Division Director Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA **Supplement #**	21549 #25
Applicant Name	Merck Sharp and Dohme Corporation
Date of Submission	July 28, 2014
PDUFA Goal Date	August 28, 2015
Proprietary Name / **Established (USAN) Name**	Emend aprepitant
Dosage Forms / Strength	capsule/80mg, 125 mg
Proposed Indication(s)	1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy in pediatric patients
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Karyn Berry, MD/Anil Rajpal, MD
Statistical Review	Wen-Jen Chen, PhD/Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Sushanta Chakder, PhD
CMC Review	Not applicable
Clinical Pharmacology Review	Elizabeth Shang, PhD/Sue Chih Lee, PhD/ Jian Wang, PhD/Nitin Mehrotra, PhD
OPDP	Meeta Patel, PharmD
OSI	Susan Leibenhaut, MD/Susan D. Thompson, MD/Kassa Ayalew, MD, MPH
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OND=Office of New Drugs
DPMH=Division of Pediatric and Maternal Health
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
OSI=Office of Scientific Investigations

Division Director Review

1. Introduction

The trials submitted in this NDA supplement for aprepitant capsules were conducted to fulfill the PREA requirements associated with its approvals for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC), including high-dose cisplatin, and moderately emetogenic chemotherapy (MEC). Emend capsules are currently marketed in a 40 mg, 80 mg and 125 mg dose presentation. The 125mg and 80 mg capsules are used for the chemotherapy induced nausea and vomiting (CINV) indication. The 40 mg capsule is used for the prevention of post-operative nausea and vomiting indication, which was approved on June 30, 2006.

In order to address the full age range covered by the PMRs (ages 6 months to 17 years), the applicant developed an oral suspension, (b) (4) The supplemental NDA for the capsule is ready for approval; (b) (4) (b) (4) A single key pediatric trial establishes the efficacy and safety of both formulations for CINV. Patients 12 years of age and older in the trial received a flat dose of aprepitant capsules (same as the adult CINV dose) and the patients ages >12 years received aprepitant suspension (dose calculated based on patient weight). There was no planned efficacy analysis based on age/formulation. My efficacy and safety review for the capsule formulation will include all of the information from the full age range enrolled in this trial, including the patients who received the suspension.

(b) (4) both formulations studied in the key efficacy and safety trial created review issues related to labeling the pediatric indication for the capsule approval. There were substantive discussions regarding whether the information on the full clinical trial could be presented in Section 14 of the label if only a subset of the studied population would be included in the Indication and the Dosage and Administration sections. In addition, the review team evaluated whether capsule dosing could be appropriately extended to patients <12 years of age and who weigh ≥30 kg. In the trial, the aprepitant suspension dose for patients <12 who weighed at least 30 kg was the same as the capsule dose administered to the older patients.

This review serves as both the CDTL review and the Division Director Summary review.

2. Background

As stated above, aprepitant is approved for prevention of acute and delayed phase CINV, based on adult phase 3 trials. Acute phase refers to the first 24 hours after initiation of chemotherapy, and the delayed phase refers to the subsequent period, between 24 and 120 hours after initiation of chemotherapy. Children receive chemotherapy drugs and regimens that qualify as MEC and HEC,

and they experience acute and delayed CINV. The underlying pathophysiology of CINV is not known to differ between children and adults. Categorization of whether an agent (or combination of agents) is moderately or highly emetogenic in published treatment guidelines is based on the proportion of patients that would be expected to vomit if they received the drug without antiemetic

prophylaxis. According to publications on the ASCO Guidelines for antiemetics in oncology[1], highly emetogenic agents are associated with vomiting in ≥90% of patients. These categories are based on experience with adult patients. The applicant categorized emetogenicity based on the Children's Oncology Group (COG) Emetogenicity of Commonly Used Chemotherapeutic Agents, which uses different terminology, e.g., Very High Risk of Emetogneicity, High Risk of Emetogenicity, Moderate risk of emetogenicity, in its aprepitant pediatric program. The COG categorization references Altman AJ, ed Supportive Care of Children with Cancer (3rd edition: The Johns Hopkins University Press; 2004), Perry MC et al, ed. Companion Handbook to Chemotherapy Source Book (2nd ed. Lippinkott, Williams and Wilkins; 2004) and Antiemetics: National Comprehensive Cancer Network Practice Guidelines in Oncology (V3. 2008). The Very High Risk category (VHRC) from COG is the same as the HEC list in the ASCO guidelines, with the following exceptions:

1. High dose cyclophosphamide appears in both lists; however, the cyclophosphamide dose for HEC is ≥1500 mg/m^2, whereas the dose in VHRC is >1500 mg/m^2.
2. Dacarbazine appears in both lists; however, there is no dose specified for HEC, whereas VHRC is specifically cites doses ≥500 mg/m^2.
3. Dactinomycin is considered HEC in adults, whereas it is not in the VHRC list (it is considered the next emetogenicity level lower, i.e., "High Risk" (60-90% frequency).
4. Ifosfamide is considered MEC in the ASCO guidelines, whereas ifosfamide doses of ≥1500 mg/m^2 are categorized VHRC in COG guidelines.
5. Lomustine appears in the VHRC list and does not appear in the HEC list.

Aprepitant was the first NK-1 inhibitor approved in the US for CINV, and there has only been one other NK-1 inhibitor approved since (in September 2014). Aprepitant is administered as part of a combination antiemetic regimen that includes a 5HT-3 antagonist and dexamethasone. In the HEC combination regimen, aprepitant is administered on Days 1-3, dexamethasone is administered on Days 1-4, and the 5HT-3 antagonist is administered on Day 1. The aprepitant dose on Day 1 is 125 mg, and the dose is reduced to 80 mg on Days 2 and 3. The MEC regimen is the same, with the exception that dexamethasone is only administered on Day 1. There are currently no NK-1 inhibitors approved for use in the pediatric population in the U.S. There are no data available to support that full extrapolation of efficacy from adults to the pediatric age group is appropriate for this class of drugs, for this indication. The applicant conducted a randomized, controlled pediatric CINV trial that was powered to establish aprepitant's efficacy in pediatric patients.

See the Clinical Review for a comprehensive and detailed summary of the regulatory history of the pediatric development program. Emend capsules were approved on March 26, 2003, for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC), including high-dose cisplatin. At that time the FDA's Pediatric Rule had been challenged in court and the court ruled (October 17, 2002) that the FDA did not have the authority to issue the Pediatric Rule. It barred FDA from enforcing it. The approval letter encouraged the

[1] Basch E, et al. JCO.Vol 29, No 31. Nov 1 2011. pp.4189-4198.

applicant to submit a pediatric plan; it did not list any PMCs or PMRs related to pediatric studies. Passage of PREA later in the same year (2003) retroactively impacted the Emend NDA, as PREA contained a provision that for applications submitted between April 1, 1999 and the date of enactment, applications with no pediatric study waiver or deferral would be "deferred for at least 1-year unless FDA defers for longer period or waives the requirement." On September 15, 2004, the applicant submitted a proposed pediatric study request (PPSR) for Emend capsules, which stated, "The proposed studies are also intended to fulfill the Pediatric Research Equity Act of 2003 obligations for NDA 21-549." In that same letter, they proposed a partial waiver for the age group of <2 years "because necessary studies are impossible or highly impractical." The Division responded in a letter dated January 21, 2005, denying a waiver of pediatric studies in patients < 2 years of age, and instructing the applicant to submit their pediatric drug development plan for this age group. That letter also granted a deferral for pediatric studies in patients 2 years to 17 years of age for the HEC CINV indication. Ultimately, the age range required in the PMR associated with the HEC approval was 2 years and greater; however, in the Written Request, the age extends down to birth (Written Request Amendment #1, dated April 8, 2011). The HEC approval PMR states:

> 1395-7: Deferred pediatric studies in patients 2 years to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Note that the lower limit of the age required for study in the HEC PMR also differs from that of PMR associated with the MEC PMR, presented next below.

Emend capsules were subsequently approved on October 28, 2005, for prevention of nausea and vomiting associated with initial and repeat courses of MEC chemotherapy. The approval letter stated that FDA waived the pediatric study requirement for ages 0 to less than 6 months of age and deferred pediatric studies for ages 6 months to less than 17 years of age. The deferred PREA studies listed in the letter were:

1. Deferred pediatric study under PREA for the use of Emend ™ (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in pediatric patients 6 months to less than 17 years of age.

   Final Report Submission: December 31, 2007

2. Conduct an appropriately powered randomized controlled clinical trial, in patients receiving moderately emetogenic chemotherapy (MEC), designed to document generalizability among various chemotherapies and an evaluation of efficacy in male patients.

Protocol Submission:	by March 31, 2006
Study Start:	by December 31, 2006
Final Report Submission:	by December 31, 2008

A Written Request (WR) was issued on February 2, 2009. In the interim between the PPSR and the issuance of the WR, there were many communications between the applicant and FDA regarding the

pediatric studies that should be included in the WR, the age range the studies should cover, and timeline extensions for submission of pediatric PMR studies. Subsequently there were a number of amendments to the WR and further requests for deferral extensions. On November 6, 2013, the Applicant was issued PREA non-compliance letters for NDA 21549 (original HEC approval) and NDA 21549/S-008 (MEC approval), as the pediatric assessments had not been submitted by the required PREA target date of October 31, 2013 (the most recent deferral extension that had been granted). The applicant then requested, and FDA granted, another deferral extension (July 31, 2014).

The (b) (4) aprepitant capsule (b) (4) NDA supplement was submitted on July 28. (b) (4) (b) (4) (b) (4) (b) (4) The CMC information was then submitted on March 26, 2015. As outlined in the Clinical review, there was a clock extension for the capsule NDA supplement prompted by the applicant's responses to clinical information requests.

The Written request included pediatric studies for CINV and PONV. The applicant has indicated they will not meet the deadline for the WR to qualify for pediatric exclusivity.

3. CMC

This NDA proposes a pediatric dosage regimen for prevention of CINV in pediatric patients 12 years of age and older. The pediatric capsules for CINV are identical to the currently approved adult aprepitant capsules. For this reason, no new CMC or Biopharmaceutics information was submitted for review. The CMC reviewers evaluated product labeling, and their recommendations were incorporated during labeling negotiations.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. The applicant conducted an oral toxicity study of aprepitant in juvenile rats to support the pediatric development program. In addition, the applicant conducted an IV toxicity study in juvenile dogs, primarily to evaluate the effects of the EDTA present in the IV formulation.

The Pharmacology/Toxicology review noted that the juvenile rat toxicity study was designed to evaluate the potential effects of aprepitant on development, growth, behavior and reproductive performance from postnatal day 10 through postnatal week 17. The study supported the youngest pediatric age of 6 months. The highest dose studied was 2000 mg/kg/day (administered 1000 mg/kg BID). In female rats, the systemic exposures, as measured by $AUC_{0\text{-}24h}$ at the highest tested dose, were similar to the exposure observed in pediatric patients. However, the exposures in male rats were less than that of pediatric patients (11.5 microgram·hr/ml vs. 20.9 microgram·hr/ml). The reviewer

noted that there were minimal treatment related effects across the full panel of evaluations, and he commented that the highest dose was well-tolerated. There were no treatment related effects on tests of passive avoidance, auditory startle habituation or open field motor activity. There were transient decreases in mean body weight gain in all drug treated groups and slight changes in clinical pathology parameters in all groups. These effects were similar to those that had been observed in prior adult animal studies. There were slight decreases in hemoglobin, hematocrit, MCV, MCH and MCHC and increased platelet counts in both males and females at the 250 mg/kg BID and the 1000 mg/kg BID doses. At Week 7, a dose related increase in cholesterol levels was noted in female rats only, which was statistically significant; however, it had diminished by Study Week 13. There was significantly early vaginal opening in mid- and high dose group females and significantly delayed preputial separation in all male groups; however, the reviewer did not find these to be clinically significant. Increased organ weight and hepatocellular hypertrophy and increased thyroid weight with follicular cell hypertrophy were also observed, but these findings had also been observed in prior adult rat studies and were determined to be secondary to hepatic enzyme induction. There were no significant treatment related effects on mating performance and fertility parameters observed in any group, and no treatment related effects on embryonic/fetal survival.

The juvenile rat study was preceded by a dose-ranging study in juvenile rats (to identify appropriate doses for the definitive study). The reviewer stated that aprepitant was tolerated to doses up to 1000 mg/kg BID (the upper level studied in the definitive study). Dose and treatment related decreases in mean weight gain were noted relative to control, starting at 125 mg/kg BID. Of note, there were 11 deaths during the study ("found dead"), of which only one occurred in the control group. However, the reviewer didn't consider the deaths treatment related because the "incidences were not dose-related." There were 3 deaths in the 5 mg/kg BID group, 2 in the 125 mg/kg BID group, 3 in the 500 mg/kg BID group and 2 in the 1000 mg/kg BID group. Furthermore, there were no deaths in the definitive juvenile rat study discussed above.

The 4 week juvenile beagle dog study evaluated daily IV dosing, up to a maximum dose of 6 mg/kg/day. The reviewer concluded that there were no findings in this study that were attributable to EDTA in the intravenous product. The dog age in this study corresponded to a human age of <1 month, based on overall CNS and reproductive development. Systemic exposure at the highest dose was approximately 6X the exposure associated with the pediatric oral dose. The 4 mg/kg dose was determined to be the NOAEL, however, the reviewer stated that the higher 6 mg/kg dose studied was well tolerated. An approximate 23% decrease in relative heart weight was noted at the 6 mg/kg/day dose level, however, there were no histopathological changes associated with this observation. Endometrial and myometrial hypertrophy of the uterine horns and body, hypertrophy of the cervical muscularis and edema of the vaginal lamina propria and submucosa were observed in females at the 4 mg/kg/day and 6 mg/kg/day dose levels. In males, reduced size of Leydig cells of the testes was observed, associated with "more compact connective tissue surrounding the seminiferous tubules when compared with controls" at the 6 mg/kg/day dose level. Reduced testicular weight was also observed at this dose level. The applicant stated these changes were "considered to be reversible, to have no impact on further development, and to be of minimal toxicological significance," and the reviewer did not disagree with this conclusion. No treatment related effects on ECG, heart rate or arterial blood pressure were observed. On Day 35 of dosing, a statistically significant decrease (9.8%) decrease in prothrombin time was observed in the female dogs administered 6 mg/kg day; however, on Day 42 the values were comparable to control.

The Pharmacology/Toxicology reviewer's recommendations for revisions of Sections 8.1, 8.2, 8.4 (addition of Juvenile Animal Study information) and 13.1 of the product label were incorporated in final labeling.

5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The reviewers concluded that the proposed fixed dose regimen for pediatric patients 12 years of age and older, which is identical to the adult aprepitant doses, is appropriate. Patients in the phase 3 efficacy trial who were less than 12 years of age were treated with aprepitant suspension. Their doses were calculated on the basis of weight, i.e., 3.0 mg/kg (up to a maximum of 125 mg, which is the adult and adolescent dose) on Day 1, followed by 2.0 mg/kg (up to a maximum dose of 80 mg, which is the adult and adolescent dose) on Days 2 and 3. The efficacy in this subgroup was consistent with the efficacy in the adolescent subgroup. The reviewers noted in their review of the pediatric PK data that the simulated aprepitant exposures in the pediatric population (particularly in adolescents and in children ages 6 months to 2 years of age) appeared lower than has been observed in adults, based on cross study comparisons. Such an observation in a pediatric program often prompts recommendations to explore higher doses to assure efficacy; however, the reviewers found the doses acceptable, given the favorable efficacy outcome observed in the phase 3 trial.

No PK/PD or exposure-response analyses could be performed in this NDA because PK samples were not collected in the phase 3 trial.

The following table, reproduced from the Clinical Pharmacology review, summarizes the Cmax and AUC associated with the Day 1 aprepitant dose (125 mg capsule in adolescents and 3 mg/kg suspension in patients <12 years of age). These data came from two PK studies, P134 and P097.

Table 1. Mean (%CV) Cmax and AUC in Pediatric Patients following oral aprepitant for CINV on Day 1

Age Group (years) (N)	Study ID	Dose Day 1	Formulation	Cmax (ng/mL) (CV%)	AUC0-24hr (hr*ng/mL) (CV%)
0.5 – 2 (N=6)	P134 Part IV	3 mg/kg	Suspension	1810 (51)	21000 (56)
2 – 6 (N=6)				1840 (51)	17300 (29)
6 – 12 (N=7)				1800 (89)	24400[§] (65)
12 – 17 (N=18)	P097	125 mg	Capsule	1269 (60)	16649 (43)
[§] N=6					

A more detailed description of the two PK studies follows below.

Study P097. Before conducting the major phase 3 trial that supports this application (see Section 7), the applicant conducted Study 097, which was originally designed to be a blinded, randomized, placebo controlled, multi-center, international pilot study in adolescents (ages 12-17). The protocol was ultimately amended to change to an uncontrolled, open-label study, reportedly to address slow enrollment to the study. The portion of the study that was blinded and controlled is referred to as Part 1. The open label, uncontrolled portion is referred to as Part 2. The applicant referred to this trial as an "estimation study", in which the goals were to assess safety and efficacy when patients ages 12-17 years are administered the labeled adult doses of aprepitant oral capsules with ondansetron (3 doses) administered on Days 1 AND 2 (unlike the labeled adult regimen) and dexamethasone administered daily x 4 (with dose reduction similar to the adult dexamethasone schedule labeled for adults in the aprepitant combination regimen). The trial in its original design (Part 1) randomized, in a 2:1 fashion, between the aprepitant combination regimen vs. the same combination regimen without aprepitant.

PK samples were drawn in this study predose (-2 hours), 1 hour (immediately prior to chemotherapy infusion), 2 hours, 3h, 4h, 8 h, 12h, 24 h, 48 h and 72 hours. The multiday PK data are summarized in the table below, reproduced from the Clinical Pharmacology review.

Table 2. Study 097 Multi-day PK data for aprepitant capsules in patients 12 years of age and older

	AUC0-24hr (hr*ng/mL)	CMAX (ng/mL)	C24 (ng/mL)	C48 (ng/mL)	C72 (ng/mL)	TMAX (hour)
N	18	18	9	8	16	18
Mean	16648.5	1268.6	512.4	624.7	595.8	--
SD	7143.3	763.7	250.6	472.4	549.2	--
%CV	42.9	60.2	48.9	75.6	92.2	--
Median	17133.0	1251.1	448.2	499.8	499.2	**4**
Min	--	--	--	--	--	2
Max	--	--	--	--	--	24.05

Source data: Reviewer's analysis based upon individual parameters submitted.

Cross study comparisons of these data to PK data from healthy adult subjects suggested that the Cmax and $AUC_{0\text{-}24h}$ in adolescents may be 24-30% lower than in healthy adult subjects. The following table, provided by the pharmacometric reviewer, summarizes these cross study comparisons. Relative exposures between adolescent and adult patients were also explored in cross study comparisons. The exposures in adolescent patients also appear lower than those observed in the adult patients.

Table 3. Cross Study Comparisons of aprepitant PK in Adolescent patients, Healthy Adults and Adult Patients.

Pharmacokinetic Parameter	Geometric Mean			Geometric Mean Ratio	
	Adolescent Patients (95% CI)	Healthy Adult Subjects (95% CI)	Adult Patients (95% CI)	Adolescent Patients / Healthy (90% CI)†	Adolescent Patients / Adult Patients (90% CI)†
$AUC_{(0\text{-}24hr)}$ (ng*hr/mL)	14318.4 (10273.3, 19956.3)	19455.8 (17974.3, 21057.2)	25666.4 (19939.6, 33038.0)	0.74 (0.56, 0.97)	0.56 (0.40, 0.78)
C_{max} (ng/mL)	1070.1 (771.2, 1484.8)	1539.2 (1339.0, 1769.2)	1899.5 (1359.5, 2653.8)	0.70 (0.52, 0.93)	0.56 (0.39, 0.81)
C_{24hr} (ng/mL)	449.7 (287.0, 704.7)	554.1 (447.8, 685.5)	NA	0.81 (0.55, 1.20)	NA
C_{48hr} (ng/mL)	460.5 (205.9, 1030.2)	516 (349.1, 762.6)	NA	0.89 (0.44, 1.79)	NA
C_{72hr} (ng/mL)	367 (197.5, 681.9)	612.8 (417.9, 898.6)	355.8 (129.3,979.4)	0.6 (0.34, 1.07)	1.03 (0.41,2.60)
† Based on the t-distribution and Satterthwaite's approximation for the degrees of freedom using natural log-transformed values.					

Study 134. The applicant conducted another preliminary study to explore dosing with aprepitant in the full age range, birth to 17 years. (Although the applicant intended to enroll patients <6 months in this study, none were enrolled.) This study consisted of a number of parts, each with varying exploratory goals:

- Intravenous fosaprepitant dosing was explored in Parts IA and IB, in age brackets of 12-17 years, 6-12 years, and 2-6 years.
- In Part 2, aprepitant oral dosing was explored in children ages 6 months to <2 years. A single dose of aprepitant was administered in Part 2, and two dose levels were evaluated: a dose estimated to be equivalent to an adult dose of 80 mg and a dose estimated to be equivalent to an adult dose of 125 mg. Nineteen patients in this age range were treated at each dose level. (Ondansetron was co-administered.)
- Part 3 was designed to be a "control", in which patients who would go on to treatment in Part 4 were not treated with aprepitant. Their antiemetic regimen in Part 3 was limited to intravenous ondansetron x 3 days. Three age brackets under the age of 12 were enrolled in Parts 3 and 4: 6 months to <2 years, 2 years to <6 years and 6 year to <12 years.
- In Part 4, oral aprepitant dosing x 3 daily doses was added to ondansetron daily dosing in the same three age brackets <12 years of age: 6 months to <2 years, 2 years to <6 years and 6 years to <12 years. Dosing in these children was weight based. Aprepitant dosing in Part 4 mimicked the labeled adult dosing: the Day 1 dose was estimated to match the exposure associated with the adult 125mg dose and the Day 2/3 doses were estimated to match the exposure associated with the adult 80mg dose. Twenty patients were treated.

The PK data from the patients <12 years of age in Study 134 differed from those that had been observed in adolescents. Cross study comparisons suggest that exposures were 11% and 23% higher in pediatric patients ages 2 years to 6 years than observed in healthy adults administered aprepitant 125 mg. However, the reviewers concluded that for the overall 6 months to 12 year old age group, the systemic exposure (Cmax and $AUC_{0\text{-}24hours}$) appeared comparable to healthy adults in cross study

comparisons. The summary data for each subgroup administered suspension in Part 2 of Study 134 are summarized below (table reproduced from the Clinical Pharmacology review):

Table 4. Study 134 Part 2: Geometric mean of Cmax and AUC from Day 1 in pediatric patients <12 years of age and adult healthy volunteers following oral aprepitant 3 mg/kg and 125 mg, respectively.

Age range (years)	Dose	Median Dose (Min, Max) converted to mg/kg	Cmax (ng/mL)	AUC0-24hr (hr*ng/mL)
0.5 – 2 (N=5)	1.3 mg/kg	1.3	651	6070
2 – 6 (N=7)	74 mg/m^2	3.3 (3.1, 3.4)	1890	21600
6 - 12 (N=6)	74 mg/m^2	2.4 (1.6, 3.0)	1720	20100
Adults (N=12)‡	125 mg	N/A	1539	19455

In Part 4 of Study 134, patients received a 3mg/kg regimen on Day 1 and 2mg/kg on Days 2 and 3. The summary PK data, with cross study comparisons to healthy adults, are included in the table below, which is reproduced from the Clinical Pharmacology review. In this analysis, the Clinical Pharmacology reviewer concluded that the geometric means of systemic exposure in pediatric patients ages 6 months to 12 years are comparable to healthy adults administered a 125 mg dose of aprepitant.

Table 5. Study 134 Part 4: Geometric mean of Cmax and AUC from Day 1 in pediatric patients <12 years of age and adult healthy volunteers following oral aprepitant 3 mg/kg and 125 mg, respectively.

Age range (years)	Dose	Cmax (ng/mL)	AUC24 (hr*ng/mL)
0.5 – 2	3 mg/kg	1590	18400
2 - 6	3 mg/kg	1690	16600
6 - 12	3 mg/kg	1470	20800
Adults‡	125 mg	1539	19455

‡ Study P067

Evaluation of appropriate age range for labeling the Emend capsule. (b) (4) (b) (4) (b) (4) the Clinical Pharmacology reviewers were asked to consider whether PK data supported modifying the proposed pediatric dose in the aprepitant capsule to include children less than 12 years of age whose weight based suspension dose is equivalent to the adolescent (and adult) dose, i.e., patients less than 12 years of age who weigh ≥30 kg. There was no dedicated relative bioavailability study (b) (4), and the PK sampling schedule in the efficacy trial also limited the ability to assess the relative bioavailability (b) (4). The population PK data were evaluated by the pharmacometric reviewers to address this question. They noted that body weight, age and dose are significant covariates for apparent clearance. Body weight is also a significant covariate for apparent volume of distribution. Formulation type was not a significant covariate. The median clearance was similar between the age groups: 4.4 L/hour in 48 patients ages 12 to through 17 years, and 4.8 L/hour in 16 patients aged less than 12 years and weighing at least 30

kg. Based on this, the pharmacometric reviewers concluded that no significant difference in AUC would be expected between the formulations. They concluded that the data support extending the capsule dosing in labeling to include children less than 12 years of age who weigh ≥30 kg.

The Dosage and Administration Section of the label will state:

> **2.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)**
> Adults and Pediatric Patients 12 Years of Age and Older and Patients Less Than 12 Years of Age who Weigh at least 30 kg
> The recommended oral dosage of EMEND capsules, dexamethasone, and a 5-HT_3 antagonist in adults and pediatric patients 12 years of age and older and patients less than 12 years of age who weigh at least 30 kg, who can swallow oral capsules, for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted the results of a randomized, double-blind, active-control, parallel group trial to fulfill its PREA requirements related to CINV for Emend capsules and to support product labeling for the pediatric population, ages 6 months to17 years. The trial was a multi-center, international trial. Two of 51 centers were in the U.S. Randomization was stratified based on age (6 months to < 2 years; 2 to < 6 years; 6 to <12 years; or 12 to 17 years), whether or not dexamethasone would be administered (see below), and whether a "Very High Risk of Emetogenicity" chemotherapy agent would be administered in Cycle 1. Randomization was not stratified based on whether or not a patient would receive ondansetron doses after day 1 due to planned additional days of chemotherapy dosing.

Patients ages ≥12 years to 17 years were treated with the same aprepitant fixed dose schedule labeled for adults, i.e. aprepitant 125 mg capsule Day 1, followed by aprepitant 80 mg capsule on Days 2 and 3. Consistent with adult aprepitant labeling, this age subgroup received a 5HT3 antagonist, ondansetron, on Day 1 in both study arms; however, the dose used was left to the discretion of the investigator (based on the labeled pediatric dose or local standard of care) and the dose could be repeated on subsequent days (see below). Unlike the labeled adult aprepitant combination antiemetic regimen, dexamethasone was not a standardized part of the regimen in this pediatric study. In adults receiving HEC chemotherapy, aprepitant is to be administered with dexamethasone on Days 1-3 and there is an additional dose of dexamethasone on Day 4, whereas for MEC chemotherapy, dexamethasone is only administered on Day 1. In this study, use of dexamethasone (administered IV) was left to the discretion of the investigator. If used, consistent with dexamethasone dosing in the adult aprepitant regimen, the dose was reduced by 50%, taking into account aprepitant's drug drug interaction with dexamethasone (via CYP3A4 inhibition), which results in increased systemic dexamethasone exposures in adults. The applicant did not assess the effects of aprepitant on dexamethasone exposures in children in this development program.

Patients 6 months to <12 years of age were treated with the same combination regimen, with the exception that the aprepitant suspension was used and the dose was weight based. The control arm received matching placebo. The Day 1 dose of suspension was 3 mg/kg (maximum dose of 125 mg), and the dose on Days 2 and 3 was 2 mg/kg (up to a maximum of 80 mg).

This trial differed in a number of ways from those that supported the approval of the adult CINV indications. Use of dexamethasone was left to the discretion of the investigator, the 5HT3 antagonist dose was not standardized across centers, and the 5HT3 antagonist dosing was not limited to Day 1. Patients in this trial who were receiving chemotherapy on days subsequent to Day 1 during the efficacy assessment period could receive ondansetron on those chemotherapy administration days only. The latter difference is a pragmatic one, related to differences in the common malignancies between adult and pediatric populations, and the chemotherapy regimens used to treat them. Multi-day regimens of emetogenic chemotherapeutic agents are not uncommon in treatment of pediatric malignancies. Adult antiemetic trials intended to support NDAs have generally limited enrollment within an individual study to HEC or MEC. This trial did not.

A summary of the treatment by study arm and by age group appears in the table below, which is reproduced from the Statistical Review.

Table 6. Summary of Combination Antiemetic Treatment Regimens Studied in Study P208

Regimen (N)	Study Medication	Subject Age	Day 1 Dose	Day 2 Dose	Day 3 Dose
Aprepitant [A] (150)	Aprepitant	12 to 17 years	125 mg capsule PO 60 minutes prior to initiation of chemotherapy	80 mg capsule PO[B]	80 mg capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) powder for suspension (PFS) PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) PFS PO[B]	2.0 mg/kg (up to 80 mg) PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		
Control [A] (150)	Placebo for aprepitant	12 to 17 years	125 mg placebo capsule PO 60 minutes prior to initiation of chemotherapy	80 mg Placebo capsule PO[B]	80 mg Placebo capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) placebo PFS PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		

A Intravenous dexamethasone was permitted to be administered to both treatment arms as part of the anti-emetic regimen, at the discretion of the investigator. If dexamethasone was administered as part of the anti-emetic regimen for patients receiving aprepitant, dexamethasone was to be administered at 50% of the established dose in children.
B For patients receiving chemotherapy on Days 2 or 3, aprepitant was to be administered 60 minutes prior to initiation of chemotherapy.
C Branded ondansetron (Zofran™) was required for Cycle 1 of this study. Zofran™ was not be supplied by the SPONSOR, meaning Merck Headquarters or IVRS. Zofran™ was to be provided (b) (4) If procurement of Zofran™ was not feasible, discussion with the Merck Clinical Monitor and/or delegate was required. Generic ondansetron was permitted during the Optional Cycles 2-6.
D Preventative antiemetic treatment with ondansetron was permitted ONLY on days that chemotherapy is administered. Once the chemotherapy treatment regimen was complete, ondansetron was no longer permitted as prophylactic treatment.

The primary endpoint was Complete Response (defined as no vomiting, no retching and no use of rescue medication) during the delayed phase (25 hours to 120 hours following initiation of chemotherapy) in Cycle 1. Secondary endpoints included Complete Response (CR) in the acute phase (0-24 hours), CR in the overall phase (0-120 hours), and No Vomiting (regardless of use of rescue medication) over 120 hours. The data were captured with a paper patient diary in which episodes of vomiting/retching and/or use of rescue medication were recorded. The primary efficacy analysis was limited to the first cycle of treatment. The analysis was based on a Cochran-Mantel-Haenzel test stratified by age (<2 years, 2-17 years), whether dexamethasone was used, and whether a "very high risk" chemotherapy agent was administered. Statistical tests were conducted at a significance level of 0.05 (two-sided). The Statistical review states that although the applicant reported there was no plan to adjust alpha for multiplicity, the applicant provided an analysis strategy for the primary and secondary endpoints, which were tested in a hierarchical order. Patients with missing data were classified as non-responders in the ITT efficacy analyses.

Subjects could continue on the trial for multiple cycles of treatment (open label, uncontrolled). The primary objective in subsequent cycles was to evaluate safety. Efficacy data were not collected. .

Three hundred forty-two subjects were screened, and 307 were randomized (155 to aprepitant and 152 to control). Of those, 149 in each arm completed the study. Five were excluded from the ITT population because they didn't take study medication: 3 in the aprepitant arm and 2 in the placebo arm. Three hundred two patients were included in the ITT population. The baseline demographics are summarized in the table below, which is reproduced from the Statistical review. Slightly more than half were male. The majority were White. The age distribution was fairly evenly distributed across the 4 age brackets, with the exception of the <2 years subgroup, which represented only 11-12% of the study population.

Table 7 Baseline demographic and characteristics of ITT population – Study P208

Variable	Aprepitant Regimen (N=152)	Control Regimen (N=150)	Total (N=302)
Sex, n (%)			
Female	68 (44.7)	71 (47.3)	139 (46)
Male	84 (55.3)	79 (52.7)	163 (54)
Age Groups, n (%)			
6 month to <2 years	19 (12.5)	16 (10.7)	35 (11.6)
2 years to < 6years	45 (29.6)	43 (28.7)	88 (29.1)
6 years to < 12 years	41 (27)	43 (28.7)	84 (27.8)
12 years to 17 years	47 (30.9)	48 (32)	95 (31.5)
Mean (months) ± SD	97.7 ±	99.4 ±	98.5 ±
Median (months) [Minimum, Maximum]	86.5 (6,213)	91.5 (6, 214)	89.45 (6, 214)

Race			
American Indian or Alaskan Native	2 (1.3)	0	2 (0.7)
Asian	11 (7.2)	16 (10.7)	27 (8.9)
Black or African American	0	2 (1.3)	2 (0.7)
Multiple	20 (13.2)	22 (14.7)	42 (13.9)
White	119 (78.3)	110 (73.3)	229 (75.8)
Ethnicity			
Hispanic or Latino	36 (23.7)	32 (21.3)	68 (22.5)
Not Hispanic or Latino	111 (73)	112 (74.7)	223 (73.8)
Not reported	2 (1.3)	4 (2.7)	6 (2.0)
Unknown	3 (2.0)	2 (1.3)	5 (1.7)
Use of Dexamethasone as part of the antiemetic regimen in Cycle 1			
Yes	44 (28.9)	42 (28)	86 (28.5)
No	108 (71.1)	108 (72)	216 (71.5)
Very High Risk Emetogenicity Chemotherapy			
Yes	99 (65.1)	101 (67.3)	200 (66.2)
No	53 (34.9)	49 (32.7)	102 (33.8)

The most common malignancies were Ewings sarcoma and osteosarcoma (11%), rhabdomyosarcoma and neuroblastoma (8%), medullablastoma and acute lymphocytic leukemia (7%) and nephroblastoma (5%).

Approximately 2/3 of patients were treated with a chemotherapeutic agent that was categorized “Very High Risk Emetogenicity Chemotherapy”. The proportion was similar between arms (randomization was stratified for this factor). The majority of patients did NOT receive dexamethasone as part of their combination antiemetic regimen (71.5%). The proportion who did receive dexamethasone was similar between arms (randomization was stratified for this). Randomization was not stratified based on whether or not patients were scheduled to receive repeat doses of 5HT3 antagonist due to multi-day administration of chemotherapy. The majority 126/152 (83%) in the aprepitant arm and 134/150 (89%) in the control arm were treated with multiday chemotherapy in this trial, and the distribution between arms was similar, although numerically higher in the control arm.

The efficacy results are summarized in the table below, reproduced from the Statistical review. The results were statistically significant for the primary endpoint of delayed phase and the two secondary endpoints acute phase and overall phase.

Table 8 Number (%) of Patients with Complete Response† by Phase and Treatment Group - Cycle 1 using ITT Population – Study P208

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	101 / 152 (66.4) *	78 / 150 (52.0)
Delayed Phase	77 / 152 (50.7) **	39 / 150 (26.0)
Overall Phase	61 / 152 (40.1) **	30 / 150 (20.0)

* p<0.05 when compared with Control Regimen.
** p<0.01 when compared with Control Regimen.
† Complete Response = No vomiting or retching and no use of rescue medication.
Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.
n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.
Source: Table 11-1 at page 138 in Study P208 Report.

CR is defined as no vomiting/retching and no use of rescue medication. As a component of the definition of CR, "no use of rescue medication" is intended to capture how well the antiemetic manages significant nausea. The applicant prespecified secondary analyses of "No vomiting" (a component of the primary endpoint CR definition), in the delayed, acute and overall phases. Responders in these analyses could have taken rescue medication for their nausea. The "No vomiting" analyses reveal a higher response in both the aprepitant and control arms, although somewhat greater incremental increase in aprepitant relative to control. In the delayed phase, the "No vomiting" response rates were: 55.3% aprepitant vs. 28% control (compared to the primary composite definition of CR: 50.7% vs. 26%, respectively). In the acute phase, the "No vomiting" response rates were: 71.1% aprepitant vs. 53.3% control (compared to the primary composite definition of CR: 66.4% vs. 52%, respectively). (b) (4) The reviewers did not consider the information clinically meaningful because the endpoint is a subcomponent of the primary, and the results could have been influenced by the use of rescue medication. The applicant contended that the endpoint was meaningful in the pediatric population because "rescue medication use may be less reliable in children compared to adults, which may undermine confidence in the use of Complete response in these patients." The reviewers requested information to verify that contention. The applicant submitted the following table summarizing, by age subgroup, the number of patients who took rescue medication (yes/no) and who vomited/didn't vomit, in each study arm.

Table 9. Applicant's Summary of Vomiting Status versus Use of Rescue Medication Status by Age Group and Treatment Group in the Overall Phase (ITT population)

		Emend			Control	
Age		Vomiting			Vomiting	
Group		No	Yes		No	Yes
6 months to <2 years	Rescue Use			Rescue Use		
	No	9	**7**	No	4	**5**
	Yes	0	3	Yes	0	7
2 to <6 years	Rescue Use			Rescue Use		
	No	22	**10**	No	13	**15**
	Yes	1	12	Yes	0	15
6 to <12 years	Rescue Use			Rescue Use		
	No	12	**15**	No	9	**15**
	Yes	4	10	Yes	1	18
12 to 17 years	Rescue Use			Rescue Use		
	No	18	**8**	No	4	**8**
	Yes	5	16	Yes	1	35

In the overall population in the table above, 9% of patients who took rescue medications didn't vomit, i.e., 91% of the overall patient population who took rescue medication vomited. Therefore, the secondary analysis that eliminated the use of rescue medication from the efficacy composite, only eliminates a relatively small proportion of events from the analysis. Furthermore, in the patients who took rescue medication and vomited, there is no information on whether rescue medication was administered before or after vomiting started. In the overall population in the table above, 48% (83/174) of patients who didn't take rescue medication vomited. In the overall Emend group, 40% of patients who didn't take rescue medication vomited. In the overall control group, 59% of patients who didn't take rescue medication vomited.

The applicant desired counting patients who took rescue medication and didn't vomit as a responder. The meaningfulness of this additional analysis remains in question. The observation that may have led to this proposal was that in the overall Emend group, 20% of patients who took rescue medication didn't vomit, while in the overall control group, 2.5% of patients who took rescue medications didn't vomit. Based on this the applicant could have concerns that relying on the composite unfairly lower the efficacy results, as patients might have been taking rescue medication unnecessarily. The latter might happen if parents had a low threshold for administering rescue medication in a very young child or if a more independent pediatric patient did not understand what the rescue medication was for. Given that such a high proportion of patients in the trial who took rescue medication vomited (suggesting "rescue" was administered after vomiting had started or in a setting of severe nausea), and that there is a disparity between the proportion of patients who took rescue medication and didn't vomit between the Emend and control arms (I would expect to see a similar proportion of use between arms if this was due to patients not understanding what the medication was for or if parents were

administering it with a low threshold), I don't agree that the use of rescue medication in the pediatric population is unreliable for consideration as part of the primary endpoint to capture significant nausea.

Examination of the proportion of patients who used rescue medication by age group and treatment group indicates that the proportion of patients who were administered/took rescue medication was similar between the 6 mo-12 yo and adolescent subgroups. The proportion in the subgroup ages 2 to <6 years was somewhat lower than the older age groups. There was a disparity noted in the very youngest age group (6 months to <2 years), which may reflect the much lower sample size in this group. These data are summarized below. However, it should be noted that in the two youngest subgroups, nearly 100% of patients who were administered rescue medication vomited, suggesting that rescue medication was administered after vomiting started. In the older age groups the proportion of patients who took rescue medicine who also vomited is similar between the 6-12 year old and adolescent age subgroups, as is the distribution between treatment arms. The distribution between arms suggests that the older pediatric patients were taking rescue medication for nausea, not necessarily waiting until vomiting occurred. The difference between arms in the 6 years and older subgroups in the proportion that vomited despite rescue medication, suggests that Emend may enhance the efficacy of rescue antiemetics when taken for significant nausea post chemotherapy.

Table 10. Proportions of Patients who took rescue medication and Proportions who took rescue medication and vomited by control arm and age subgroup.

Age Group	Emend	Control	Emend+Control	Emend	Control
	% subjects that took rescue medication	% subjects that took rescue medication	% of subjects that took rescue medication who vomited	% of subjects that took rescue medication who vomited	% of subjects that took rescue medication who vomited
6 mo to <2 y	16%	44%	100%	100%	100%
2 to <6 y	29%	35%	96%	92%	100%
6 to<12 y	45%	45%	85%	71%	95%
12 to 17 y	44%	75%	95%	76%	97%

Ultimately, the Division determined [redacted] (b) (4) the product labeling of the pediatric trial.

Subgroup analyses of the primary endpoint and key secondary endpoints. The Statistical reviewer conducted exploratory analyses of the primary and key secondary (acute and overall phase) endpoints, and did not identify issues that raised concerns regarding the reliability of the applicant's efficacy analyses and conclusions.

The Statistical reviewer also conducted subgroup analyses for the three key endpoints (delayed, acute and overall phases) in the subgroup of the patients ages 12 years and older who were treated with oral aprepitant capsules (the subject product of this supplemental NDA), and the results, which were favorable, are shown in the table below (reproduced from the Statistical Review). This was not a pre-specified analysis and there was no prespecified plan to control Type I error. Therefore, the p values in the following table are unadjusted (nominal) p values, presented only for exploratory consideration.

Table 11: FDA Statistical Reviewer's Efficacy comparison by phase for patients ages 12 to 17 years.

Phase	Aprepitant Regimen (A) n/N (%)	Control regimen (C) n/N (%)	95% 2-sided C.I. for Diff. (A-C)	p-value
Delayed Phase	24/47 (51.1)	5/48 (10.4)	(0.23, 0.56)	P < 0.0001
Acute Phase	26/47 (55.3)	18/48 (37.5)	(-0.02, 0.37)	P = 0.099
Overall Phase	18/47 (38.3)	4/48 (8.33)	(0.14, 0.46)	P = 0.001

Numerically similar and favorable results were observed in an exploratory analysis of the younger subgroup (6 months to <12 years of age), which are summarized below (reproduced from the Statistical review).

Table 12: FDA Reviewer's Efficacy comparison by phase for patients ages 6 months to 12 years

Phase	Aprepitant Regimen (A) n/N (%)	Control regimen (C) n/N (%)	95% 2-sided C.I. for Diff. (A-C)	p-value
Delayed Phase	53/105 (50.5)	34/102 (33.3)	(0.04, 0.3)	P=0.013
Acute Phase	75/105 (71.4)	60/102 (58.8)	(-0.004, 0.25)	P =0.057
Overall Phase	43/105 (41.0)	26/102 (25.5)	(0.026, 0.28)	P=0.021

The nominal p-values for the acute phase, which exceeded 0.05 in both subgroup analyses above, were primarily due to the small sample sizes. The trial was not directly powered to detect treatment differences of CR within the age subgroups. The p value for the adolescent subgroup was much larger than 0.05, but the treatment difference was 17.8%, which was larger than the treatment gain for the overall study population. The sample size in the >12 years of age subgroup is much smaller than the younger subgroup (about 1/3 of the size). Even though the treatment difference observed in the acute phase in the younger subgroup (<12 years of age) is smaller than that observed for the overall study population, the nominal p value in this subgroup was very close to 0.05. The acute phase subgroup analysis p values do not raise concerns that the product is not effective in the acute phase.

As discussed in Section 5 Clinical Pharmacology, the pharmacometric reviewers determined that the capsule can be safely and effectively administered (at the same dose as adolescents) to pediatric patients <12 years of age who weigh ≥30 kg, as long as they can swallow capsules. Patients <12 years of age who weigh ≥30 kg were administered the equivalent suspension dose in the clinical trial. Emend capsule product labeling will be extended to this younger age

group, accordingly. The following subgroup analysis of efficacy from the phase 3 trial data (Table 13 below), which is limited to those patients dosed with the capsule formulation in the clinical trial (≥12 years of age) PLUS the patients who were <12 years of age AND weighed ≥30 kg, was submitted to support product labeling in Section 14. It was not a prespecified analysis. It included 16 Emend arm subjects and 21 control arm subjects who were <12 years of age (and whose weight was in the target weight band of ≥30 kg). This group of patients represented 44% of the entire trial <12 years of age subgroup who were treated with the suspension formulation.

Table 13. Applicant's Subgroup Efficacy comparison by phase including patients >12 years PLUS patients <12 years of age who weighed ≥ 30 kg (all patients who received aprepitant 125 mg Day 1 and 80 mg Days 2 and 3 in either capsule or suspension formulation).

	EMEND Regimen n/m (%)	Control Regimen n/m (%)
Patients Aged 12 to 17 Years or Body Weight ≥ 30 kg		
PRIMARY ENDPOINT		
Complete Response* - Delayed phase	31/63 (49.2)	13/69 (18.8)
OTHER PRESPECIFIED ENDPOINTS		
Complete Response* – Acute phase	35/63 (55.6)	26/69 (37.7)
Complete Response* – Overall phase	22/63 (34.9)	9/69 (13.0)
No Vomiting§ – Overall phase	29/63 (46.0)	11/69 (15.9)

*Complete Response = No vomiting or retching and no use of rescue medication.
§No Vomiting = No emesis or retching or dry heaves
n/m = Number of patients with desired response/number of patients included in time point.
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

The treatment gains observed in this larger subgroup analysis are similar to those observed in the 12 years and older subgroup, with the exception of the delayed phase, in which the treatment gain is numerically smaller.

The subgroup analyses of efficacy based on sex and race follow below.

Sex. The following tables reproduced from the Statistical review summarize efficacy in the delayed phase by sex. The results favored the aprepitant arm in both subgroups and were nominally statistically significant; however, the treatment difference in females was numerically smaller than males (the larger sample size of the two subgroups).

Table 14 FDA Reviewer's Comparison of Complete Response in Delayed Phase by Sex (ITT population) – Study P208

Females	n	Number (%) of Patients Responding	Aprepitant versus Control[a] % Difference	P-value
Control Regimen	68	30 (44.1%)		
Aprepitant Regimen	71	20 (28.2%)	15.9	0.049*

Males	n	Number (%) of Patients Responding	Aprepitant versus Control[a] % Difference	P-value
Control Regimen	84	47 (56.0%)		
Aprepitant Regimen	79	19 (24.1%)	31.9	<0.0001*

[a]: Analysis via Cochran Mantel-Haenszel test stratified by gender.
*: Significant at two-sided significance level of 0.05

Race. The subgroup analysis by race was conducted evaluating White vs. Non-White. There were only two Black/African American patients randomized in this trial, and they were both randomized to the control arm. The sample size of the non-white subgroup was much smaller than the white subgroup. A larger treatment difference was observed in the non-white subgroup.

Table 15 FDA Reviewer's Comparison of Complete Response in Delayed Phase by Race (ITT population) – Study P208

White	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	119	59 (49.6%)		
Aprepitant Regimen	110	32 (29.1%)	20.5	0.0008*

Non-White	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	33	18 (54.6%)		
Aprepitant Regimen	40	7 (17.5%)	37.1	0.0015*

Analysis via Cochran Mantel-Haenszel test stratified by gender.*: Significant at two-sided significance level of 0.05

The Clinical reviewer presented additional exploratory analyses in her review. They included an exploration of delayed phase efficacy in the following subgroups: Use of dexamethasone (yes/no), Receipt of Very High Risk Emetogenic Chemotherapy in Cycle 1 (yes/no), and Chemotherapy administered beyond Day 1 in Cycle 1 (yes/no). The latter could be considered a surrogate exploration of the impact of taking additional days of 5HT3 antagonist (beyond Day 1), which was allowed if a patient received multi-day chemotherapy. The results of these exploratory analyses are summarized in the tables below.

Dexamethasone use subgroup analyses. Dexamethasone was optional in the trial and it was a part of the antiemetic regimen in only approximately 28% of patients. This contrasts with the adult aprepitant trials, in which all patients received dexamethasone (four days with HEC, one day with MEC). The Clinical reviewer noted in her review that the 2011 ASCO Guidelines recommend inclusion of dexamethasone in the antiemetic regimen for both HEC and MEC; however, she reported that this is not necessarily standard of care in pediatric

patients due to safety concerns, such as the potential for increasing the risk of fungal infections.

The following table summarizes the exploratory analyses of CR in overall and delayed phase based on whether or not patients were treated with dexamethasone as part of their antiemetic regimen. Omission of dexamethasone from the regimen does not appear to have negatively impacted efficacy. The delta between aprepitant and control was higher in patients who did not receive dexamethasone, in both the delayed and overall phase. Within the control arm, the CR rate was higher in patients who did not receive dexamethasone, in both the delayed and overall phase. These data suggest that investigators may have chosen to use dexamethasone for more emetogenic chemotherapy regimens; however, as stated in the demographic summary, approximately 2/3 of the study population received Very High Risk Emetogenic agents. The within arm difference (dex vs. no dex) was greatest in the aprepitant arm in both the delayed and overall phase analyses, but most striking in the delayed phase analysis.

Table 16. Subgroup Analysis of CR in Overall Phase and Delayed Phase based on whether dexamethasone is administered as part of the antiemetic regimen

Use of Dexamethasone as an Antiemetic	Aprepitant Regimen	Control Regimen	Estimated Treatment Difference
	Complete Response in the Overall Phase n/N (%)		
Yes	15/44 (34.1%)	7/42 (16.7%)	17.4%
No	46/108 (43%)	23/108 (21.3%)	21.3%
Within arm difference based on decadron (no minus yes)	**8.9**	4.6	
	Complete Response in the Delayed Phase n/N (%)		
Yes	16/44 (36.4%)	9/42 (21.4%)	15%
No	61/108 (56.5%)	30/108 (27.8%)	28.7%
Within arm difference based on decadron (no minus yes)	**20.1**	6.4	

Very High Risk Emetogenic Chemotherapy subgroup analyses. The following table explores the CR rates in delayed and overall phases, within and between treatment arms, based on whether or not (yes/no) a patient received Very High Risk Emetogenic Chemotherapy (VHREC) agent in Cycle. The CR rates in the delayed and overall phase in the No VHREC cells for both aprepitant and control arms are higher than in the +VHREC cells, as might be expected. The treatment gain for aprepitant relative to placebo was numerically nearly identical in the overall and delayed phase in patients who receive a VHREC (suggesting that acute phase vomiting did not reduce the overall CR relative to delayed phase). However, in the No VHREC subset, the treatment gain for aprepitant appears higher in the delayed phase

than the overall phase (22.6% vs. 16.4%), suggesting acute phase vomiting was more of an issue in the No VHREC subgroup. Comparisons of the denominators in the dexamethasone subgroup analyses in the table above to the denominators in the VHREC table below reveal that more than twice as many patients in each arm were treated with a VHREC agent than received dexamethasone as part of their antiemetic therapy regimen, indicating that despite the high emetogenicity of the chemotherapy, the investigator chose not to include dexamethasone in the antiemetic regimen.

Table 17. Exploratory Subgroup Analysis of CR in Overall Phase and Delayed Phase based on whether or not patients received a Very High Risk Emetogenic Chemotherapeutic agent

Receipt of Very High Risk Emetogenic Chemotherapy (VHREC)	Aprepitant Regimen	Control Regimen	Estimated Treatment Difference
	Complete Response in the Overall Phase n/N (%)		
Yes	35/99 (35.4%)	14/101 (13.9%)	21.5%
No	26/53 (49.1%)	16/49 (32.7%)	16.4%
Within arm difference based on VHREC (no minus yes)	13.7	18.8	
	Complete Response in the Delayed Phase n/N (%)		
Yes	42/99 (42.4%)	20/101 (19.8%)	22.6%
No	35/53 (66%)	19/49 (38.8%)	27.2%
Within arm difference based on VHREC(no minus yes)	23.6	19	

Single vs. Multi-day chemotherapy analyses. The following table presents the CR results for overall and delayed phases, by arm, based on whether a patient received single day chemotherapy vs. multiple days of chemotherapy. A high proportion of patients received multiday chemotherapy (83% in the aprepitant arm and 89% in the control arm). The treatment differences between arms appear highest if only a single day of chemotherapy is given; however, note the very small sample size of patients who only received a single day of chemotherapy. Focusing on the control arm only, the CR rate in multiple day regimens was lower in the delayed phase than in single day regimens; however, this was not true for the overall phase, suggesting that acute phase nausea and vomiting was particularly problematic in the single day chemotherapy regimens administered. In the aprepitant arm analyses, the CR rate was numerically lower in the multiple day regimens in both the delayed and overall phases. It is difficult to draw any conclusions from these comparisons, in light of the very small sample size in the patients who received single day treatment.

Table 18. Exploratory Subgroup Analysis of CR in Overall Phase and Delayed Phase based on whether or not patients received Multi-day chemotherapy

No. of Days of chemo	Aprepitant Regimen	Control Regimen	Estimated Treatment Difference
	Complete Response in the Overall Phase n/N (%)		
Single	15/26 (57.7%)	2/16 (12.5%)	45.2%
Multi	46/126 (36.5%)	28/134 (20.9%)	15.6%
Within arm difference Multi minus Single	Minus 21.2	+8.4	
	Complete Response in the Delayed Phase n/N(%)		
Single	21/26 (80.8%)	5/16(31.3%)	49.5%
Multi	56/126 (44.4%)	34/134 (25.4%)	19%
Within arm difference Multi minus Single	Minus 36.4	Minus 5.9	

Comparison of the aprepitant treatment gain data in the last column above to the treatment gain observed for aprepitant in the prespecified ITT analyses of the overall trial population (where the difference between treatment groups in the delayed phase was 26% and the difference in overall phase was 20%; see Table below) reveals the overall and delayed phase results in the larger multiday subgroup are numerically similar but lower than the trial's ITT results. The higher ITT overall results suggest that the large CR treatment effect observed in single day treatment had an impact on the overall trial results.

Table 19. Overall ITT analyses results

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	101 / 152 (66.4) *	78 / 150 (52.0)
Delayed Phase	77 / 152 (50.7) **	39 / 150 (26.0)
Overall Phase	61 / 152 (40.1) **	30 / 150 (20.0)

Summary. The Statistical and Clinical reviewers all determined that Study P208 provided substantial evidence of efficacy to support approval of aprepitant for the overall pediatric population. I concur. However, the patients <12 years of age in this trial were administered the aprepitant suspension formulation, not the capsules. (b) (4) (b) (4) (b) (4) The pharmacometric team from Clinical Pharmacology was able to confirm that the population PK data support labeling the capsule formulation for use in pediatric patients <12 years of age who weigh ≥30 kg (and who are able to swallow the capsule). (See discussion in Section 5 Clinical Pharmacology.) Based on the CDC Growth Charts for boys,

30 kg is the 50th percentile weight for a 9.5 year old boy, and the 75th percentile weight for an 8.5 year old boy. Based on the CDC Growth Charts for girls, 30 kg is the 50th percentile weight for a 9.25 year old girl and the 75th percentile for a 8.25 year old girl.

Given that the Indication and Dosage and Administration sections of the label will not be limited to the Study P208 subgroup that received the capsules in the trial, the full results of the trial will be presented in Section 14, to support including those patients under the age of 12 years whose weight is ≥ 30 kg in the indication and to support including dosage and administration instructions for those younger patients. DPMH expressed significant concerns about the plan to include the full population results of Study P208 in Section 14 because presenting the entire study could promote off label use in younger patients. I disagreed because it is important to be consistent in supporting the indication with data in Section 14 and the label will include statements to make it clear that an age appropriate dosage formulation is not available to provide a safe and effective dose that is required for pediatric patients who weigh less than 30 kg. Emend is currently being used off label across the pediatric age range (see postmarketing safety discussion in Section 8 Safety below). Review of the reports did not identify a significant safety issue related to this off label use. Overdoses of aprepitant were reported in the aprepitant pediatric clinical development program, and no significant adverse outcome was identified. There were no substantive adverse reactions identified in the pediatric development program that were clearly attributable to aprepitant. Overall, the risk/benefit of aprepitant in the pediatric population is favorable, and I do not have concerns that inclusion of the full study data in Section 14 will cause an incremental increase in existing off label use of aprepitant in children <30 kg. If it does, I cannot identify a significant safety issue that would arise from administering the labeled dose in these smaller children.

The indication statement will read:

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND®, in combination with other antiemetic agents, is indicated in patients 12 years of age and older and patients less than 12 years who weigh at least 30 kg 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 *[see Dosage and Administration (2.1)]*.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.1)]*.

Section 8.4 Pediatric Use will state:

Prevention of Nausea and Vomiting Associated with HEC or MEC

The safety and effectiveness of EMEND have been established in pediatric patients 6 months of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin, and moderately emetogenic cancer chemotherapy. Use of EMEND in these age groups is supported by evidence from 302 pediatric patients (n = 207 patients aged 6 months to less than 12 years, n = 95 patients aged 12 through 17 years. There were 37 patients who were less than 12 years of age who weighed at least 30 kg in a randomized,

double-blind, active comparator controlled clinical study. EMEND was studied in combination with ondansetron with or without dexamethasone (at the discretion of the physician) *[see Clinical Studies (14.3)]*. Adverse reactions were similar to those reported in adult patients *[see Adverse Reactions (6.1)]*.

Although the safety and efficacy results from the trial support the use of EMEND for the prevention of nausea and vomiting associated with HEC or MEC in pediatric patients 6 months to 12 years, there is no commercially available dosage formulation appropriate for patients less than 12 years of age or weighing less than 30 kg. Therefore, (b) (4) [redacted] *[see Dosage and Administration (2.1)]*.

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.

There were also review discussions regarding how to describe the use of concomitant antiemetic agents in the label's Dosage and Administration section, given the differences between regimens used within Study P208, the fact that the adult regimen recommends use with dexamethasone, and ASCO guidelines recommend use with dexamethasone. Ultimately, the review team determined that the instructions should be similar to those followed in the clinical trial, leaving it up to the prescriber to decide whether to use dexamethasone. Most of the patients in the clinical trial did not receive dexamethasone as part of the antiemetic regimen. If dexamethasone is selected, the Dosage and Administration section will recommend dose reduction, similar to the adult dosage recommendation, to account for the increased exposure of dexamethasone that has been observed in adults when aprepitant and dexamethasone are administered concomitantly. The content of the Dosage and Administration section for CINV is shown below, including the tables summarizing the recommended dosing (including concomitant use of 5HT3 antagonist and optional dexamethasone). Note that there is an option for intravenous Day 1 dosing in adults, which is not available to pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Adults and Pediatric Patients 12 Years of Age and Older and Patients Less Than 12 Years of Age who Weigh at least 30 kg

The recommended oral dosage of EMEND capsules, dexamethasone, and a 5-HT_3 antagonist in adults and pediatric patients 12 years of age and older and patients less than 12 years of age who weigh at least 30 kg, who can swallow oral capsules, for the prevention of nausea and vomiting associated with administration of HEC or MEC is shown in Table 1 or Table 2, respectively.

In adults only, EMEND for injection (115 mg), a prodrug of aprepitant, may be substituted for EMEND capsules (125 mg), 30 minutes prior to chemotherapy, on Day 1 of the CINV regimen as an intravenous infusion administered over 15 minutes, followed by oral EMEND (80 mg) on Days 2 and 3. See the prescribing information for EMEND for injection.

Table: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with HEC

	Population	Day 1	Day 2	Day 3	Day 4
EMEND capsules*	Adults, Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone†	Adults	12 mg orally	8 mg orally	8 mg orally	8 mg orally
	Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4 *[see Clinical Studies (14.3)]*.			
5-HT_3 antagonist	Adults, Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning on Days 2 and 3.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone reflects a 50% dosage reduction to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

Table: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with MEC

	Population	Day 1	Day 2	Day 3
EMEND capsules*	Adults, Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	125 mg orally	80 mg orally	80 mg orally
Dexamethasone†	Adults	12 mg orally	none	none
	Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4 *[see Clinical Studies (14.3)]*.		
5-HT_3 antagonist	Adults, Pediatric Patients 12 Years and Older, and Pediatric Patients less than 12 Years Who Weigh at least 30 kg	See the selected 5-HT_3 antagonist prescribing information for recommended dosage	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning on Days 2 and 3.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone reflects a 50% dosage reduction to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

8. Safety

The integrated safety population included patients treated in the major efficacy trial, P208, and the exploratory dose finding/PK studies, P097 and P134. As stated in the Clinical Review: "Of the 372 subjects who received study medication in Protocols 208, 097 and 134 (Part IV), 308 subjects received aprepitant either in Cycle 1 and/or in an optional Cycle 2 to 10 (Protocols 208 and 097 only). Additionally, an additional 49 subjects were exposed to aprepitant either as single doses or as part of a combined regimen with intravenous fosaprepitant in Parts I (11 subjects) and II (38 subjects) of Protocol 134. Thus, 357 subjects were exposed to oral aprepitant within the three pediatric CINV studies included in this application." The following table, reproduced from the Clinical review summarizes the number of patients exposed to aprepitant in the three studies, by age subgroup.

Table 20. Number of patients exposed to aprepitant by age category in Protocols 208, 097 Combined (Cycles 1-10) and 134 (Parts I, II and IV)

		Aprepitant Exposure†			
Age Group	PN208 and PN097 Combined (Cycles 1-10)	PN134 (Part I)	PN134 (Part II)	PN134 (Part IV)	Total
6 months to < 2 years	31	0	11	7	49
2 years to < 6 years	63	0	15	6	84
6 years to < 12 years	72	0	12	7	91
12 years to < 18 years	120	11	0	0	131
18 years to 19 years	2	0	0	0	2
Total	288	11	38	20	357

†Number of subjects who received at least one dose of aprepitant.

Deaths. There were 3 deaths reported in the application; none were considered to be drug related. Two of the patients had been treated with aprepitant. One death occurred in Study 208 (aprepitant treated patient who died 9 months after study discontinuation from progression of neuroblastoma) and the other two in Study 097 (aprepitant treated patient who died >300 days post last exposure, due to progressive lung metastases and the other occurred in a control group patient who died approximately 120 days after study).

Nonfatal SAEs. The proportion of patients treated with aprepitant who experienced one or more nonfatal SAEs was similar to that observed in the control arm: 29.3% vs. 25.6%, respectively. The most common SAE in the overall safety database was febrile neutropenia: 15.8% in the aprepitant group and 14.3% in the control. Within the phase 3 trial, Study P208, the proportion of patients in the aprepitant arm that had SAEs was 30.3%, whereas the proportion in the control arm was 27.3%. The proportion with febrile neutropenia in this trial was nearly identical between arms, 15% vs 14.7%. In the dose exploration, PK study (Study 097), a higher proportion of patients treated with aprepitant had SAEs of febrile neutropenia than control, 25% (8 patients) vs 11% (2 patients); however, no meaningful conclusions can be drawn based on this difference, given the study's small sample size.

There were two nonfatal SAEs in Study 208 that the investigator considered drug related. One was a case of C. difficile infection, which was diagnosed 3 days post starting study drug. The investigator attributed it to ondansetron and study drug. The second was T-wave inversion on Day 8 post initiation of chemotherapy in a 16 year old female. Aprepitant was administered on Days 1-3. The event was Grade 1 and resolved spontaneously. The subject discontinued.

Table 39 in the Clinical review lists the clinically relevant nonfatal SAEs reported in Cycle 1 only, in patients who received aprepitant in Study 208 and Study 097. Most are expected toxicities associated with chemotherapy, including cytopenias, febrile neutropenia, stomatitis/mucosal inflammation and infections. There were two hypersensitivity reactions that were considered unrelated to aprepitant: **anaphylactic shock** and **"drug hypersensitivity**". (See description of these two cases in the next subsection, "Discontinuations for adverse events".) There was an SAE of "drug clearance reduced" (methotrexate) and "hepatoxicity" (in a 4 year old treated with 3.35g methotrexate; transaminases increased on Day 7 post treatment), both of which were also considered unrelated. The Clinical reviewer reported that there was **an additional anaphylaxis SAE in a**

subsequent cycle (Cycle 2) attributed to study drug. These events are described below, with the adverse events that led to study discontinuation.

Discontinuations for adverse events. Two patients in Study 208 discontinued study drug due to an adverse event in Cycle 1. No patients on the control arm discontinued due to adverse event. One of the events was the **"drug hypersensitivity"**event noted above. The event was described as severe in intensity, grade 4, and occurred with administration of carboplatin and aprepitant. The patient experienced generalized erythema, facial edema, mild cyanosis and severe abdominal pain 10 minutes after carboplatin. She was treated with hydrocortisone, dipyrone magnesium, dexchlopheniramine and ranitidine. This was likely a case of anaphylaxis. Carboplatin is associated with anaphylaxis. Another was the case of **"anaphylactic shock"** reported above, which occurred in the first Cycle in the setting of coadministration with etoposide. The event was described as severe in intensity, grade 4, and the patient was treated with epinephrine, methylprednisolone, and saline. Etoposide is known to be associated with anaphylaxis.

There were 4 patients in Study 208 who discontinued treatment in a subsequent cycle during its open label extension phase.

- One was the additional Cycle 2 **anaphylaxis** case mentioned in the previous subsection. This occurred in a 9 year old female with osteogenic sarcoma who received aprepitant and 12 grams of methotrexate and had "anaphylactic shock" on the same day, which reportedly resolved in an hour. The event was accompanied by **marked elevation in transaminases (ALT = 1059.0 IU/L; AST=2031.0 IU/L) and LDH (1070 IU/L).** Study medication was discontinued on the same day, Day 1 of Cycle 2. The transaminase elevation resolved in 11 days. The elevation in transaminases could have resulted from methotrexate or hypotension secondary to anaphylactic shock. The methotrexate product label statess that "anaphylactoid reactions" have been reported. This case of anaphylaxis is possibly related to aprepitant.

- One case was marked **elevation of transaminases, bilirubin and LDH** after a dose of high dose methotrexate (13.2 g) and aprepitant in Cycle 2, in a patient with osteosarcoma (ALT=2238 IU/L; AST=2738 IU/L; Bilirubin = 2.18 mg/dL). The transaminase elevation occurred on Day 1 and resolved in 15 days. The bilirubin increased on Day 2 and resolved in 8 days. LDH returned to normal in 21 days. These toxicities were most likely related to methotrexate.

- A c**onvulsion** occurred in Cycle 2 in a 6 year old with gliosarcoma. The investigator attributed it to study drug. Given the underlying diagnosis, the tumor may also have contributed.

- A case of **febrile neutropenia**, not considered related to study drug, led to a discontinuation in a 4 year old with alveolar rhabdomyosarcoma.

In summary, nearly all these SAES could be attributed to the concomitant chemotherapeutic agent or underlying tumor. There was one case of anaphylaxis in which there was not a

concomitant medication that seemed more likely to have been the underlying cause, i.e. methotrexate. In that case, I consider the event possibly related to aprepitant. The Emend label currently mentions anaphylactic reactions.

Common adverse events. The most common adverse events observed were events that are associated with chemotherapy. The following table will be presented in Section 6 of the product label:

Table: Most Common Adverse Reactions in EMEND-Treated Pediatric Patients in HEC and MEC Pooled Studies 5 and 6*

(b) (4)

Hepatic safety. The Clinical Review contains a table (Table 43) which summarizes adverse events with incidence ≥ 2% in one or more treatment groups in Cycle 1 of Studies 208 and 097. The percentages in each treatment group with any ALT increase (3.3% in aprepitant arm and 4.8% in the control group) and AST increase (2.7% in aprepitant and 3.6% in control) were similar between groups. Table 44 in the Clinical Review summarizes the mean changes from baseline for selected laboratory measures in the same two trials. The mean change from baseline in ALT was higher in the aprepitant group: 41.3 IU/L (increase from 32.7 to 74) vs. 17.0 IU/L in the control (increase from 35.5 to 52.4). The mean change from baseline in AST was also higher in the aprepitant group: 19.9 IU/L (increase from 32.7 to 52.6) vs. 4.5 IU/L in the control (increase from 38.5 to 43.0). The mean change from baseline in bilirubin in the aprepitant group was similar to control: 0.1mg/dL and 0.2 mg/dL, respectively.

The following table, reproduced from the Clinical Review summarizes the proportions of patients who had specified incremental increases of ALT, AST, bilirubin, alkaline phosphatase, and combinations intended to explore whether any approached Hy's Law criteria. No patient met Hy's Law criteria. Furthermore, there were no patients with a substantial increase in ALT concurrent with a bilirubin >2 ULN, which the DILI Guidance states "identifies a drug likely to cause severe DILI….at a rate roughly 1/10 the rate of Hy's Law cases. (Note that the table below utilizes a more conservative bilirubin criterion of ≥ 2 ULN rather than > 2X ULN.)

Table 21 Summary of Incremental Increases in Transaminases, Bilirubin and Alkaline Phosphatase in Studies 208 and 097

Criteria	Aprepitant Regimen		Control Regimen		Total	
	n/m	(%)	n/m	(%)	n/m	(%)
Alanine Aminotransferase						
>5 x ULN	12/181	(6.6)	13/166	(7.8)	25/347	(7.2)
≥10 x ULN	8/181	(4.4)	4/166	(2.4)	12/347	(3.5)
≥20 x ULN	3/181	(1.7)	1/166	(0.6)	4/347	(1.2)
Aspartate Aminotransferase						
>5 x ULN	5/181	(2.8)	4/166	(2.4)	9/347	(2.6)
≥10 x ULN	2/181	(1.1)	2/166	(1.2)	4/347	(1.2)
≥20 x ULN	2/181	(1.1)	1/166	(0.6)	3/347	(0.9)
Aminotransferase (ALT or AST)						
>5 x ULN	12/181	(6.6)	13/166	(7.8)	25/347	(7.2)
≥10 x ULN	8/181	(4.4)	5/166	(3.0)	13/347	(3.7)
≥20 x ULN	3/181	(1.7)	1/166	(0.6)	4/347	(1.2)
Bilirubin						
≥2 x ULN	0/179	(0.0)	0/166	(0.0)	0/345	(0.0)
Alkaline Phosphatase						
≥1 5 x ULN	14/178	(7.9)	9/163	(5.5)	23/341	(6.7)
Aminotransferase (ALT or AST) and Bilirubin						
AT ≥3 x ULN and BILI ≥1.5 x ULN	1/181	(0.6)	0/166	(0.0)	1/347	(0.3)
AT ≥3 x ULN and BILI ≥2 x ULN	0/181	(0.0)	0/166	(0.0)	0/347	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase						
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/181	(0.0)	0/166	(0.0)	0/347	(0.0)

plicant's table

As can be seen in the table above, there was a slightly numerically higher proportion of patients in the aprepitant group who experienced elevations of ALT ≥ 10 X ULN and ≥ 20 X ULN than in the control. There were no patients with a bilirubin that increased ≥ 2 X ULN. A slightly numerically higher proportion of aprepitant treated patients experienced alkaline phosphate elevations that were ≥ 1.5 X ULN. There were no cases that met Hy's Law criteria. The Clinical Reviewer noted that the analyses of laboratory measures in subsequent cycles, revealed no evidence of rising proportions of patients with incremental increases of these biomarkers relative to the control and relative to Cycle 1.

Aprepitant/chemotherapeutic agent drug drug interaction. Section 7 Drug Interactions of the aprepitant label states (b) (4) (b) (4) (b) (4) patient who experience somnolence and confusion when ifosfamide and aprepitant were co-administered, the Clinical reviewers requested a summary of adverse events that occurred in

the pediatric clinical trials associated with ifosfamide coadministration. In the safety population of Studies 208 and 097 combined, there were 49 patients treated with ifosfamide in an aprepitant arm and 49 patients treated with ifosfamide in a control arm. Of those patients, 7 in an aprepitant arm had adverse events related to the nervous system, compared to 4 on the control arm. The applicant's summary table is reproduced below. Most of the events were headaches. Two patients (one 17 years old who received 4.3g ifosfamide and one 16 years old who received 4.2 g ifosfamide) experienced behavioral changes in an aprepitant arm, both of whom also experienced dizziness. No patient experienced a behavioral changed in a control arm. It is difficult to discern whether this numeric difference between treatment arms is due to higher ifosfamide exposures in the patients who received aprepitant. The product label already states (b) (4). Aprepitant is a moderate inhibitor of CYP3A4 and an inducer of CYP3A4. The ifosfamide label states that "CYP3A4 inducers may increase the metabolism of ifosfamide to its active alkylating metabolites. CYP3A4 inducers may increase the formation of the neurotoxic/nephrotoxic ifosfamide metabolite, chloroacetaldehyde." Information on the behavioral adverse events will be included in Section 6 Adverse Reactions. It will include the statement: "Aprepitant has the potential for increasing infosfamide mediated neurotoxicity through induction of CYP3A4."

Table 22. Applicant's summary of patients who were treated with ifosfamide and experienced a nervous system disorder in Study 208 and Study 097.

Subject	Treatment Group	Ifosfamide Dose	Adverse Event	AE Study Day	AE Severity
10184	Aprepitant Regimen	1.2 gm	Headache	1	MILD
10184	Aprepitant Regimen	1.2 gm	Headache	2	MILD
10218	Aprepitant Regimen	4.3 gm	Dizziness	1	MILD
10218	Aprepitant Regimen	4.3 gm	Abnormal behaviour	2	MODERATE
10218	Aprepitant Regimen	4.3 gm	Dizziness	2	MILD
070004	Aprepitant Regimen	2640.0 mg	Headache	1	MILD
070420	Aprepitant Regimen	2650.0 mg	Dizziness	2	MILD
070506	Aprepitant Regimen	1200.0 mg	Headache	1	MODERATE
070529	Control Regimen	3340.0 mg	Headache	1	MILD
070406	Control Regimen	2000.0 mg	Headache	1	MILD
070204	Aprepitant Regimen	4200.0 mg	Dizziness	1	MODERATE
070204	Aprepitant Regimen	4200.0 mg	Agitation	1	MODERATE
070204	Aprepitant Regimen	4200.0 mg	Insomnia	1	MILD
070204	Aprepitant Regimen	4200.0 mg	Dysgeusia	1	MILD
070125	Control Regimen	4350.0 mg	Headache	1	MILD
070126	Aprepitant Regimen	3200.0 mg	Headache	1	MILD

070517	Control Regimen	2610.0 mg	Convulsion	1	MILD

Overdose. There were multiple aprepitant suspension overdoses in Study 208, in patients <12 years of age. There was one aprepitant overdose in Cycle 1. Six additional subjects were overdosed during the extension cycles. Four of the patients experienced more than one overdose in a cycle (Days 1, 2 and 3). One of the patients received overdoses in two cycles. The maximum overdose was a 2.1 fold increase over the intended dose. The distribution of percentage overdoses were:

<10% overdose:
One subject: Day 1 = 3.3%, Days 2 and 3 = 2.6% each
One subject: Day 1= 5%, Days 2 and 3 = 6.7% each

>40% overdose:
One subject: Days 2 and 3 47% each
One subject: Day 2 50%
One subject: Day 2 Cycle 2 50%
Day 1 Cycle 3 108%
One subject: Day 1 67%

These patients experienced TEAEs, but none were attributed to the aprepitant overdose. Review of the adverse events reveals they were consistent with chemotherapy toxicity or symptoms of underlying malignancy. There were no seizures reported or hepatic toxicity.

The applicant reviewed the underlying causes of these overdoses and most of them were related to using the wrong weight or transcription errors (for example, substituting the Day 1 dose for a subsequent day's dose).

There were two patients who received overdoses in Study 134. The percentage increase in dose was 11% in one subject and 24% in the other. Both were single doses on Day 1 only.

Postmarketing safety review. Aprepitant capsules have been marketed since 2003. It is approved for use in adolescent patients in Japan. The applicant identified 2555 spontaneous adverse event reports in their own Adverse Event Reporting and Review System (MARRS) database in the period between March 26, 2003 and March 25, 2014. Thirty-nine were for pediatric reports. The following table, reproduced from the Clinical review, summarizes the age and sex distribution of the pediatric reports.

Table 23. Summary of pediatric postmarketing spontaneous adverse event reports in applicants MARRS database (2003-2014): distribution by age and sex

Age (years)	Total	Male	Female	Unknown
< 2	1	1	0	0
2 - < 6	7	3	1	3
6 - < 12	12	9	0	3

12 - < 18	19	8	6	5
Total	39	21	7	11

Applicant's table

Most events occurred in children 6 years and older. This distribution likely reflects that most of the off label use occurs in patients who are able to swallow the capsules. The similar number of events reported in the 6 to 12 year old group compared to the adolescent age group in the table above, suggests that there is a similar amount of off label use of this product in this younger age group relative to the adolescent subgroup. Review of the actual events reported does not suggest there is a safety issue associated with off label use in the pediatric population. In Table 50 of the Clinical Review, which summarizes the most frequently reported adverse events in pediatric patients, the vast majority were reports of "off label use" (N=20). The next four most common reports (all N's 5 or less) were "no adverse event", "drug administration error", "drug ineffective" and "nausea".

The Clinical reviewer summarized the reports of the pediatric serious events found in the postmarket database. The single fatal outcome was a death in a 17 year old, due to disease progression of Ewings sarcoma; the event reported was constipation. The five additional serious events all occurred in adolescents, with the exception of a report in a 7 year old male who developed palpitations and tachycardia "at an unspecified time after aprepitant administration." The patient was being treated with aprepitant 80 mg twice a day for cyclic vomiting syndrome. Aprepitant is dosed only once daily x3 on an intermittent basis (based on chemotherapy cycle interval duration) in adults, and the apparent terminal half-life of aprepitant in adults is 9-13 hours. Duration of the exposure to this dose level and frequency in this 7 year old was not reported, and there was no information on the patient's weight. At the time of admission, the patient had sinus bradycardia and the ECG was normal. Concomitant medications included chlorpromazine, ondansetron, dexamethasone and propranolol. It is difficult to attribute the patient's palpitations/tachycardia to aprepitant, given the lack of information regarding timing of onset of symptoms related to administration; however, the dosing was BID, which is more frequent that approved for adults. Chlorpromazine and ondansetron have been associated with arrhythmias. Dexamethasone's corticosteroid effects on CNS could result in excitability and tachycardia. The patient's physician reported that he didn't know if the event was related to aprepitant.

The remaining four serious events (in adolescents: one 17 year old, two 14 year olds and one 15year old) were reports of "drug ineffective" (nausea associated with migraine), tachycardia at an unspecified time after receiving a dose of 125mg aprepitant (a 17 year old with testicular cancer also taking dexamethasone, granisetron and a proton pump inhibitor), somnolence and confusion in a 14 year old, and a case of probable anaphylaxis. I will describe the latter two cases in more detail below.

The 14 year old patient with somnolence and confusion was treated with aprepitant, ondansetron and dexamethasone to prevent CINV associated with ifosfamide and doxorubicin, which were administered for peripheral nerve sheath tumor. Symptom onset occurred 2 days after starting treatment. Aprepitant was discontinued. There was no assessment of causality provided by the reporter. Ifosphamide is associated with CNS effects, without coadministration of aprepitant. Dexamethasone can cause confusion, but somnolence

is unusual. This event could have been related to aprepitant, although ifosfamide is the likely underlying cause of the event. Contribution of aprepitant via increasing ifosfamide exposure due to its CYP3A4 inhibition must be considered. The Emend product label Section 5.1 (b) (4) (b) (4) The label notes that ifosfamide is metabolized by CYP3A4. (b) (4) (b) (4) (b) (4) Section 6.2 Postmarketing Experience of the label states, (b) (4) (b) (4) i

The 15 year old with probable anaphylaxis received a one-time dose of aprepitant 125 mg, combined with ondansetron and dexamethasone, prior to chemotherapy with methotrexate. During the methotrexate infusion he developed dyspnea, hypotension and itching. The patient was rechallenged with aprepitant on a subsequent day and had no recurrence of the events. Therefore, the events are more likely to have been associated with methotrexate.

Summary. I concur with the Clinical reviewers that the safety database from the pediatric development program and the post marketing data revealed no significant adverse reactions associated with the use of aprepitant in pediatric patients over the age of 6 months, at the doses studied, that preclude its approval for use in the pediatric population. There was a case of anaphylaxis that may have been related to aprepitant; however, the product label already states that anaphylaxis has been reported with aprepitant use in Section 6.2 Postmarketing Experience. There were no safety signals that warrant requiring a post marketing safety trial/study. No safety findings or signals warrant a REMS. There is no need for a Medication Guide. Emend is currently marketed with a patient package insert (PPI) as part of approved labeling, and the PPI was updated during this review to reflect changes in the label.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held to discuss this NDA supplement. There were no issues identified that required discussion with an advisory committee.

10. Pediatrics

DPMH was consulted to assist with labeling. (b) (4) (b) (4) DPMH strongly advocated for labeling the capsule below 12 years of age, to the weight that could be justified based on the weight based dosing with the suspension used in the phase 3 trial. The pharmacometric team has confirmed that the capsules could be used for children ≥30 kg who are able to swallow capsules. The Division concurred with the recommendation from DPMH to extend the indicated population to include children ≥30 kg. However, see Section 7 above

regarding DPMH's recommendation regarding presentation of the phase 3 pediatric trial data in Section 14. I did not concur with their recommendation to limit the data to 12 and older, or to limit the presentation of efficacy data to the subset analyses of the clinical trial data that included patients 12 and older plus patients <12 years of age who weighed ≥30 kg. I did not agree that inclusion of the intact clinical trial in Section 14 will result in a significant increase in off label use in younger children, particularly with including cautionary statements in Sections 6.1, 8.4 and 14.3 throughout the label stating, "There is no commercially available dosage formulation appropriate for patients less than 12 years of age and weighing less than 30 kg" and "The efficacy results from the trial support the use of EMEND for the prevention of nausea and vomiting associated with HEC or MEC in pediatric patients 6 months to 12 years; however, there is no commercially available dosage formulation appropriate for patients less than 12 years of age and weighing less than 30 kg. Therefore, EMEND is indicated for the prevention of nausea and vomiting associated with HEC or MEC in patients 12 years of age and older and patients less than 12 years of age who weigh at least 30 kg." See Section 7 above for a description of final labeling in Section 8.4 Pediatric Use.

This NDA supplement was presented to PeRC before the pharmacometric evaluation that supports extending the dose to children less than 12 years of age who weigh ≥30 kg was available, and this option was not presented to the Committee. However, the Division Director from DPMH, PeRC Chair, participated in the final labeling meetings. PeRC supported labeling the oral capsules for patients ages 12-17. The Committee did not consider the PREA PMR fulfilled, (b) (4) (b) (4) (b) (4). PeRC recommended against a deferral extension, and stated that a formulation that can be administered accurately is essential. PeRC noted that the applicant had missed their date to request a deferral extension, and therefore there is no option for the applicant to request another extension.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations. Three clinical investigator sites that participated in the phase 3 trial Study 208 were inspected. All received an NAI classification. The OSI summary states, "The studies appear to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indication."

Financial Disclosures. The Clinical reviewer stated the following in her review:
"The Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts."

12. Labeling

See labeling discussions presented above in previous sections (Section 5, 7, 8 and 10). The reviewers from the DMPP reviewed the applicant's proposed Patient Package Insert (PPI). Emend has been marketed with a PPI, however, the PPI was updated during this review cycle to reflect changes in the product label. Recommended revisions were intended to simplify wording and clarify concepts and to ensure consistency with the prescribing information. Unnecessary or redundant information was removed. Their recommendations were incorporated in labeling negotiations.

The DMEPA reviewers evaluated the Emend capsule product label for aspects that may lead to medication errors. They concluded that the prescribing information was acceptable from a medication error perspective.

The OPDP reviewers' review comments regarding the proposed product label were incorporated in labeling negotiations.

DPMH was consulted to review and update the label subsections related to Pregnancy and Lactation (Section 8.1 and 8.2). They recommended restructuring the Pregnancy and Lactation subsections to be consistent with the Pregnancy and Lactation Labeling Rule (PLLR). They conducted a search of the published literature on the use of aprepitant and fosaprepitant during pregnancy, and no information was found. They noted that in the applicant's animal reproduction studies there is no evidence of fetal harm in rats at exposure 1.6 X the exposure at the recommended adult human dose and in rabbits at1.4 X the exposure at the maximum recommended adult human dose of 125 mg. Their recommendations for the Risk Summary in Subsection 8.1 Pregnancy were based on this information. Because there is no current safety information to recommend against breastfeeding, they recommended inclusion of the following statement in Subsection 8.2 Lactation, as required by the PLLR: "The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EMEND and any potential adverse effects on the breastfed infant from EMEND or from the underlying maternal condition."

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - approval (of capsules)

- Risk Benefit Assessment – There are no NK-1 inhibitors that have been approved for pediatric use. NK-1 inhibitors have a key role in decreasing delayed phase nausea and vomiting associated with chemotherapy. Children receive chemotherapeutic agents that cause delayed phase nausea and vomiting. Aprepitant has previously been shown to improve prevention of CINV in the setting of HEC and MEC when added to a 5HT3 antagonist and dexamethasone in adults. The phase 3 trial submitted in this application to support the pediatric indication of CINV established the efficacy of aprepitant for prevention of CINV in pediatric patients 6 months of age and older. The majority of patients in the phase 3 trial received highly emetogenic chemotherapy. Efficacy was

demonstrated in the acute and delayed phase in the overall study population. The efficacy data in this trial support that the current adult CINV indication can be extended to include the pediatric population for whom the capsule dose is appropriate (patients 12 years of age and older and patients less than 12 years of age who weigh at least 30 kg). The application established that aprepitant can be safely and effectively administered in pediatric patients with or without dexamethasone in a combination regimen that includes a 5HT3 antagonist for prevention of CINV. There were no safety issues identified in the pediatric studies that preclude aprepitant's approval for use in the pediatric population for the CINV indication, and there were no safety issues that warrant a Medication Guide, a REMS or a PMR safety study/trial. Review of the data submitted in this NDA supplement establish that the risk/benefit ratio favors aprepitant's approval for use in the pediatric population for prevention of CINV; (b) (4) (b) (4). Dosing with the suspension is weight based, and the population PK data support approving the aprepitant capsules for use in children under the age of 12 who weigh ≥30 kg and who can swallow capsules.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – Not necessary

- Recommendation for other Postmarketing Requirements and Commitments – The approval letter will remind the applicant of their PREA postmarketing requirements that are still open:

  1395-7 Deferred pediatric studies in patients 2 years to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin

  331-1 Deferred pediatric study under PREA for the use of Emend (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in pediatric patients 6 months to less than 17 years of age

  574-1 Deferred pediatric study under PREA for the treatment of post-operative nausea and vomiting pediatric patients ages 0 to less than 17 years of age

The CINV PREA requirements remain unfulfilled because an age appropriate formulation has not been approved.

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/s/

DONNA J GRIEBEL
08/28/2015