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

Pediatric Postmarketing Pharmacovigilance Review

Date:	June 21, 2018
Safety Evaluator:	Thao Tran, PharmD, BCPS Division of Pharmacovigilance-I (DPV-I)
Medical Officer:	Ivone Kim, MD, FAAP DPV-I
Team Leader:	Mihaela Jason, PharmD, BCPS DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, MS, BCPS DPV-I
Product Name:	Renvela (sevelamer carbonate)
Pediatric Labeling Approval Date:	November 25, 2016
NDA Numbers:	022127, 022318
Applicant/Sponsor:	Genzyme
OSE RCM #:	2018-826

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for sevelamer carbonate (Renvela) in pediatric patients (0-18 years of age).

Sevelamer carbonate was first approved in 2007 and is indicated for the control of serum phosphorus in adults with chronic kidney disease on dialysis. The approved pediatric indication is for the control of serum phosphorus in patients 6 years of age and older with chronic kidney disease on dialysis.

The Division of Pharmacovigilance (DPV) evaluated all FDA Adverse Event Reporting System (FAERS) reports of adverse events associated with sevelamer carbonate in pediatric patients received between October 19, 2007 to April 5, 2018. DPV did not retrieve any pediatric cases with an outcome of death. Four non-fatal pediatric cases with serious outcomes were identified and described unlabeled adverse events such as unspecified chest infection, hypereosinophilia, hyperammonemic encephalopathy, and acute gastritis. The four non-fatal cases reported events of high background rate, confounded by other concomitant medications or disease state, or provided limited clinical information for causality assessment.

No new safety signals were identified with sevelamer carbonate. DPV will continue routine pharmacovigilance of adverse events associated with sevelamer carbonate use in pediatric patients.

1 INTRODUCTION

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for sevelamer carbonate (Renvela) in pediatric patients (0-18 years of age).

1.1 PEDIATRIC REGULATORY HISTORY

Sevelamer carbonate is a phosphate binder that binds dietary phosphate in the gastrointestinal tract, thereby decreasing its absorption and lowering serum phosphorus levels. Sevelamer carbonate tablets and powder for oral solution were approved on October 19, 2007 (NDA 22127) and August 12, 2009 (NDA 22318), respectively, for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.[1] Both approvals included a postmarketing requirement to conduct deferred pediatric studies under PREA in patients with CKD on dialysis [age <1 month to 16 years (NDA 22127) and age 0 to 18 years (NDA 22318)]. On May 21, 2016, the Sponsor submitted a prior approval labeling supplement (S-008) with proposed changes to pediatric labeling based on the study results.[2]

On November 25, 2016, sevelamer carbonate was approved for controlling serum phosphorous in pediatric patients 6 years of age and older with CKD on dialysis based on the efficacy and safety results of Study SVCARB07609.[2] This study included a 2-week, randomized, placebo-controlled, fixed-dose period followed by a 6-month, single-arm, open-label, dose-titration period. The study provided evidence of safety and effectiveness of sevelamer carbonate in pediatric patients 13 years of age and older with CKD on dialysis, but the treatment effect on serum phosphorus was not observed in patients 6 to <13 years of age.[2] However, based on the mechanism of action of the drug and data in older patients, extrapolation of efficacy was made to the pediatric population.[2] No patients younger than 6 years of age were enrolled; therefore, the safety and efficacy of sevelamer carbonate has not been established in pediatric patients younger than 6 years of age. Adverse events reported in this study were consistent with the known safety profile observed in studies in adult patients.[2]

1.2 HIGHLIGHTS OF SAFETY ISSUES[1]

RENVELA

Below are the current highlights of the labeled safety issues:

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

- Bowel obstruction. (4)
- Known hypersensitivity to sevelamer carbonate, sevelamer hydrochloride, or to any of the excipients. (4)

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

- Serious cases of dysphagia, bowel obstruction, and perforation have been associated with sevelamer use, some requiring hospitalization and surgery. (5.1)

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

- Most of the safety experience is with sevelamer tablets and sevelamer hydrochloride. In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%) and constipation (8%). (6.1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Sevelamer carbonate is not absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure to the drug.

Clinical Considerations

Sevelamer carbonate may decrease serum levels of fat soluble vitamins and folic acid in pregnant women *[see Clinical Pharmacology (12.2)]*. Consider supplementation.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	04/05/2018
Time Period of Search	10/19/2007* - 04/05/2018

Table 2.1.1 FAERS Search Strategy	
Search Type	FBIS Product Manufacturer Reporting Summary, Quick Query
Product Active Ingredient	Sevelamer carbonate; Sevelamer
NDA#	022127; 022318
Search Parameters	All ages, all outcomes, worldwide

[*] U.S. Approval date

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports*[October 19, 2007 through April 5, 2018] with Renvela (sevelamer carbonate)

	All reports (U.S.)	**Serious[†] (U.S.)**	**Death (U.S.)**
Adults (≥ 19 years)	995 (899)	568 (473)	204 (185)
Pediatrics (0 - <19 years)[‡]	24 (12)	**15[§] (3)**	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.

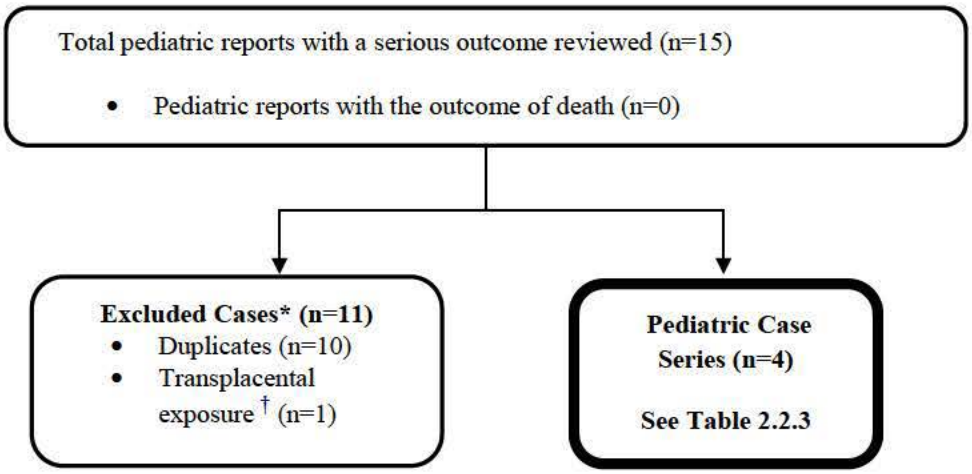
[‡] Pediatric efficacy and safety study SVCARB07609 enrolled patients from 0 to 18 years old

[§] See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 15 pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3** and **2.4.**

Figure 2.2.2 Selection of Serious Pediatric Cases with Renvela



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
† This case describes transplacental exposure to sevelamer carbonate in a 30-year-old female within the first two months of pregnancy. The mother delivered premature twins with no other complications reported.

2.2.3 Characteristics of Pediatric Case Series

Table 2.2.3 Characteristics of Pediatric Case Series with Renvela (N=4)

Age (n=4)	1 year	1
	7 and 10 years	2
	14 years	1
Sex	Male	2
	Female	2
Country	United States	1
	Foreign	3
Reported Reason for Use	Renal failure	1
	Hyperphosphatemia	1
	Unknown	2
Serious Outcome*	Hospitalization	2
	Other serious	3

* 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. Reports may have more than one outcome.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There are no pediatric cases with an outcome of death.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

Unlabeled Events:

Chest infection (n=1) (FAERS# 12965832, MFR# GB-SA-2016SA210812, Great Britain, November 2016)

The patient's mother reported that her 10-year-old daughter experienced "chest infection" after an unknown duration of treatment with sevelamer carbonate, azithromycin, levothyroxine, warfarin, salbultamol, and folic acid. Azithromycin was discontinued but it is unknown what action was taken for the other concomitant medications. Her daughter was treated with unspecified antibiotics and no further clinical details were provided (i.e., unknown outcome, unknown medical history).

Reviewer's comment: This case describes an unspecified chest infection with limited clinical information such as clinical course, outcomes, and medical history, which limits our causality assessment.

Hypereosinophilia (n=1) (FAERS# 11414071, MFR# FR-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2015-BI-45130FF, France, August 2015)

A healthcare authority reported that a 1-year-old female patient experienced hypereosinophilia one month after initiating sevelamer carbonate 2.4 g, 2 packets once daily. The patient also initiated treatment with the following medications one to two months prior to experiencing hypereosinophilia: Bicavera peritoneal dialysate solution, alfacalcidol (vitamin D analogue), calcifediol (vitamin D analogue), polystyrene sulfonate, epoietin beta, ursodiol, losartan, nicardipine, bisoprolol, and clonidine. The patient was diagnosed with renal failure requiring dialysis secondary to hypertension 1.5 months prior to hypereosinophilia occurrence and also experienced an asthma attack 5 months prior to the event. Two weeks after the development of hypereosinophilia, the patient recovered from the event while continuing treatment with all the listed medications. Treatment information for the event was not provided.

Reviewer's comments: The short duration of "hypereosinophilia" reflects transient eosinophilia instead of hypereosinophilia syndrome, which is defined as elevated eosinophil counts of > 1500 eosinophils/mcL for 6 months or more leading to organ dysfunction.[3] Multiple medications and conditions (i.e. allergic and autoimmune diseases) may be potential alternative explanations for "hypereosinophilia" as all concomitant medications were initiated at the same time as sevelamer. The event resolved despite continuing treatment with all the listed medications. Of note, none of the concomitant medications are labeled for hypereosinophilia.

Acute gastritis (n=1) (FAERS# 9681406, MFR# US-SA-2013SA111233, USA, November 2013)

The investigator from a phase 4 study[4] reported that a 14-year-old male patient experienced acute gastritis requiring hospitalization after five months of sevelamer carbonate treatment. Sevelamer carbonate dose was adjusted to elevated serum phosphorous levels and titrated to a maximum reported dose of 3200 mg three times a day. The symptoms were described as acute non-bloody, non-bilious emesis (3-4 episodes) with increased nausea and acute right lower quadrant abdominal pain (pain scale of >8/10). The patient received ondansetron for vomiting. Appendicitis was ruled out and white blood cell count was normal. The patient recovered from his symptoms overnight, but the action taken with sevelamer carbonate was unknown. About two weeks after the event, the patient discontinued sevelamer carbonate and was withdrawn from the study due to renal transplant. The patient's medical history included hypertension, hypocomplementemic glomerulonephritis secondary to post-streptococcus glomerulonephritis, end stage renal disease (ESRD), migraine, secondary hyperparathyroidism, vitamin D deficiency, post-concussion syndrome, nausea and dyspepsia associated with dialysis, iron deficiency anemia, and dialysis catheter occlusion due to hemodialysis. The patient's concomitant medications included amlodipine, lisinopril, vitamin B complex, omeprazole, sodium ferric gluconate complex, alteplase, heparin, ondansetron, ibuprofen, calcitriol, acetaminophen, clindamycin phosphate, and epoetin alfa.

Reviewer's comments: The high prevalence of gastrointestinal symptoms in pediatric patients and ESRD patients due the effect of uremia[5] and concomitant medications such as ibuprofen are potential alternative explanations for this patient's acute gastritis occurring five months after sevelamer use.

Hyperammonemic encephalopathy (n=1) (FAERS# 11629098, MFR# GB-SA-2015SA159545, Great Britain, October 2015)

A physician reported that a 7-year-old male patient experienced hyperammonemic encephalopathy and acute confusional status after two days of receiving sevelamer carbonate 400mg three times daily. The patient's medical history included liver portal hypertension and ESRD (dialysis dependent) secondary to autosomal recessive polycystic kidney disease (ARPKD). The patient's concomitant medications included darbepoetin alfa, calcium carbonate, midodrine, ursodeoxycholic acid, iron sucrose, and cephalexin. Sevelamer carbonate was discontinued one day prior to the onset of the event. The patient required hospitalization and was treated with sodium benzoate. The reporting physician noted that the patient's liver portal hypertension and ARPKD may be the contributing factors to the event.

Reviewer's comments: This patient experienced hyperammonemic encephalopathy and confusion, suggestive of hepatorenal syndrome, which is a known complication of his underlying portal hypertension and ARPKD. Additionally, the patient discontinued sevelamer one day prior to the onset of encephalopathy making it unlikely related to sevelamer. None of the concomitant medications are labeled for hepatotoxicity.

3 DISCUSSION

Of the four cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with sevelamer carbonate. These four cases reported events of high background rate, confounded by other concomitant medications or disease state, or provided limited clinical information for causality assessment.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

5 RECOMMENDATIONS

DPV will continue routine pharmacovigilance monitoring for sevelamer carbonate.

6 REFERENCES

[1] Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed April 20, 2018.

[2] Letter of Supplemental Approval for NDAs 22127 s015 and 22318 s008, Renvela Tablet and Powder for Oral Suspension in Pediatric Patients 6 years of Age and Older. October 31, 2016. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed May 3, 2018.

[3] American Academy of Allergy Asthma & Immunology. Hypereosinophilic Syndrome (HES). http://www.aaaai.org/conditions-and-treatments/related-conditions/hypereosinophilic-syndrome. Accessed May 3, 2018.

[4] Clinical Trials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 April 10 - Identifier NCT01574326, A 2-Week, Randomized, Placebo-Controlled, Fixed Dose Period Followed by a 6-Month, Single-Arm, Open-Label, Dose Titration Period Study to Investigate the Efficacy and Safety of Sevelamer Carbonate in Hyperphosphatemic Pediatric Patients With Chronic Kidney Disease- 2016 July 25; [cited 2018 April 20]. Available from https://clinicaltrials.gov/ct2/show/NCT01574326

[5] Etemad B. Gastrointestinal Complications of Renal Failure. Gastrointestinal disorders and systemic disease, Part II. *Gastroenterol Clin N Am 1998*; 27 (4): 875.

7 APPENDICES

7.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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/

THAO T TRAN
06/21/2018

IVONE E KIM
06/22/2018

MIHAELA P JASON
06/25/2018

MONICA MUNOZ
06/25/2018