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

Pediatric Postmarketing Pharmacovigilance

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Product Name:	Emend (fosaprepitant dimeglumine), fosaprepitant dimeglumine
Pediatric Labeling Approval Date:	April 3, 2018
Application Type/Number:	NDA# 022023, 210064, Multiple ANDAs
Applicant:	Merck Sharp & Dohme Corp, Teva, Multiple Applicants
OSE RCM #:	2021-1101

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for fosaprepitant in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events associated with fosaprepitant in pediatric patients.

The FDA approved fosaprepitant for injection on January 25, 2008 as an alternative to oral aprepitant for Day 1 of the aprepitant oral 3-day regimen for chemotherapy-induced nausea and vomiting in adult patients. This review was triggered by FDA's approval of fosaprepitant for prevention of (1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and (2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in patients 6 months of age and older on April 3, 2018.

Our FAERS search did not identify any unlabeled pediatric adverse events reports associated with fosaprepitant from January 25, 2008 to April 30, 2021.

DPV-I did not identify any pediatric safety concerns for fosaprepitant at this time. DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of fosaprepitant.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for fosaprepitant dimeglumine in pediatric patients through age 17 years. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events associated with fosaprepitant in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Fosaprepitant dimeglumine (Emend) for injection is a prodrug of aprepitant. Aprepitant oral capsule (Emend) was approved on March 26, 2003 and aprepitant oral suspension was approved on December 17, 2015. Both are indicated, in combination with other antiemetic agents, for prevention of: (1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and (2) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). Currently, aprepitant oral capsule is indicated in patients 12 years of age and older and the oral suspension is indicated in patients 6 months of age and older.

Table 1 shows the U.S. regulatory history of fosaprepitant dimeglumine for injection, which was initially approved on January 25, 2008, in adult patients as an alternative to oral aprepitant for Day 1 of the aprepitant oral 3-day regimen.

Table 1. U.S. Regulatory History of Fosaprepitant Dimeglumine for Injection

Date	Indication
January 25, 2008	Fosaprepitant 115 mg was approved, in combination with other antiemetic agents, for prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin • nausea and vomiting associated with initial and repeat courses of MEC
November 12, 2010	Fosaprepitant 150 mg was approved in adults as a single-day dosing regimen for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin
February 1, 2016	Fosaprepitant 150 mg was approved in adults as single-day dosing regimen for prevention of delayed nausea and vomiting associated with initial and repeat courses of MEC
April 3, 2018	Fosaprepitant was approved in patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of HEC • delayed nausea and vomiting associated with initial and repeat courses of MEC

Abbreviations: HEC=highly emetogenic cancer chemotherapy, MEC=moderately emetogenic cancer chemotherapy

This review was triggered by pediatric studies completed under PREA and BPCA resulting in approval of fosaprepitant on April 3, 2018 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and delayed nausea and vomiting associated with initial and repeat courses of MEC in patients 6 months of age and older. Phase 1 and phase 2b trials were conducted to assess and evaluate pharmacokinetics/pharmacodynamics, safety, and tolerability of fosaprepitant in pediatric patients (age 0 to 17 years of age) receiving emetogenic chemotherapy. Patient as young as 6 months of age were recruited. The efficacy of a 1-day fosaprepitant regimen in pediatric patients receiving one day of chemotherapy is extrapolated from adult patients with similar exposures and receiving chemotherapy for a single day. The AUCs of the fosaprepitant group were similar to that of the aprepitant group, while the C_{max} of fosaprepitant were 1.5 to 2 times higher than that observed with oral aprepitant likely due to differences in route of administration. Safety information for the higher Day 1 C_{max} is adequate from the pharmacokinetic studies used to support bridging and extrapolation.[1]

This is the first review of fosaprepitant conducted for the Pediatric Advisory Committee (PAC). DPV previously presented an evaluation of postmarketing adverse event reports for aprepitant in pediatric patients to the PAC; the DPV evaluation, dated December 11, 2017, did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with aprepitant.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Warnings and Precautions and Adverse Reactions (from the Highlights of Prescribing Information), and Pediatric Use sections of the fosaprepitant product labeling are reproduced below.[3]

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

- CYP3A4 Interactions: Fosaprepitant is a weak inhibitor of CYP3A4, and aprepitant, the active moiety, is a substrate, inhibitor, and inducer of CYP3A4; see Full Prescribing Information for recommendations regarding contraindications, risk of adverse reactions, and dosage adjustment of EMEND and concomitant drugs. (4, 5.1, 7.1, 7.2)
- Hypersensitivity Reactions (including anaphylaxis and anaphylactic shock): May occur during or soon after infusion. If symptoms occur, discontinue the drug. Do not reinitiate EMEND if symptoms occur with previous use. (4, 5.2)
- Infusion Site Reactions (including thrombophlebitis, necrosis, and vasculitis): Majority of reactions reported in patients receiving vesicant chemotherapy. Avoid infusion into small veins. Discontinue infusion and administer treatment if a severe reaction develops. (5.3)
- Warfarin (a CYP2C9 substrate): Risk of decreased INR of prothrombin time; monitor INR in 2–week period, particularly at 7 to 10 days, following initiation of EMEND. (5.4, 7.1)
- Hormonal Contraceptives: Efficacy of contraceptives may be reduced during and for 28 days following administration of EMEND. Use effective alternative or back-up methods of contraception. (5.5, 7.1, 8.3)

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

- Most common adverse reactions in adults (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (6.1)
- Adverse reactions in pediatrics are similar to adults.

8.4 Pediatric Use

The safety and effectiveness of a single dose regimen of EMEND for injection and a 3-day IV/oral/oral EMEND regimen have been established in pediatric patients 6 months to 17 years for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

Use of EMEND in this age group is supported by evidence from adequate and well-controlled studies of EMEND for injection in adults, with additional safety, efficacy and pharmacokinetic data in pediatric patients 6 months to 17 years. Efficacy was also supported by data from an adequate and well-controlled study of a 3-day oral aprepitant regimen in pediatric patients 6 months to 17 years. See the full prescribing information for EMEND capsules for complete clinical information regarding studies performed with oral aprepitant. Adverse reactions were similar to those reported in adult patients. *[See Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3)].*

The safety of EMEND for injection administered on consecutive days has not been established in pediatric patients 6 months to 17 years for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

The safety and effectiveness of EMEND for the prevention of nausea and vomiting associated with HEC or MEC have not been established in patients less than 6 months of age.

Juvenile Animal Toxicity Data

In juvenile dogs treated with fosaprepitant, changes in reproductive organs were observed. In juvenile rats treated with aprepitant, slight changes in sexual maturation were observed without an effect on reproduction. No effects on neurobehavior, sensory and motor function, or learning and memory were observed in rats.

In a toxicity study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a newborn human) to day 42 (approximately equivalent to a 2 year old human), decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day. A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male and female rats lower than the exposure at the recommended pediatric human dose) from the early postnatal period (Postnatal Day 10 (equivalent to a newborn human) through Postnatal Day 58 (approximately equivalent to a 15 year old human)). Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 2. FAERS Search Strategy*	
Date of Search	May 10, 2021
Time Period of Search†	January 25, 2008† to April 30, 2021
Search Type	FBIS Quick Query, Profile Manufacturer Report
Product Terms	Product Active Ingredient: Fosaprepitant, fosaprepitant dimeglumine, fosaprepitant or fosaprepitant dimeglumine
MedDRA Search Terms (Version 24.0)	All PTs

* See Appendix A for a description of the FAERS database.

† U.S. approval date for fosaprepitant

Abbreviations: FBIS=FAERS Business Intelligence System, 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 3 presents the number of adult and pediatric FAERS reports from January 25, 2008 to April 30, 2021 with fosaprepitant.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From January 25, 2008 to April 30, 2021 With Fosaprepitant			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	953 (386)	831 (309)	81 (31)
Pediatrics (0 - <18 years)	28 (7)	24 (5)	0 (0)

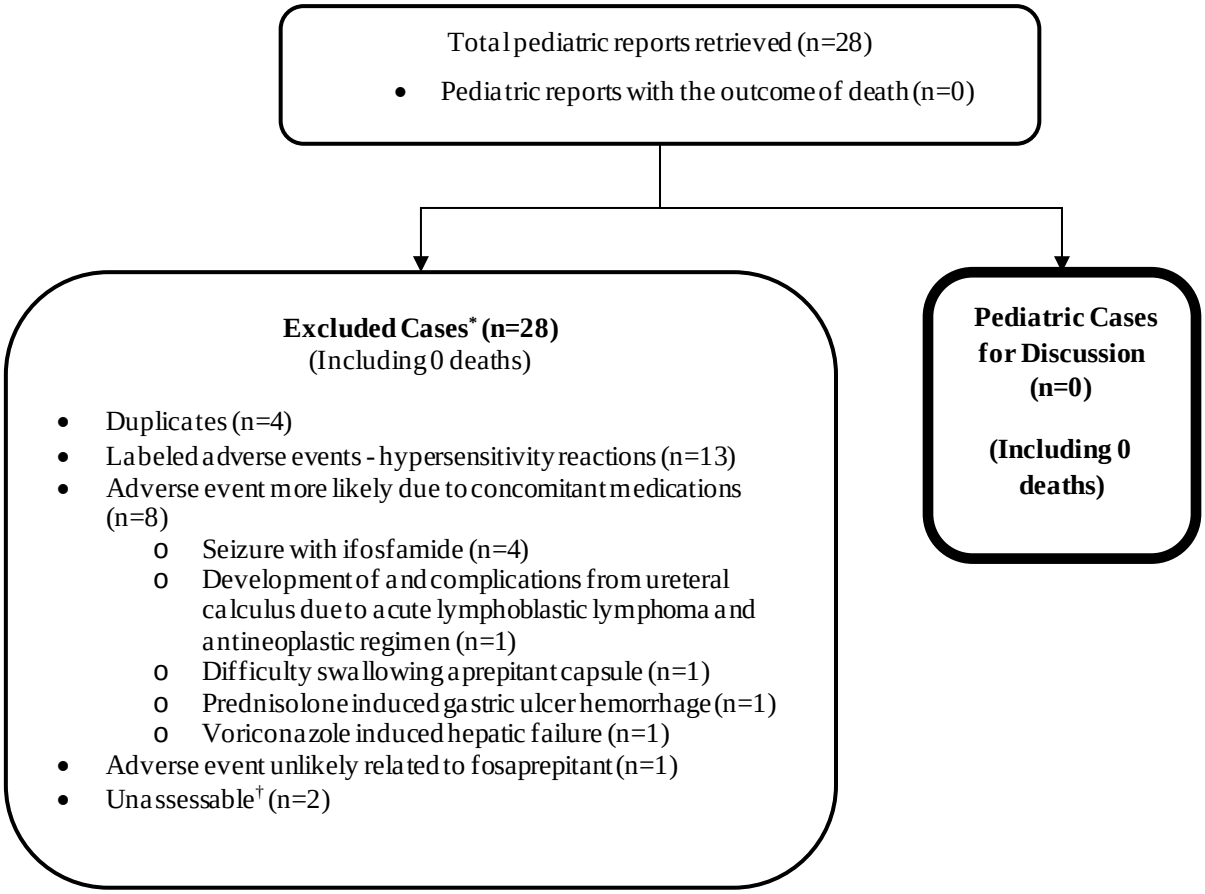
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 Pediatric Cases in FAERS

Our FAERS search retrieved 28 pediatric reports from January 25, 2008 to April 30, 2021. We reviewed all 28 pediatric reports. We excluded reports from the case series for labeled adverse events for fosaprepitant. We further excluded reports from the case series for various reasons such as duplicate reports, unlikely related to fosaprepitant, unassessable reports (i.e., cannot be clinically assessed for causality because information is insufficient or lacking), and adverse event was more likely due to concomitant medications. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Fosaprepitant



* 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 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases associated with fosaprepitant.

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

We did not identify any unlabeled non-fatal adverse event cases associated with fosaprepitant in the pediatric population.

4 DISCUSSION

DPV-I reviewed all FAERS reports associated with fosaprepitant use in the pediatric population (ages 0 to <18 years) from January 25, 2008 to April 30, 2021. During this time, the majority of

FAERS reports described adverse events that were consistent with labeled events described in the fosaprepitant labeling. We did not identify an increase in severity in the labeled adverse events. We did not identify any new safety concerns with fosaprepitant use in the pediatric population.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for fosaprepitant at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of fosaprepitant.

7 REFERENCES

1. Johnson A. Medical Officer Clinical Review of Emend® (fosaprepitant). March 2018. https://www.fda.gov/media/112703/download.
2. Swank K HL, Muñoz. Pediatric Postmarketing Pharmacovigilance Review for Emend (aprepitant) capsule and oral suspension. December 11, 2017. https://www.fda.gov/media/111483/download.
3. Emend®(fosaprepitant) for injection, for intravenous use [Prescribing Information]. Whitehouse Station, NJ: Merck & Co., Inc.; November 2019.

8 APPENDICES

8.1 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 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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