed to establish the safety and effectiveness of colesevelam for use in improving glycemic control in pediatric patients with type 2 diabetes mellitus

A pediatric safety review for colesevelam has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all serious reports with colesevelam in pediatric patients less than 18 years of age through August 28, 2023, and identified four reports. However, all 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 directly associated with colesevelam in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Welchol (colesevelam hydrochloride) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with colesevelam in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Welchol (colesevelam hydrochloride) is a bile acid sequestrant currently indicated as an adjunct to diet and exercise to[1,2]:

- Reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia
- Reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familiar hypercholesterolemia (HeFH), unable to reach LDL-C target levels despite an adequate trial of diet and lifestyle modification
- Improve glycemic control in adults with type 2 diabetes mellitus

There are four dosage forms for Welchol. **Table 1** describes Welchol dosage forms with corresponding application numbers, initial FDA approval dates, and current marketing status.

Table 1. Welchol (colesevelam hydrochloride) Dosage Forms

Dosage Form	Dosage Strength	New Drug Application (NDA)	FDA Approval Date	Current Marketing Status
Capsule[3]	375 mg	021141	May 26, 2000	Discontinued*
Tablet[1]	625 mg	021176	May 26, 2000	Marketed
Oral suspension[2]	1.875 g	022362	October 2, 2009	Discontinued†
	3.75 g			Marketed
Bar, chewable[4]	3.75 g	210895	April 3, 2019	Discontinued‡

* The Applicant has never manufactured or distributed any commercial products under NDA 021141[5]
† NDA 022362 (1.875 g dosage strength only) has been withdrawn from marketing per the Federal Register[6]
‡ NDA 210895 was withdrawn from marketing effective January 22, 2021[7]

This pediatric postmarketing safety review was prompted by the following pediatric labeling:

- Pediatric labeling on April 3, 2019, at initial approval for NDA 210895 that included use in pediatric patients aged 10 years and older for the reduction of LDL-C levels in boys and postmenarchal girls with HeFH
- Pediatric labeling on October 20, 2021, for NDA 021176 and NDA 022362 that included information about studies that failed to establish the safety and effectiveness of colesevelam for use in improving glycemic control in pediatric patients with type 2 diabetes mellitus

A pediatric safety review for colesevelam has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Welchol labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Welchol labeling information, please refer to the full prescribing information.[1,2]

_____ CONTRAINDICATIONS _____

- Patients with serum triglyceride levels >500 mg/dL (4)
- Patients with a history of hypertriglyceridemia-induced pancreatitis (4)
- Patients with a history of bowel obstruction (4)

_____ WARNINGS AND PRECAUTIONS _____

- Hypertriglyceridemia and Pancreatitis: WELCHOL can increase TG. Hypertriglyceridemia can cause acute pancreatitis. Monitor lipids, including TG. Instruct patients to discontinue WELCHOL and seek prompt medical attention if the symptoms of acute pancreatitis occur (5.1).
- Gastrointestinal Obstruction: Cases of bowel obstruction have occurred. WELCHOL is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction (5.2).
- Vitamin K or Fat-Soluble Vitamin Deficiencies: WELCHOL may decrease absorption of fat-soluble vitamins. Patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins may be at increased risk. Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to WELCHOL (5.3).
- Drug Interactions: Due to the potential for decreased absorption of other drugs that have not been tested for interaction, consider administering at least 4 hours prior to WELCHOL (5.4, 7, 12.3).
- Risks in Patients with Phenylketonuria (PKU): Phenylalanine can be harmful to patients with phenylketonuria. WELCHOL for oral suspension contains 27 mg phenylalanine per 3.75 gram packet (5.5, 11).

_____ ADVERSE REACTIONS _____

In clinical trials, the most common (incidence ≥2% and greater than placebo) adverse reactions with WELCHOL included constipation, dyspepsia, and nausea (6.1).

8.4 Pediatric Use

Primary Hyperlipidemia

The safety and effectiveness of WELCHOL to reduce LDL-C levels in boys and postmenarchal girls 10 to 17 years of age with HeFH who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification have been established. Use of WELCHOL for this indication is supported by a study in 129 WELCHOL-treated pediatric patients aged 10 to 17 years with HeFH [see Clinical Studies (14.1)]. Adverse reactions commonly observed in pediatric patients compared to placebo, but not in adults, included headache (3.9%), creatine phosphokinase increase (2.3%), and vomiting (2.3%) [see Adverse Reactions (6.1)]. There were no significant effects on fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo. Due to WELCHOL tablet size, WELCHOL for oral suspension is recommended for use in the pediatric population [see Dosage and Administration (2.2, 2.4)]. The safety and effectiveness of WELCHOL in pediatric patients with HeFH less than 10 years of age or in premenarchal females have not been established.

Type 2 Diabetes Mellitus

The safety and effectiveness of WELCHOL to improve glycemic control in pediatric patients with type 2 diabetes mellitus have not been established. Effectiveness was not demonstrated in a 6-month, adequate and well-controlled study conducted in 141 WELCHOL-treated pediatric patients aged 10 to 17 years with type 2 diabetes mellitus.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	August 29, 2023
Time period of search	All dates through August 28, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredient: colesevelam, colesevelam hydrochloride
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

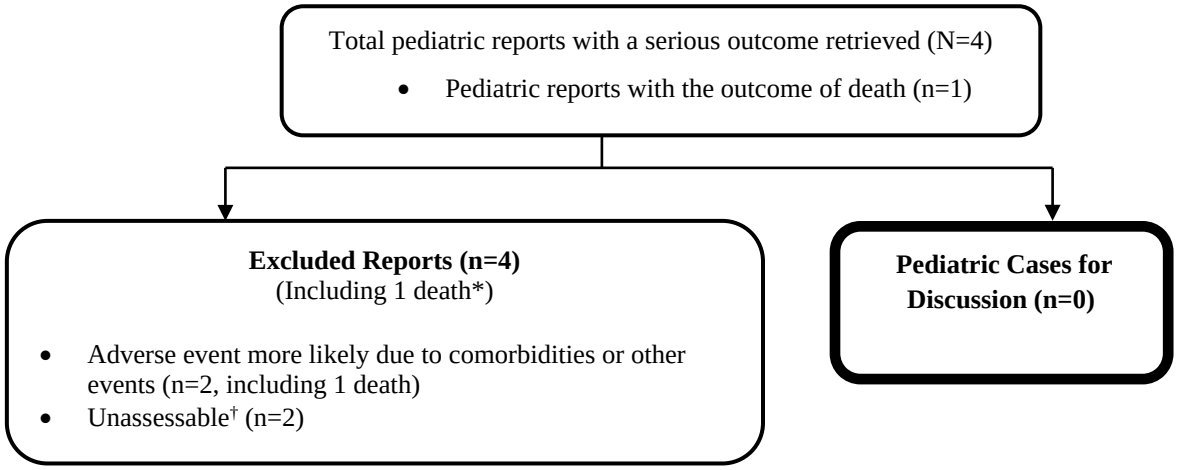
Table 3 presents the number of adult and pediatric FAERS reports through August 28, 2023, with colesevelam.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA Through August 28, 2023, with Colesevelam			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	2062 (1841)	575 (376)	15 (15)
Pediatrics (0 - < 18 years)	14 (13)	4 (3)	1 (1)
* 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 Serious Pediatric Cases in FAERS

Our FAERS search retrieved four serious pediatric reports through August 28, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all four 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 Serious Pediatric Cases With Colesevelam



* One excluded FAERS report described a fatal outcome. The report described a child who died from intracranial hemorrhage following a closed head injury. Death was not determined to be attributed to colesevelam.

† 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 Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV searched FAERS for all serious reports with colesevelam in pediatric patients less than 18 years of age through August 28, 2023, and identified four reports. However, all 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 directly associated with colesevelam in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Welchol (colesevelam hydrochloride) tablets. [Prescribing information]. Basking Ridge, NJ; Daiichi Sankyo, Inc.: October, 2021.
2. Welchol (colesevelam hydrochloride) oral suspension. [Prescribing information]. Basking Ridge, NJ; Daiichi Sankyo, Inc.: October, 2021.
3. Welchol (colesevelam hydrochloride) tablets. [Prescribing information]. New York, NY; Sankyo Pharma, Inc.: May, 2000.
4. Welchol (colesevelam hydrochloride) chewable bars. [Prescribing information]. Basking Ridge, NJ; Daiichi Sankyo, Inc.: May, 2020.
5. Welchol (colesevelam hydrochloride) Capsules, 375 mg. NDA 021141. Annual report. July 24, 2023.
6. Federal Register. Vol 85, No. 204. Wednesday, October 21, 2020. (2020-23300). Available at: https://www.govinfo.gov/content/pkg/FR-2020-10-21/html/2020-23300.htm. Accessed September 11, 2023.
7. Federal Register. Vol 85, No. 247. Wednesday, December 23, 2020. (2020-28374). Available at: https://www.govinfo.gov/content/pkg/FR-2020-12-23/pdf/2020-28374.pdf. Accessed August 30, 2023.

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 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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