

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

**Pediatric Postmarketing Pharmacovigilance Review**

**Date:** December 11, 2017

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**Product Name:** Emend (aprepitant) Capsule and Oral Suspension

**Pediatric Labeling  
Approval Date:** August 28, 2015 (capsule)  
December 17, 2015 (suspension)

**Application Type/Number:** NDA 021549 (capsule)  
NDA 207865 (suspension)

**Applicant/Sponsor:** Merck & Co., Inc.

**OSE RCM #:** 2017-2088

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## EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance I (DPV-I) evaluated postmarketing adverse event reports with a serious outcome for Emend (aprepitant) capsules and oral suspension in pediatric patients. This review was triggered by the pediatric indications for aprepitant.

Aprepitant is a substance P/neurokinin 1(NK<sub>1</sub>) receptor antagonist approved in the United States (U.S.) for treatment of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Aprepitant was first approved on March 26, 2006, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC), including high-dose cisplatin in adult patients. On October 28, 2005, the indication for aprepitant, in combination with other antiemetic agents, was expanded to include the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). On June 30, 2006, aprepitant capsules were approved for the prevention of PONV in adults. The pediatric indication for aprepitant capsules was approved for children 12 years to 17 years of age and patients less than 12 years of age who weigh at least 30 kg on August 28, 2015 for the CINV indications. On December 17, 2015, aprepitant oral suspension was approved for use in pediatric patients 6 months to less than 12 years of age or pediatric and adult patients unable to swallow capsules for the CINV indications; the pediatric indication for use of aprepitant capsules in patients less than 12 years of age who weigh at least 30 kg was removed at that time.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for aprepitant capsules and oral suspension in the FAERS database from March 26, 2014 through October 10, 2017. This start date was chosen to capture all reports from the data lock date of a previous Division of Gastroenterology and Inborn Errors Products (DGIEP) medical officer review for NDA 21549/S-025, which reviewed all pediatric postmarketing adverse event reports with aprepitant from March 26, 2003 (U.S. approval date for capsules) through March 25, 2014.<sup>2</sup> Of the 63 pediatric postmarketing reports, 33 were duplicates, 11 contained strong alternative causes for the reported adverse events (labeled event for concomitant drug (n=10), event more likely associated with concomitant drug (n=1)), 2 contained limited information for assessment, and 2 described transplacental exposures.

The remaining 13<sup>a</sup> reports described labeled CYP3A4 drug interactions between aprepitant and ifosfamide (n=10), vincristine (n=3), or clarithromycin (n=1). The majority of drug interactions resulted in the labeled adverse event neurotoxicity. Aprepitant is a substrate, a weak-to-

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<sup>a</sup> Cases are not mutually exclusive; one case reported a drug interaction between aprepitant, ifosfamide, and vincristine.

moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Clinically significant CYP3A4 drug interactions with aprepitant are contained in the Warnings and Precautions, Adverse Reactions, Drug Interactions, and Clinical Pharmacology sections of the aprepitant product label. Ifosfamide, vincristine, and clarithromycin are specifically listed in CYP3A4 drug interactions with aprepitant in the aprepitant product label; no change in severity or frequency of the labeled adverse events were noted.

No new safety signal was identified with aprepitant capsules or oral suspension. DPV-I plans to continue postmarketing surveillance of all adverse events with aprepitant.

# 1 INTRODUCTION

This review evaluated postmarketing adverse event reports with a serious outcome for Emend (aprepitant) capsules (NDA 021549) and oral suspension (NDA 207865) in pediatric patients.<sup>b</sup> This review was triggered by the pediatric indication for Emend (aprepitant) capsules and oral suspension.

## 1.1 PRODUCT FORMULATIONS AND INDICATIONS<sup>1</sup>

Aprepitant is a substance P/neurokinin 1(NK<sub>1</sub>) receptor antagonist approved in the United States (U.S.) for treatment of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Aprepitant is available in two oral formulations; capsules (NDA 021549/ 40, 80, 125 mg strengths) and an oral suspension (NDA 207865/ 125 mg to be suspended in 4.6 mL of water for a final concentration of 25 mg/mL). The two formulations can be differentiated by approved indications and populations for use (see Table 1.1 for aprepitant oral formulations and U.S. approval information).

<b>Formulation</b>	<b>NDA</b>	<b>U.S. Approval Dates</b>	<b>Approved Indications*</b>	<b>Approved Population for Use</b>
Capsule	021549	March 26, 2003	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC), including high-dose cisplatin in adult patients	Adults
		October 28, 2005	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	Adults
		June 20, 2006	PONV <sup>†</sup>	Adults
		August 28, 2015	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC	Children 12 to 17 years of age or patients < 12 years of age who weigh ≥ 30 kg <sup>‡</sup>
Oral suspension	207865	December 17, 2015	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC	Pediatric patients 6 months to < 12 years of age or pediatric and adult patients unable to swallow capsules

<sup>b</sup> Emend for injection (NDA 022023) contains a prodrug of aprepitant, fosaprepitant dimeglumine, which is not FDA approved for use in pediatric patients; therefore, Emend for injection is not included in this review.

\* Aprepitant is approved in combination with other antiemetic agents for all CINV indications.

† The recommended oral dosage of aprepitant capsules in adults is 40 mg.

‡ The capsule dosing instructions for patients < 12 years of age who weigh  $\geq$  30 kg was removed when the oral suspension was approved on December 17, 2015, as this subgroup would be covered by oral suspension dosing.

## 1.2 PEDIATRIC REGULATORY HISTORY

In July 2014, the Sponsor, Merck Sharp & Dohme Corp., submitted Efficacy Supplement 25 to NDA 021549 (capsules) and NDA 207865 (oral suspension) to fulfill the Pediatric Research Equity Act (PREA) postmarket requirement (PMR) to evaluate the pharmacokinetic, safety, and efficacy of aprepitant in the prevention of CINV with HEC and MEC in pediatric patients 6 months to 17 years of age. The sponsor was seeking approval for aprepitant oral capsules in pediatric patients aged 12 to 17 years (NDA 021549/S-025) and aprepitant oral suspension for patients 6 months to less than 12 years for the prevention of CINV (NDA 207865).

The following regulatory history was reproduced from Dr. Karyn Berry's (Medical Officer (MO) in the Division of Gastroenterology and Inborn Errors Products (DGIEP)) clinical review of the pediatric supplement to extend the indication to patients 6 months to 17 years of age for aprepitant.<sup>2</sup>

Study Protocol 208 (P208) was a randomized, double-blind, active-comparator controlled, parallel-group study designed to assess the efficacy and safety of aprepitant for the prevention of CINV in pediatric patients, ages 6 months to 17 years, receiving emetogenic chemotherapy for a documented malignancy. The safety analysis was based on 357 pediatric patients. A potential issue with the safe use and administration of the oral suspension was identified during the review. No other safety signals were identified in the clinical data submission.

The overall efficacy and safety for NDA 21549/S-025 (capsules) for use in pediatric patients ages  $\geq$  12 to 17 years for the prevention of CINV associated with HEC and MEC demonstrated an acceptable risk/benefit profile. In general, the safety profile of aprepitant was typical of a patient population with cancer and/or receiving chemotherapeutic drugs.

During the review of NDA 207865 (oral suspension), critical task failures were identified in the results of the Human Factor (HF) studies submitted by the Sponsor. The failures, which included measuring the reconstitution volume and dose volume of the product, would result in pediatric patients receiving either an underdose or overdose of the medication. Based on the inability of the intended population to safely and effectively use the product as labeled, additional data was requested from the Sponsor. The review clock for the oral suspension NDA 207865 was extended to receive additional information to support appropriate labeling instructions for reconstitution and

measurement of doses. Pharmacokinetic data was used to support extending the capsule dosing in labeling to include children less than 12 years of age who weigh  $\geq 30$  kg.

The following regulatory history was reproduced from Dr. Aisha Johnson's (MO in DGIEP) clinical review of aprepitant oral suspension.<sup>3</sup>

On July 1, 2015, the Sponsor submitted an additional HF validation study using a revised protocol based on the Agency's recommendations. The repeat HF study was unable to show that the intended user population is able to use the product safely and effectively. Participants were only able to perform critical task functions safely and effectively 36/67 instances. Most of the task failures noted in the study would result in pediatric patients receiving an underdose, overdose, or not receiving the medication at all. Based on these findings, the Agency recommended that an additional HF study in healthcare providers using revised instructions for use (IFU) and incorporating redesigns recommended by the Division of Medication Error Prevention and Analysis (DMEPA) be conducted by the Sponsor. These study results were submitted as a major amendment.

On October 29, 2015, the Sponsor submitted two additional HF validation studies, one in Oncology nurses and another in lay caregivers. DMEPA reviewed the HF studies and concluded that the results were generally acceptable since most of the intended user population was able to use the product safely and effectively. Based on these findings, the Agency and the Sponsor agreed that reconstitution and measurement of the aprepitant suspension would be limited to health care providers and the measured doses would be dispensed to the patient/caregiver in a prefilled oral dose dispenser/syringe. Given the revised recommendations, it was determined that the nomogram-based dosing would be replaced with individualized dosing used in the phase 3 trial (i.e., 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3). This in turn led to re-examination of the dosing recommendations using the capsule formulation in pediatric patients < 12 years of age who weighed  $\geq 30$  kg. The reviewers noted that for patients < 12 years of age who weigh < 40 kg, administration of the currently labeled capsule dose would result in exposures up to 30 % higher than would be associated with the suspension formulation dosed by weight. The review team concurred with the Sponsor's proposal to remove the capsule dosing instructions for children < 12 years of age who weigh  $\geq 30$  kg, as that subgroup would be covered by suspension dosing.

### **1.3 SUMMARY OF RELEVANT PREVIOUS FDA SAFETY REVIEWS**

In 2008, the Division of Pharmacovigilance I (DPV- I) performed a review evaluating the Adverse Event Reporting System (AERS) database for postmarketing reports of cardiac adverse events associated with aprepitant (oral dosage form) and fosaprepitant (intravenous dosage form). The search of the AERS database from the U.S. approval dates of aprepitant (March 26, 2003) and fosaprepitant (January 25, 2008) to September 25, 2008, identified 57 unduplicated

cases reporting cardiac-related adverse events. After review of all 57 cases, 50 were excluded from the analysis based on various reasons (i.e., related to underlying disease, no temporal relationship, labeled and non-serious events, and concomitant medication). An analysis of the remaining seven cases did not identify any new cardiac safety concerns with aprepitant or fosaprepitant.<sup>4</sup>

In 2014, DGIEP requested DPV-I to search the FDA Adverse Event Reporting System (FAERS) database for reports of hepatotoxicity associated with the use of ondansetron and palonosetron<sup>c</sup> to inform DGIEP as they reviewed NDA 205718 Akynzeo (netupitant/palonosetron). During DGIEP's review of NDA 205718, potential cases of drug-induced liver injury (DILI) with Aloxi (palonosetron) were identified. DPV-I searched the FAERS database for serious cases of DILI associated with the use of palonosetron and ondansetron. Additionally, aprepitant and fosaprepitant were included in the search because they have the same mechanism of action as netupitant. The search identified four reports of possible liver injury with aprepitant, two reports with palonosetron, 72 reports with ondansetron, and no reports with fosaprepitant. Of the 72 reports with ondansetron, concomitant chemotherapy was reported in 45 of the cases. All patients in the aprepitant and palonosetron cases received concomitant cancer chemotherapy prior to the development of liver injury. After a case level analysis, DPV-I did not identify any safety concerns of hepatotoxicity associated with ondansetron, palonosetron, fosaprepitant, or aprepitant.<sup>5</sup>

As discussed in section 1.2 above, DGIEP conducted a clinical review of Efficacy Supplement 25 for NDA 21549. In the Efficacy Supplement, the Sponsor submitted an assessment of postmarketing data on aprepitant use in pediatrics from March 26, 2003 to March 25, 2014. The clinical reviewer also conducted an independent review of the postmarketing pediatric reports of serious adverse events. It was determined that most cases were reported in adolescents (patients aged 12 to < 18 years) receiving aprepitant for off label use. For postmarketing reports of death and serious adverse events, the reviewer concluded that the ability to determine causality was limited by insufficient data and that, in cancer patients, association between adverse events and aprepitant is difficult to assess because of cancer and/or concomitant chemotherapy.

## **1.4 HIGHLIGHTS OF LABELED SAFETY ISSUES<sup>1</sup>**

### **-----CONTRAINDICATIONS-----**

- Known hypersensitivity to any component of this drug (4).
- Concurrent use with pimozide (4).

### **-----WARNINGS AND PRECAUTIONS-----**

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<sup>c</sup> Palonosetron is a 5-HT<sub>3</sub> receptor antagonist; palonosetron is indicated for CINV in adults and pediatric patients aged 1 month to less than 17 years and for PONV in adults.



- Clinically significant CYP3A4 drug interactions: Aprepitant is a substrate, weak-to-moderate inhibitor and inducer of CYP3A4 (4, 5.1, 7.1, 7.2).
- 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 (5.2, 7.1).
- Hormonal contraceptives: Efficacy of contraceptives may be reduced during administration of and for 28 days following the last dose of Emend. Use effective alternative or back-up methods of contraception (5.3, 7.1, 8.3).

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

- Most common adverse reactions are (6.1):  
Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)  
 Adults ( $\geq 3\%$ ): fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransferase increased.  
 Pediatrics ( $\geq 3\%$ ): neutropenia, headache, diarrhea, decreased appetite, cough, fatigue, hemoglobin decreased, dizziness, and hiccups.  
  
Postoperative nausea and vomiting (PONV)  
 Adults ( $\geq 3\%$ ): constipation and hypotension.

-----DRUG INTERACTIONS-----

- Aprepitant is a substrate, a weak-to-moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. See Full Prescribing Information for a list of clinically significant drug interactions. (5.1, 5.2, 5.3, 7.1, 7.2)

## 2 POSTMARKET ADVERSE EVENT REPORTS

### 2.1 METHODS AND MATERIALS

#### 2.1.1 FAERS Search Strategy

DPV-I 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	October 10, 2017
Time Period of Search	March 26, 2014* - October 10, 2017
Search Type	Quick Query Product-Manufacturer Reporting Summary (Profile report)
Product Name	Product Active Ingredient: aprepitant
Search Parameters	All ages, all outcomes, worldwide

\*This start date was chosen to capture all reports from the data lock date of a previous DGIEP MO review for NDA 21549/S-025, which reviewed all pediatric postmarketing adverse event reports with aprepitant from March 26, 2003 (U.S. approval date for capsules) through March 25, 2014.

### 2.2 RESULTS

#### 2.2.1 Total number of FAERS reports by Age

**Table 2.2.1 Total Adult and pediatric FAERS reports\* (March 26, 2014 to October 10, 2017) with aprepitant**

	All reports (U.S.)	Serious <sup>†</sup> (U.S.)	Death (U.S.)
<b>Adults (&gt; 17 years)</b>	984 (304)	829 (181)	132 (75)
<b>Pediatrics (0 - &lt;17 years)</b>	68 (8)	<b>63<sup>‡</sup> (3)</b>	<b>0 (0)</b>

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

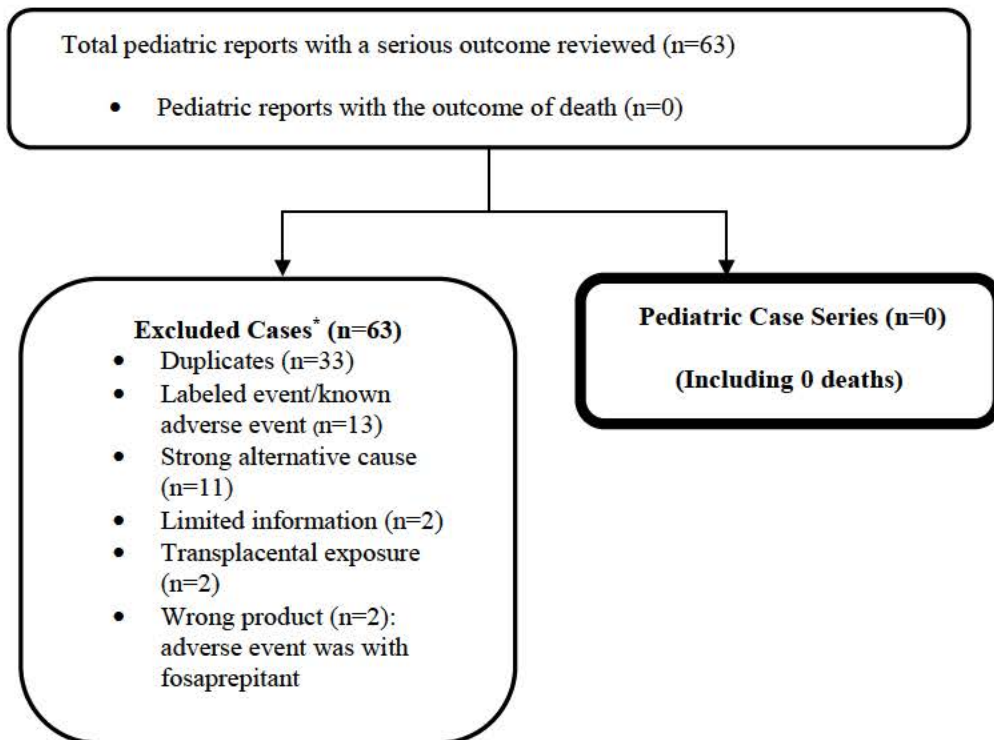
<sup>†</sup> For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

<sup>‡</sup> See Figure 2.2.2

### 2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 63 pediatric reports with a serious outcome (See Table 2.2.1). See Figure 2.2.2 below for the specific selection of cases.

**Figure 2.2.2 Selection of Serious Pediatric Cases with Aprepitant**



\* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

We retrieved 63 pediatric reports with non-fatal serious outcomes in the FAERS database from March 26, 2014 through October 10, 2017. All 63 pediatric reports with a serious outcome were

excluded after review. Eleven reports<sup>d</sup> that had a non-fatal serious outcome had a strong alternative cause for the adverse events; 10 described labeled events for concomitant drugs (such as aphasia after receiving high dose methotrexate, hyperammonemic encephalopathy and cardiotoxicity with fluorouracil, cardiotoxicity with cyclophosphamide, bone marrow suppression and neuralgia with vinblastine) and one described an unlabeled event attributable to a concomitant drug because of the presence of a strong temporal association and positive dechallenge (ear canal stenosis and difficulty hearing after initiation of methotrexate).

Thirteen of the 63 excluded reports<sup>e</sup> described labeled cytochrome P450 (CYP3A4) drug interactions resulting in adverse events between aprepitant and ifosfamide (n=10), vincristine (n=3), or clarithromycin (n=1).

Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4.<sup>1</sup> Clinically significant CYP3A4 drug interactions with aprepitant are contained in the Warnings and Precautions, Adverse Reactions, Drug Interactions, and Clinical Pharmacology sections of the aprepitant product label. Ifosfamide, vincristine, and clarithromycin are specifically listed in CYP3A4 drug interactions with aprepitant in the aprepitant product label.

Ifosfamide-mediated neurotoxicity, occurring through CYP3A4 induction when ifosfamide is administered concomitantly with aprepitant, is contained in the Adverse Reactions— Clinical Trial Experience section and Postmarketing Experience section of the aprepitant product label. The 10 aprepitant and ifosfamide drug interaction cases reported the following adverse events: encephalopathy (n=8), somnolence (n=2), cerebellar syndrome (n=1), diplopia (n=1), hyperreflexia (n=1), amnesia (n=1), feeling abnormal (n=1), depersonalization (n=1), altered state of consciousness (n=1), involuntary muscle contractions (n=1), seizure (n=1), hallucination (n=1), dizziness (n=1), and tachycardia (n=1).

*Reviewer comment: Most of the adverse events reported in the aprepitant and ifosfamide drug interaction cases were related to neurotoxicity, consistent with aprepitant product labeling. After review of the 10 cases, no change in severity or frequency of the labeled adverse event was noted.*

The Drug Interactions section of the aprepitant product label describes interactions between aprepitant and chemotherapeutic agents that are metabolized through the CYP3A4 pathway, including vincristine, that may result in increased risk of adverse reactions from increased exposure of the chemotherapeutic agent. The three aprepitant and vincristine drug interaction cases<sup>f</sup> reported the adverse events of peripheral neuropathy (n=2), cerebellar syndrome (n=1), motor dysfunction (n=1), and neurotoxicity (n=1).

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<sup>d</sup> See Appendix B for the FAERS case numbers, version numbers, and manufacturer control numbers of the 11 reports.

<sup>e</sup> Cases are not mutually exclusive; one case reported a drug interaction between aprepitant, ifosfamide, and vincristine. See Appendix B for the FAERS case numbers, version numbers, and manufacturer control numbers of the 13 reports.

<sup>f</sup> A case may report more than one adverse event.

*Reviewer comment: Vincristine product labeling notes that drug interactions related to inhibition of metabolism of vincristine<sup>6</sup> can be associated with increased severity of neuromuscular side effects; the reported adverse events in the three cases are related to potential neurotoxicity and do not represent a new safety signal.*

Lastly, the Drug Interactions section lists the effects of other drugs, including clarithromycin, on the pharmacokinetics of aprepitant. Clarithromycin is a strong inhibitor of CYP3A4 and it is recommended within the aprepitant product label to avoid concomitant use. We identified a single case of aprepitant and clarithromycin drug interaction resulting in tachycardia (n=1).

*Reviewer comment: The current aprepitant product label accurately contains drug interactions between aprepitant and clarithromycin and no change in the severity was noted.*

### **3 DISCUSSION**

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for aprepitant capsules and oral suspension in the FAERS database from March 26, 2014 through October 10, 2017. This start date was chosen to capture all reports from the data lock date of a previous DGIEP MO review for NDA 21549/S-025, which reviewed all pediatric postmarketing adverse event reports with aprepitant from March 26, 2003 (U.S. approval date for capsules) through March 25, 2014.<sup>2</sup> Of the 63 pediatric postmarketing reports, 33 were duplicates, 11 contained strong alternative causes for the reported adverse events (labeled event for concomitant drug (n=10), event more likely associated with concomitant drug (n=1)), 2 contained limited information for assessment, and 2 described transplacental exposures.

The remaining 13<sup>§</sup> reports described labeled CYP3A4 drug interactions between aprepitant and ifosfamide (n=10), vincristine (n=3), or clarithromycin (n=1). The majority of drug interactions resulted in the labeled adverse event neurotoxicity. Aprepitant is a substrate, a weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Clinically significant CYP3A4 drug interactions with aprepitant are contained in the Warnings and Precautions, Adverse Reactions, Drug Interactions, and Clinical Pharmacology sections of the aprepitant product label. Ifosfamide, vincristine, and clarithromycin are specifically listed in CYP3A4 drug interactions with aprepitant in the aprepitant product label; no change in severity or frequency of the labeled adverse events were noted.

### **4 CONCLUSION**

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<sup>§</sup> Cases are not mutually exclusive; one case reported a drug interaction between aprepitant, ifosfamide, and vincristine.

There is no evidence from these data that there are pediatric safety concerns with aprepitant capsules or oral suspension at this time.

## **5 RECOMMENDATIONS**

DPV-I recommends returning to routine pharmacovigilance monitoring for all adverse events with aprepitant.

## **6 APPENDICES**

### **6.1 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.

**6.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS**

<b>FAERS Case Numbers</b>	<b>FAERS Version Numbers</b>	<b>Manufacturer Control Numbers</b>	<b>FAERS Case Numbers</b>	<b>FAERS Version Numbers</b>	<b>Manufacturer Control Numbers</b>
12400451	1	FR-009507513-1605FRA010796	10732153	1	GB-AUROBINDO-AUR-APL-2015-00416
13114481	1	FR-009507513-1701FRA005639	12400455	1	FR-009507513-1605FRA011328
11309583	4	FR-009507513-1507FRA011094	11080295	2	FR-BAXTER-2015BAX023070
10717860	2	FR-009507513-1501FRA005858	11037504	2	FR-009507513-1504FRA014624
12073318	1	FR-TEVA-632958ISR	103598872	1	2455137
10360841	1	2455138	10533857	4	FR-009507513-1410FRA010209
10538317	3	2577111	10308605	1	FR-GLAXOSMITHKLINE-B1012201A
11999101	2	FR-009507513-1602FRA001472	12985841	1	FR-009507513-1611FRA012777
13754571	2	FR-ACCORD-053618	13357130	1	FR-BAXTER-2017BAX011345
10213230	3	JP-009507513-1406JPN000128	11972685	1	PHHY2016JP008884
13792686	1	GB-TEVA-381514ISR	13727009	1	JP-PFIZER INC-2016598140
11928014	2	CH-009507513-1601CHE005118	13082098	2	FR-TEVA-723436ROM

## 7 REFERENCES

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- <sup>2</sup> Berry, K. Medical officer review of Emend (aprepitant) capsules and oral suspension. August 7, 2015. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/207865Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207865Orig1s000MedR.pdf)
- <sup>3</sup> Johnson, A. Medical officer review of Emend (aprepitant) powder for oral suspension. December 2, 2015. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/207865Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207865Orig1s000MedR.pdf)
- <sup>4</sup> Corken Mackey, A. Postmarketing review of cardiac adverse events with aprepitant and fosaprepitant. November 6, 2008. OSE RCM # 2008-1528.
- <sup>5</sup> Cao C, Swank K, Brinker A, Wu E (personal communication, August 15, 2014).
- <sup>6</sup> Vincristine sulfate injection [package insert]. Hospira, Lake Forest, Illinois. Label revised July 2013.

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