CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207865Orig1s000

SUMMARY REVIEW

Division Director Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA	207865
Applicant Name	Merck Sharp and Dohme Corporation
Date of Submission	March 26, 2015
PDUFA Goal Date	December 26, 2015
Proprietary Name / Established (USAN) Name	Emend aprepitant
Dosage Forms / Strength	Powder for oral suspension/125 mg (to be reconstituted with (b) (4) mL water to a concentration of 25 mg/mL)
Proposed Indication(s)	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/Aisha Johnson, MD, MPH, MBA/Anil Rajpal, MD
Statistical Review	Wen-Jen Chen, PhD/Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Sushanta Chakder, PhD
CMC Review	Hamid Shafiei, PhD/Moojhong Rhee, PhD (see supplemental table below for OPQ reviewer list)
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
OSE/DMEPA	Sherly Abraham, RPh/Kendra Worthy, PharmD/Lubna Merchant, MS, PharmD
DMPP	Karen Dowdy, RN, BSN/ /Marcia Williams, PhD/Meeta Patel, PharmD/LaShawn Griffiths, MSHS-PH, BSN,RN
DPMH	Amy M. Taylor, MD, MHS/Hari Cheryl Sachs, MD/Christos Mastroyannis, MD/ /Tamara Johnson, MD, MS/Lynne P. Yao, MD

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

	REVIEWER
Office of Process and Facilities	Vipul Dholakia
Biopharm	Tien Mien Chen
Environmental Assessment	James Laurenson
Microbiology	Bryan S. Riley

Division Director Review

1. Introduction

The trials submitted in this NDA for aprepitant powder for suspension 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). The Emend capsule product is 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 age appropriate oral suspension, which is subject to this new NDA, i.e., NDA 207865. The Emend capsule pediatric supplemental NDA (sNDA) for CINV was approved on August 28, 2015; however, the review clock for the oral suspension NDA was extended to receive additional information to support appropriate labeling instructions for reconstitution and measurement of oral suspension doses.

A single key pediatric trial established the efficacy and safety of both formulations (capsule and suspension) for CINV. Patients 12 years of age and older in the trial received a flat/fixed dose of aprepitant capsules (same as the adult CINV dose) and patients ages <12 years received aprepitant suspension. The dose in patients <12 years of age was calculated based on patient weight. There was no prespecified analysis to evaluate efficacy by age group or formulation (capsule/suspension). My efficacy and safety review for the capsule formulation, which was signed on August 28, 2015, included all of the information from the full age range enrolled in this trial, including the patients who received the suspension.

The inability to concurrently approve both formulations studied in the key efficacy and safety trial created review issues related to labeling the pediatric indication for the capsule sNDA. 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 weight based suspension dose (3 mg/kg Day 1; 2 mg/kg Days 2 and 3) for patients <12 years who weighed 40 kg would have been essentially the same as the flat dose of capsules studied in the subjects ≥12 years of age (trial suspension dose: 120 mg Day 1 and 80 mg Days 2 and 3 vs. capsule dose: 125 mg Day 1 and 80 mg Days 2 and 3). For subjects <12 years who weighed at least 30 kg, the weight based suspension dose was 30% lower than the flat dose of the capsules administered to the subjects ≥12 years of age (trial suspension dose: 90 mg Day 1 and 60 mg Days 2 and 3 vs capsule dose: 120 mg day 1 and 80 mg Days 2 and 3). Ultimately, the review team for the capsule sNDA concluded that the capsule could be used in patients younger than 12 years who weighed at least 30 kg (assuming that the patient is able to swallow capsules). This recommendation was based on the pharmacometric reviewers' conclusion that the applicant's

proposed nomogram dosing for the suspension NDA (volume per weight band) was reasonable, given that no safety concerns could be identified associated with the 30% higher exposures that would occur in some children dosed using the nomogram. At the time of the approval of the Emend capsule pediatric sNDA, there were significant concerns regarding whether the applicant would be able to successfully address issues about the ability of healthcare providers and caregivers to accurately reconstitute and measure the suspension doses. For this reason, it seemed important to assure that dosing instructions of the capsule be extended to the broadest age range possible. The approved pediatric indication for the capsule formulation was:

> 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)]*.

There were also substantive discussions during the capsule review 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. The reviewers concluded that the full clinical trial data could be appropriately presented in Section 14 of the Emend capsule label. (The suspension product will share the same label.)

This review of the NDA for the powder for suspension Emend product serves as both the CDTL review and the Division Director Summary review. I will reiterate the clinical efficacy and safety information presented in my review of the Emend capsule NDA for the pediatric CINV indication, and will provide additional information specific to the suspension formulation, where applicable (e.g., Sections 3 Chemistry/Manufacturing, 5 Clinical Pharmacology, 12 Labeling). The following two major review issues in this NDA were related to the applicant's proposed dosing instructions for product labeling:

1) (b) (4)

(b) (4)

2) the proposed instructions for reconstitution and measurement of the suspension doses.

The actual use studies submitted to support the adequacy of the proposed label's instructions for reconstitution and measurement of the suspension raised significant concerns about the ability of parents and healthcare providers to correctly reconstitute the suspension and measure the dose. The review team discussed these concerns with the applicant during the review, and

the applicant conducted additional actual use studies during the course of the review to evaluate instruction modifications intended to improve user performance of these actions (reconstitution and measurement). To address the feasibility of a potential mitigation strategy of having the health care provider reconstitute the dose and preload the dose into an oral dosing dispenser to be sent home with the patient for subsequent dosing, the applicant also conducted additional stability studies to evaluate the stability of the suspension within an oral dosing syringe. These studies were conducted during the review clock.

2. Background

As stated above, aprepitant capsules have been approved for prevention of acute and delayed phase CINV in adults and in pediatric patients ≥12 years of age and pediatric patients <12 years of age who weigh at least 30 kg and can swallow capsules. 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. In its aprepitant pediatric program, 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 Emetogenicity, High Risk of Emetogenicity, Moderate risk of emetogenicity. 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. Lippincott, Williams and Wilkins; 2004) and Antiemetics: National Comprehensive Cancer Network Practice Guidelines in Oncology (V3. 2008). The Very High Risk category (VHRC) list 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. There have been two other NK-1 inhibitors approved since (netupitant as part of the fixed combination with palonosetron, i.e., Akynzeo, in September 2014 and rolapitant in September 2015). In adults, aprepitant is administered

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

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. Until the recent approval of the pediatric indication for aprepitant capsules for patients 12 years and older (or <12 year and weight ≥ 30kg), there were no NK-1 inhibitors approved for use in the pediatric population in the U.S. There are no NK-1 inhibitors approved in a dosage form, e.g., oral suspension, chewable or IV, appropriate for use in children <12 years of age (and weight <30 kg). There are no data available to support that full extrapolation of efficacy from adults to the pediatric age group is appropriate for this drug class and 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 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 ages 2 years to 17 years for the HEC CINV indication. Subsequently, on April 26, 2005, a letter was issued denying the PPSR. Comments in that letter included that pediatric studies of CINV should include pediatric patients ≥ 6 months of age, and that an age appropriate formulation should be developed for pediatric patients who cannot swallow capsules. Ultimately, the age range required in the PMR associated with the HEC approval was 2 years and greater; however, in the Written Request, (b) (4) (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 FDA waived the pediatric study requirement for ages 0 to less than 6 months and deferred pediatric studies for ages 6 months to less than 17 years. 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

The applicant submitted a proposed pediatric study request (PPSR) on September 15, 2004. 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 studies that should be included in the WR, the age range the studies should cover, and timeline extensions for submission of pediatric PMR studies. In the FDA's response to the initial PPSR, on April 26, 2005, the applicant was told that the relative bioavailability of the age appropriate formulation should be assessed in adults. Subsequent to issuance of the Written Request there were a number of WR amendments 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 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 pediatric CINV NDAs for the aprepitant capsule and powder for oral suspension were both submitted in July 2014. The capsule sNDA was submitted on July 28, 2014. The NDA for the powder for oral suspension (NDA 207865) was initially submitted on July 25, 2014; however, it was not fileable because the manufacturing facilities were not ready for inspection. The applicant submitted a request for fast track designation, which was granted. A request for rolling review (of NDA 207865) followed, and it was granted (on October 29, 2014). The necessary CMC information was submitted on March 26, 2015, which started the review clock for this NDA.

The Written Request included pediatric studies for (b) (4). The applicant indicated they would not meet the deadline for the WR to qualify for pediatric exclusivity.

3. CMC

This NDA proposes a powder for oral suspension for prevention of CINV in pediatric patients less than 12 years of age. The drug substance used to produce the oral suspension [redacted] used in the approved capsule formulation. In contrast to the capsule product, API (active pharmaceutical ingredient) is formulated with soluble excipients in the suspension drug product to allow formation of a suspension when the drug product (powder for suspension) is mixed with water. The powder for suspension drug substance is [redacted]. The reviewers determined that the excipients unique to this formulation (as compared to the oral capsule formulation) are suitable, as they are compendial components.

The powder for suspension drug product is filled into [redacted] containing 125 mg of the active ingredient [redacted] Studies of potential extractables from the container detected "microgram levels of [redacted]", which the reviewers found acceptable. The stability data submitted in the application supported the applicant's proposed 30 months expiration dating period, with storage conditions of 20-25 degrees C (68-77 degrees F) and excursions between 15-30 degrees C (59-86 degrees F). The 6 months accelerated stability data for 3 registration batches from conditions of 40 degrees C and 75% relative humidity showed "no significant loss in potency". Acceptance criteria for degradation products for the proposed product are the same as those that have been approved for the oral capsule product. The data from in-use stability testing of the reconstituted suspension kept at ambient conditions for 5 hours (from the formal stability batches of the drug product) are consistent with and support a recommendation that the reconstituted dose be administered [redacted] of reconstitution if kept in ambient conditions after reconstitution. (However, see discussion of additional data submitted during the review clock regarding stability testing of product stored in oral dispensing syringes, presented below.)

The drug product will be co-packaged with a mixing cup [redacted] and oral dosing dispensers (oral syringes, Class I medical device), which the reviewers found comply with food contact materials regulations. All are intended for single use. The provider will fill the mixing cup with [redacted] of water, and the powder suspension will be emptied from the [redacted] into the mixing cup. The lid will be closed and the provider will shake the cup, resulting in a suspension of aprepitant 25 mg/ml. The appropriate dose will be drawn up into the oral dosing dispensers from the cup. The cup has been used with other CDER approved products. The oral dosing dispensers consist of [redacted] components: [redacted] which complies with the USP National Formulary (NF) requirements.

The CMC reviewers stated: "The compatibility of the mixing cup and the dosing dispenser with aprepitant suspension for the expected duration of use by the patient has been appropriately addressed by the in-use stability studies…….Both the dispenser and the mixing cup come in contact with reconstituted suspension for a short period of time (less than 15 minutes) during preparation and oral administration". However, based on concerns about the ability of caregivers/patients to reconstitute the suspension and measure doses, the review team asked the applicant to conduct an in-use stability study of the reconstituted product in the planned oral dispensing device to ensure the product remains

stable for at least 3 days when stored in the oral dispenser as a suspension under refrigerated conditions. These data would support that it is appropriate for healthcare providers to reconstitute and measure all three days' doses at one time and send the Days 2 and 3 doses home with the caregiver/patient for subsequent administration.

The applicant submitted the results of the in-use stability testing on October 29, 2015. The CMC reviewers found the data adequate to support the drug product is stable for more than 3 hours at room temperature (25 degrees C/60% RH) and for more than 3 days under refrigeration (2 degrees C – 8 degrees C). Based on these data, the reviewers concluded the product is adequately stable to allow healthcare providers to prepare the suspension, and provide caregivers the prefilled oral dispensing syringes, to be used within 3 days and stored under appropriate conditions (refrigeration). However, the CMC reviewers pointed out that the oral dispensing syringe utilized in the stability study was the 5 cc syringe, and raised concerns that dosing errors could be expected for dose volumes of <1 ml, if a 5 cc syringe is only provided for doses (given the small dose volume vs. the overall syringe size). They noted that the markings on the 5 cc syringe were increments of 0.2 cc. They recommended including a 1 cc oral dispensing syringe to measure total dose volumes of less than 1 cc. The applicant agreed to conduct a similar 3-day in–use stability study using the 1-mL oral dispenser syringe. These data were submitted on December 2, 2015, and the CMC reviewers found that the results supported dispensing total dose volumes of ≤ 1cc in the 1 cc oral dispensing syringe. The CMC reviewer also stated that "The assay results illustrated a more accurate dose volume delivery for dosage volumes of ≤ 1cc using the 1-mL oral dispenser." This conclusion was based on the observation of reduced variability in assay results and assay values that were closer to the 100% target when the 1 cc oral dosing syringe was used to measure small volume as compared to the 5 cc oral dosing syringe.

Biopharmaceutics review. The Biopharmaceutics reviewers issued a number of information requests during the course of the review, and met with the sponsor to facilitate resolution of their review issues. Ultimately, the reviewers recommended approval of the NDA, with two PMCs listed below.

Summary. The CMC reviewers have determined that the "NDA has provided sufficient information to assure the identity, strength, purity and quality of the drug product." The Office of Process and Facilities has made an overall "Acceptable" recommendation for the facilities involved in this NDA. All identified labeling issues have been satisfactorily resolved, from a CMC standpoint. I concur with the CMC reviewers' recommendation to approve this NDA. The following PMCs requested by the Biopharmaceutics reviewers will be included in the approval letter:

3013-1 Monitor the particle size distribution (PSD) of commercial drug product in the primary package (at release and on stability testing) and submit the data to support a proposed D(b) (4) specification for the particle size.

Final Report Submission: 04/18

3013-2 Generate dissolution data using the following dissolution method: USP Apparatus II (Paddle) with 50 rpm in water (with 1.2% Tween 80), 900 mL at 37°C. Submit the new dissolution data for at least three commercial/stability batches to support the dissolution acceptance criterion of Q= (b) (4)% at 10 minutes.

Final Report Submission: 12/16

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 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 in male juvenile rats vs. 20.9 microgram·hr/ml in humans 6 months to <12 years and 17 microgram·hr/ml in humans 12 -17 years).

The reviewer noted 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 sexes 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.

These changes in adult rats occurred at similar exposures (by AUC) as in the juvenile rats. In 5 week and 14 week adult rat oral dosing studies, the hepatic changes were observed at the 250 mg/kg BID dosing level, which was associated with a 7.19 microgram·hr/ml AUC in males and 33.2 microgram·hr/ml AUC in females in the 5 week dosing study, and 6.37 and 25.7 microgram·hr/ml AUCs for each sex respectively in the 14 week study; the next lowest dose studied in the 5 week study, 250 mg/kg/d, resulted in AUCs of 3.21 and 13.9 microgram·hr/ml AUCs, by sex, respectively. In the 14 week study, the next lowest dose studied - 125 mg/kg BID – resulted in respective AUCs by sex of 6.04 and 27.3 microgram·hr/ml. The thyroid changes were observed at all dose levels. 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%) 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 safety of the excipients, degradants and leachables/extractables from the primary (b) (4) container for the Emend powder for oral suspension was assessed by the nonclinical reviewer. (b) (4) The extractable study conducted on the primary (b) (4) container identified three Class 3 solvents present at levels much lower than the ICH Q3C acceptable level of 500 ppm. (The levels were (b) (4) ppm.) The reviewer concluded that there were no safety concerns with these extractables. He noted that there are no novel excipients in the product and no safety concerns with the levels of any excipients. He found the proposed acceptance criteria for degradation products acceptable, as they are the same as those approved for the Emend capsule product.

The review of the nonclinical sections of the product label was completed with the approval of the pediatric sNDA for Emend capsules. The capsule and powder for suspension will share the same label. Pharmacology/Toxicology reviewer found the nonclinical sections of product labeling

acceptable, as the format and content conformed with requirements for PLLR prescription drug labeling.

5. Clinical Pharmacology

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

The regulatory record indicates that early in the PPSR review process the FDA informed the applicant that a relative bioavailability study of the age appropriate formulation should be conducted in adults; however, no dedicated relative bioavailability study comparing the oral suspension and approved oral capsules was submitted in either NDA (capsule or powder for suspension). Furthermore, PK sampling was not performed in the pediatric phase 3 efficacy trial, which limited the ability to assess the relative bioavailability of the two formulations and made it impossible to perform exposure/response analyses.

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 observed in this age subgroup was consistent with the efficacy observed 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. However, given the favorable efficacy outcome observed in the phase 3 trial, the reviewers did not recommend further exploration of higher doses in pediatric patients.

The following table, reproduced from the Clinical Pharmacology review, summarizes the Cmax and AUC associated with the Day 1 aprepitant dose (3 mg/kg suspension in patients <12 years of age and 125 mg capsule in adolescents). 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 Study P134 PK study results in patients ≤ 12 years follows below.

Study 134. The applicant conducted a preliminary study to explore dosing with fosaprepitant/aprepitant in the full age range, birth to 17 years. Patients ≥ 12 years received fosaprepitant (intravenous) in this study. Aprepitant oral suspension was only administered to patients less than 12 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 the 12-17 age bracket..
- 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. The 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 administered 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 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 (administered aprepitant oral suspension) differed from those that had previously been observed in adolescents (administered aprepitant oral capsules). Cross study comparisons suggest that exposures in pediatric patients ages 2 years to 6 years were 11% and 23% higher than those 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 2. 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 3. 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 (b) (4) **Emend powder for oral suspension.** In the phase 3 trial, patients <12 years of age (6 months to <12 years) who were randomized to the aprepitant arm received the suspension dosage form, dosed by weight. The Day 1 powder for suspension dose 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). (b) (4) nomogram weight band dosing - based on volume of suspension to be administered (b) (4) The applicant recognized that correctly reconstituting and measuring suspension doses would be challenging for caregivers.

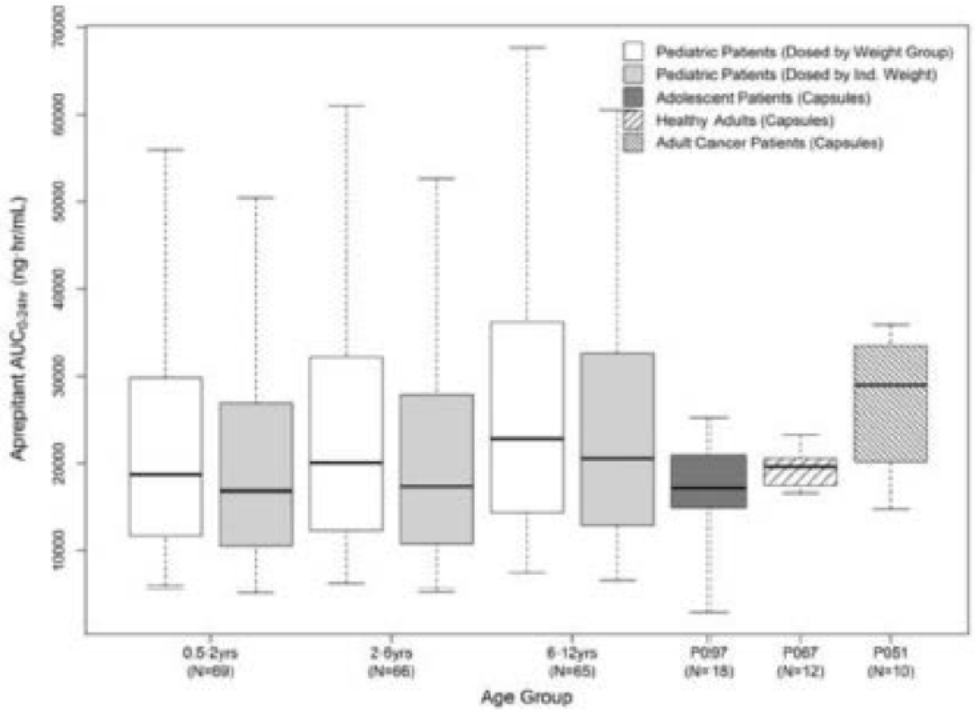
Table 4: (b) (4) nomogram weight band dosing for Emend powder for suspension

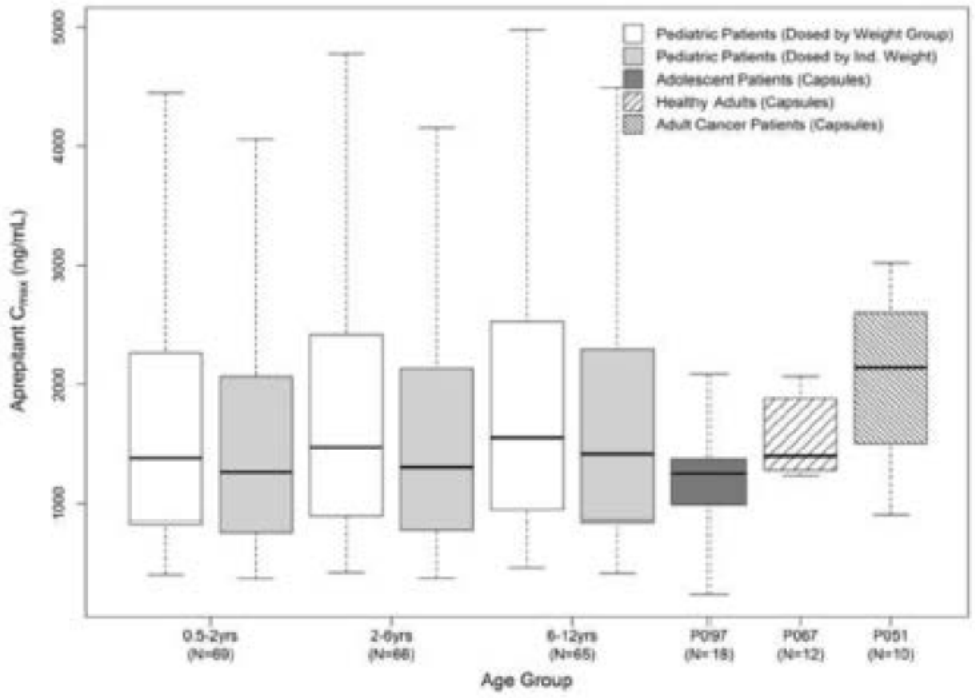
(b) (4)

The pharmacometric reviewers evaluated the (b) (4) nomogram dosing and determined that the simulated systemic exposure predicted for nomogram based dosing would be up to 30% higher than that observed with weight based dosing for patients within a given weight band who weighed less than the highest weight in the band. The applicant had set the dose per band to assure that the patients at the highest weight in the band were not underdosed, to avoid reduced efficacy. The reviewers noted that the predicted range of exposures "largely overlapped with exposures achieved in adults, with higher variability observed in the pediatric exposures." They found the overlap with adult exposures supported that weight band dosing would be safe for patients <12 years of age. This was further

supported by the fact that pharmacokinetic studies in adult cancer patients revealed 2-fold higher exposures than exposures in children, in cross study comparisons. These cross study exposure comparisons are summarized in the figures below, which are reproduced from the Clinical Pharmacology review. (Note that "Dosed by Weight Group"= simulated data from nomogram based dosing, and "Dosed by Ind. Weight"= observed PK from individual weight based dosing.)

Figure 1: Simulated aprepitant AUC0-24hr (Top Panel) and Cmax (Bottom Panel) on Day 1 in different age groups using individualized dosing by weight ("Dosed by Ind Weight") and nomogram dosing ("Dosed by Weight Group"); Includes comparison with observed aprepitant exposures in adolescents, healthy adults and adult Patients. (reproduced from Clinical Pharmacology review)


Pediatric Patients (Dosed by Weight Group)
Pediatric Patients (Dosed by Ind. Weight)
Adolescent Patients (Capsules)
Healthy Adults (Capsules)
Adult Cancer Patients (Capsules)
Aprepitant AUC0-24hr (ng·hr/mL)
10000
20000
30000
40000
50000
60000
70000
0.5-2yrs (N=69)
2-6yrs (N=66)
6-12yrs (N=65)
P097 (N=18)
P067 (N=12)
P051 (N=10)
Age Group


Pediatric Patients (Dosed by Weight Group)
Pediatric Patients (Dosed by Ind. Weight)
Adolescent Patients (Capsules)
Healthy Adults (Capsules)
Adult Cancer Patients (Capsules)
Aprepitant Cmax (ng/mL)
1000
2000
3000
4000
5000
0.5-2yrs (N=69)
2-6yrs (N=66)
6-12yrs (N=65)
P097 (N=18)
P067 (N=12)
P051 (N=10)
Age Group

Given the predicted exposure overlap between pediatric nomogram dosing and adult patient exposures, the Clinical Pharmacology reviewers considered the nomogram dosing approach acceptable for labeling, from both a safety and efficacy standpoint. Their recommendation influenced final labeling decisions for the Emend capsule pediatric sNDA (see further discussion below), specifically Sections 1.1 Indication and Usage and 2.1 Dosage and Administration.

However, after completing the review of the human factor study data submitted in this sNDA for the suspension, the DMEPA and Clinical reviewers expressed significant concern that caregivers would have difficulty accurately reconstituting and measuring the suspension, even using the nomogram. The review team suggested that reconstitution and measurement should only be performed by healthcare professionals, and the measured doses dispensed to the patient/caregiver in a prefilled oral dose dispenser/syringe. In response, the applicant conducted stability studies to confirm that the premeasured dose of suspension product is stable in an oral dispensing syringe. Based on those results, the applicant and reviewers agreed that reconstitution and measurement of the suspension could be limited to health care providers. Given this revised plan, the reviewers questioned the need to rely on nomogram-based dosing. The applicant agreed to revise the proposed Dosage and Administration section of the label to delete the weight band nomogram dosing table, and replace it with the individualized dosing used in the phase 3 trial, i.e., 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3. The DMEPA reviewers recommended that the presentation of weight based dosing should be limited to either mg/kg or ml/kg; not both. The final label will present the suspension dose in mg/kg.

These review decisions prompted reexamination of age groups for which the Emend capsule and suspension would be indicated, in Section 1 Indications and Usage of the label. (The two Emend formulations share the same Full Prescribing Information.) The pediatric sNDA for the capsule had been approved with an indication that included pediatric patients <12 years of age who weighed at least 30 kg, in order to assure that Emend would be available for younger patients who could swallow (since the suspension formulation was not approved at the same time.) The pharmacometric review of the nomogram dosing had supported that review decision. At the conclusion of the review of this new NDA for Emend powder for suspension, given the decision to label the suspension product with the dose used in the clinical trial (i.e., 3 mg/kg Day 1 and 2 mg/kg Days 2 and 3) instead of with nomogram weight band dosing, the reviewers re-examined whether the capsule dosing instructions for pediatric patients < 12 years of age who weighed ≥ 30 kg (and can swallow capsules) should be retained. The reviewers noted that for patients <12 years of age who weigh <40 kg, administration of the currently labeled capsule dose would result in exposures up to 30% higher than would be associated with the suspension formulation dosed by weight. The Division of Pediatric and Maternal Health (DPMH) reviewer noted that 40 kg is "the 50th percentile for a 12 year old boy or girl and the 75th and 90th percentile for an 11 and 10 year old, respectively." She concluded, "Because there would be fewer children less than 12 years who meet the minimum weight of 40 kg and the oral suspension would be available, DPMH concurs with DGIEP's decision to not include a minimum weight as part of the dosing of the oral capsule." The review team ultimately concurred with the applicant's proposal to remove the capsule dosing instructions for the children <12 years of age who weigh ≥30 kg, as that subgroup would now be covered by suspension dosing. I also concur.

Furthermore, the reviewers discussed whether the dosing instructions for the suspension should appropriately also include dosing for pediatric subjects ≥ 12 years of age and adults, who may benefit from a suspension product if they have difficulty swallowing capsules. The Clinical Pharmacology

reviewers referred to the population PK analysis that explored the relative bioavailability of the oral suspension and capsule formulations (since a dedicated relative bioavailability study was not conducted), which found the type of formulation was not a significant covariate for bioavailability. This analysis, which indicated the adult aprepitant exposure would be similar after administration of the same dose of either formulation – oral suspension vs capsule, supported labeling dosing instructions for the suspension product for the full pediatric age range and adults. It is important to note, however, that the Clinical Pharmacology reviewers stated in their review signed July 20, 2015 these data are not adequate (b) (4) The following Emend powder for suspension dosing information will appear in Section 2 Dosage and Administration of the product label:

> Pediatric Patients 6 Months to less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules
> The recommended dose of EMEND for oral suspension to be administered with a 5 HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of HEC or MEC is specified in Table 3. Dosing of EMEND for oral suspension is based on weight, to a maximum of 125 mg on Day 1 and 80 mg on Days 2 and 3. Dosing in pediatric patients less than 6 kg is not recommended.

Label Table 3: Recommended Dosing in Pediatric Patients 6 Months to Less than 12 Years of Age or Pediatric and Adult Patients Unable to Swallow Capsules

	Population	Day 1	Day 2	Day 3	Day 4
EMEND for oral suspension*	Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	3 mg/kg orally Maximum dose 125 mg	2 mg/kg orally Maximum dose 80 mg	2 mg/kg orally Maximum dose 80 mg	none
Dexamethasone	Adults Unable to Swallow Capsules	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2	See Table 1 or 2
	Pediatric Patients 6 Months to Less than12 Years or Pediatric Patients Unable to Swallow Capsules	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	Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*After preparation, the final concentration of EMEND for oral suspension is 25 mg/mL *[see Dosage and Administration (2.3)]*. Administer EMEND for oral suspension 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND for oral suspension in the morning.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with EMEND *[see Clinical Pharmacology (12.3)]*.

See the end of Section 7 Clinical/Statistical-Efficacy of this review for the final wording of the label's Section 1 Indications and Usage for each of the Emend suspension and capsule formulations.

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, the pediatric subjects in this trial 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 5. 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 6. 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)

Variable	Aprepitant Regimen (N=152)	Control Regimen (N=150)	Total (N=302)
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%), medulloblastoma 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 7. 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 8. 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 diminished 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 month -12 years old 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 9. 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

Age Group	Emend	Control	Emend+Control	Emend	Control
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%

(b) (4)

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) by subgroup based on whether treatment was the powder for suspension formulation (patients 6 months to <12 years of age) or capsule formulation (patients ages 12 years and older) , and the results were favorable in both subgroups. The results are shown in the tables below, which are reproduced from the Statistical Review. These were not pre-specified analyses 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 10. FDA Reviewer's Efficacy comparison by phase for patients ages 6 months to 12 years: Suspension

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

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

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

The absolute response rates were similar between both subgroups for each phase (delayed, acute, overall) in the aprepitant arm. However, the absolute response rates in the control arm were lower in the younger subgroup (6 months-12 years) than in the patients ages 12 years and older.

The nominal p-values for the acute phase exceeded 0.05 in both subgroup analyses above, likely due to the small sample sizes in the subgroups relative to the overall study population. 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 when given in combination with a 5HT3 antagonist +/- dexamethasone, given the smaller sample sizes in the

subgroups relative to the overall study population. However, the low nominal p values observed in the delayed phase in both subgroups reinforces that the major impact of NK-1 inhibition is in the delayed phase.

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 12. 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 13. 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

Additional Exploratory Analyses. The Clinical reviewer presented additional exploratory analyses in her review, including 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 subgroup analysis explored the impact of 5HT3 antagonist administration beyond Day 1, which was allowed if a patient received multi-day chemotherapy. The results of these 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 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 14.. 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 15.. 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 of patients who received single day treatment.

Table 16.. 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 17. 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. Subgroup analyses provided support that both formulations are effective. I concur.

During the review of the capsule formulation, which was ready for approval prior to the powder for suspension NDA, the pharmacometric team confirmed that population PK data supported 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 the inability to approve the suspension product concurrently with the capsule product, in order to extend access to Emend to some patients <12 years of age, the pediatric labeling approved with the sNDA for the capsule stated the following in Sections 1.1 Indication and 8.4 Pediatric Use:

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** [emphasis added] 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

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, EMEND is indicated for the prevention of nausea and vomiting associated with HEC or MEC in patients 12 years of age and older or patients less**

than 12 years who weigh at least 30 kg *[see Dosage and Administration (2.1)].* [emphasis added]

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.

The powder for oral suspension and capsules will share the same Full Prescribing Information. With the approval of the oral suspension product, there is now an available dosage formulation appropriate for patients less than 12 years of age or weighing less than 30 kg. Section 1 Indications and Usage and Section 8.4 Pediatric Use will be revised as shown below. Note that in the Indications and Usage section, the wording referring to patients <12 years of age who are ≥30 kg and can swallow capsules was removed from the capsules indication, as that pediatric subgroup <12 years of age is now covered by the suspension formulation. Note also that the wording of the indication for the suspension product is not limited to patients <12 years of age. Refer to Section 5 Clinical Pharmacology for information regarding the deliberations that led to these labeling decisions.

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND®for oral suspension, in combination with other antiemetic agents, is indicated in 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 (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

EMEND®capsules, in combination with other antiemetic agents, is indicated in patients 12 years 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 (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

8.4 Pediatric Use

Prevention of Nausea and Vomiting Associated with HEC or MEC

The safety and effectiveness of EMEND for oral suspension have been established in pediatric patients 6 months of age and older and EMEND capsules in pediatric patients 12 years of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin, and MEC. Use of EMEND in these age groups is supported by evidence from 302 pediatric patients in a randomized, double-blind, active comparator controlled clinical study (n = 207 patients aged 6 months to less than 12 years, n = 95 patients aged 12 through 17 years). 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)]*.

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.

During review of the pediatric sNDA for the oral capsules, reviewers discussed 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.

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 18. 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 states 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 is in Section 6 of the product label:

Table 19: Most Common Adverse Reactions in (b) (4) Patients (b) (4) HEC and MEC Pooled Studies (b) (4) *

	EMEND and ondansetron† (N=(b) (4))	Ondansetron‡ (N=(b) (4))
(b) (4)		
diarrhea		
(b) (4)		
fatigue		
(b) (4)		
hiccups		

*Reported in ≥3% of patients treated with the EMEND regimen and at a greater incidence than control regimen.
(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 20. 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)

applicant'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 that aprepitant is a moderate inhibitor of CYP3A4 and, (b) (4) After reviewing the post-marketing report of a pediatric 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 that (b) (4) with co-administration of aprepitant with ifosfamide. 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 was included in Section 6 Adverse Reactions, along with the statement: "Aprepitant has the potential for increasing ifosfamide mediated neurotoxicity through induction of CYP3A4."

Table 21. 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 the pharmacokinetic study, 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 22. 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. The approved CINV aprepitant capsule dose is administered only once daily x3 on an intermittent basis (based on chemotherapy cycle interval duration) in adults and pediatric patients ≥12 years of age or <12 years and ≥30 kg, 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. Ifosfamide 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 capsule product label Section 5.1 CYP3A4 Interactions states that aprepitant is a moderate (and dose dependent) inhibitor of CYP3A4, and that it should be used with caution in patients receiving concomitant medications that are principally metabolized through CYP3A4. The label notes that ifosfamide is metabolized by CYP3A4. It states that the doses of chemotherapy agents that are metabolized via CYP3A4 were not reduced in the adult clinical trials, however, "Due to the small number of patients in clinical studies who received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other agents metabolized primarily by CYP3A4 that were not studied." Section 6.2 Postmarketing Experience of the label states, "(b) (4) ".

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 for oral aprepitant 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 capsules are currently marketed with a patient package insert (PPI) as part of approved labeling. The PPI was updated to include relevant information on the powder for suspension product (the capsule and powder for suspension products share full prescribing information and a PPI), and it was reviewed by the Division of Medical Policy Programs (DMPP) and the Office Prescription Drug Promotion (OPDP), who simplified the wording, clarified concepts, removed unnecessary or redundant information and ensured that it was consistent with the prescribing Information.

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 and review issues related to pediatric dose and instructions for reconstitution and measurement of doses. See Sections 5 Clinical Pharmacology and 7 Clinical/Statistical- Efficacy of this review regarding final decisions regarding pediatric labeling.

PeRC agreed in a December 9, 2015 meeting that the PREA PMRs (HEC and MEC; see Section 2 Background) would be considered fulfilled upon approval of this NDA for Emend powder for oral suspension.

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 (Sections 5 Clinical Pharmacology, 7 Clinical/Statistical-Efficacy and8 Safety).

Review of Instructions for Use and Prescribing Information (Human Factors studies). The applicant proposed a tri-pack carton containing three mono-pack kits, which each contained a pouch (b) (4) containing the powder for suspension, a 5 ml oral dispenser, a mixing cup, instructions for use dosing instructions and prescribing information (including a patient package insert). This product presentation was proposed for use by caregivers and healthcare providers. The human factors study submitted to support this presentation, and the instructions for use (IFU), were conducted with the same product presentation, *with the exception of inclusion of an additional oral dispenser, 1 ml, for dosing volumes less than 1 cc.* (b) (4) The components of the monopack tested in the human factors study are shown below.

The IFU included (b) (4) steps. The first series of steps involved measuring 4.6 ml of water from the mixing cup, discarding the remaining water from the mixing cup, and then returning the measured 4.6 ml of water back into the mixing cup as the volume to which the (b) (4) powder should be added. This was followed by a series of mixing steps, followed then by measuring out the proper dose of the resulting suspension for the individual patient, based on the patient's weight.

The human factors study enrolled caregivers and healthcare providers (11 caregivers, 12 pharmacists, 12 nurses); however, the DMEPA reviewers noted the number of caregivers enrolled was inadequate to assess the ability of caregivers to understand the instructions and appropriately reconstitute and measure the appropriate dose. Sample sizes less than 15 may result in problems going undetected. The combined sample size of pharmacists plus nurses was considered adequate to assess healthcare providers' experience with the product.

The subjects were tested with IFU optional in one session, and IFU mandatory in another session. Six critical tasks were tested. There were 28 critical use failures that occurred in 3 critical tasks. These 3 critical tasks were: 1) failure to determine the correct dose/volume to administer using patient weight and PI, 2) failure to measure correct volume for reconstitution, and 3) failure to withdraw correct dose volume. The overwhelming majority of errors occurred in performance of #2 and #3. The errors in reconstitution included both over-filling and under-filling with water. The most commonly identified root cause was: "Measuring steps were not intuitive and clear". Failure to withdraw the correct dose volume included under-filling with medicine, over-filling with medicine, incorrect administration and administration of the entire contents of the pouch (b) (4) The most common root causes identified were: 1) lack of knowledge of proper resolution of air bubbles and sacrificed dose accuracy, 2) participant

didn't read instructions, 3) participant didn't see dosing information, 4) dispensers were not sufficiently intuitive and markings on dispensers were not sufficiently clear.

The DMEPA reviewers raised concerns about the inadequate number of caregivers tested, the results of the human factors study, and the lack of presentation of data on whether all participants completed the mixing as per the reconstitution instructions, i.e., swirling the mixture at least 20 times, slowly inverting the mixing cup five times to prevent foaming and presence of clumps. In addition, they were concerned that the applicant proposed limiting the oral dispenser in the marketed kit to a 5 ml oral dispensing syringe. Both a 1 ml and 5 ml syringe were provided in the human factors study; therefore, the ability of caregivers to measure volumes <1 ml in a 5 ml oral dosing dispenser was not tested in the study. Because most of the task failures observed in the study would result in under- or over-dosing of pediatric patients, the DMEPA reviewers strongly recommended that the applicant should implement corrective/preventative measures to address the observed failures and to validate the corrective/preventative changes actually reduced the errors.

On May 4, 2015, DMEPA's recommended changes to the IFU and product presentation were communicated to the applicant. The applicant agreed to conduct a supplementary human factors validation study, this time with 17 untrained lay caregivers. The study focused on the IFU, and its use was mandatory. The product presentation in this study lacked the 1 ml oral dosing syringe included in the prior study. The results of this study, which were submitted on July 1, 2015, did not resolve the review concerns. The reviewers noted that the task failures were similar to those observed in the first study: failure to measure the correct volume for reconstitution, failure to correctly prepare the solution, and failure to withdraw the correct dose volume. The most common critical task failure was incorrect measurement of the reconstitution volume with the dispenser. The most common root cause was confusion about the IFU, followed by an equal number of errors caused by presence of air bubbles, mistaken dose for reconstitution volume and misinterpreted markings. Similarly, the most common root cause for errors in withdrawing the correct dose was presence of air bubbles, followed by equal numbers caused by IFU confusion, not understanding the 5 mg oral dispenser gradations were in 0.2 ml, or incorrectly measuring, misunderstanding how to measure, or didn't see/read instructions.

The applicant proposed IFU and carton text, layout and fold pattern changes to mitigate some errors; however, the reviewers didn't agree these changes would comprehensively mitigate the types of errors observed. The reviewers contacted the applicant and recommended limiting the reconstitution and dose measurement tasks to healthcare providers, given the errors observed in the caregiver study. To support this mitigation strategy, it was necessary to conduct stability studies of the reconstituted product in the oral dispensing syringe, as the dose would be dispensed premeasured by the healthcare provider in the oral dispensing syringe on Day 1, and there are two additional doses for use on Day 2 and Day 3, which would need to be stored in the patient's refrigerator for subsequent use. (See Section 3 CMC regarding the results of the stability studies.) Furthermore, the DMEPA reviewers informed the applicant that an additional preapproval Human Factors study was needed to demonstrate that oncology nurses experienced in preparing chemotherapy drugs can reconstitute and measure the appropriate doses for an individual patient.

On October 29, 2015, the applicant submitted the results of the two additional human factors studies: one enrolled 21 oncology nurses and the other enrolled 16 patient caregivers. In both studies, use of the IFU was mandatory. The moderator in the study instructed the participant to use the IFU if the participant was observed to begin drug preparation or administration without referring to the IFU. The kit contained a single oral dispensing syringe, 5 ml. The oncology nurse study evaluated reconstitution and preparation of the oral suspension. The patient caregiver study evaluated administration of the pre-measured doses by the caregivers. (An IFU for the caregiver described how to store and administer the reconstituted suspension.)

A much lower critical task failure rate was observed in the health care provider study (oncology nurses) compared to earlier studies. There was a single error in which some of the powder was left in the (b) (4) pouch. There was a single error in which 0.7 ml dose was drawn up instead of 0.6 mL (caused by an air bubble). There was an error in which a 4.6 ml dose was drawn up instead of 0.6 ml, due to confusion between the reconstitution volume and the dose volume. This nurse self-corrected on a second trial.

The most common task failure was administration of the medication in the middle of the mouth rather than to the side of the cheek. The root cause was not reading the IFU and relying on previous methods of medication administration.

The DMEPA reviewers noted that the failures in previous studies were not observed in the final studies submitted. The most significant error observed in the oncology nurse study (4.6 ml instead of 0.6 ml), was self-corrected. They concluded that the results "were generally acceptable, since most of the intended user population was able to use the product safety and effectively….Most of the remaining use error tasks can be managed through improvements in the label and labeling." They noted "restriction of preparation and reconstitution of this product to health care providers and administration of premeasured doses by patient caregivers have minimized some of the risk associated with this product." The DMEPA reviewers' recommendations for changes in the prescribing information and the carton and container were incorporated in labeling negotiations.

DMPP and OPDP review. The reviewers from the DMPP and OPDP reviewed the applicant's proposed Patient Package Insert (PPI). (The capsule and powder for suspension products share full prescribing information and a PPI.) They recommended revisions that 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 OPDP reviewers' review comments regarding the proposed product label were incorporated in labeling negotiations.

DPMH review. DPMH was consulted to review and update the label subsections related to Pregnancy and Lactation (Section 8.1 and 8.2) during the review of the pediatric sNDA for Emend capsules. 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." Their recommendations were incorporated in the label approved with the approval of the pediatric capsule sNDA. (The capsule and powder for suspension product share the same Full Prescribing Information.)

During the review of this NDA for the Emend powder for suspension product, the Maternal Health Team recommended addition of Section 8.3 Females and Males of Reproductive Potential to the label's Section 8 Use in Special Populations, to reflect information regarding the potential for Emend to reduce the efficacy of hormonal contraceptive already presented in other sections of the label, i.e., Drug Interactions (7.1) and Clinical Pharmacology (12.3). The label was updated to include the following:

> 8.3 Females and Males of Reproductive Potential
> Contraception
> Upon administration of EMEND, the efficacy of hormonal contraceptives may be reduced. Advise females of reproductive potential using hormonal contraceptives to use an effective alternative or back-up non-hormonal contraceptive (such as condoms and spermicides) during treatment with EMEND and for 1 month following the last dose *[see Drug Interactions (7.1), Clinical Pharmacology 912.3)]*.

They also recommended updating Section 5 Warnings and Precautions and Section 7 Drug Interactions to add the word "effective" as a qualifier to "alternative or back-up methods of contraception". In addition, they recommended updating Section 17 Patient Counseling information by adding the following information marked here with bold italics:

> *Hormonal Contraceptives:* Advise patients that administration of EMEND may reduce the efficacy of hormonal contraceptives. Instruct patients to use ***effective*** alternative or back-up methods of contraception (***such as condoms and spermicides***) during treatment with EMEND and for 1 month following the last dose of EMEND *[see Warnings and Precautions (5.3),* ***Use in Specific Populations (8.3)]*.**

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - approval

- Risk Benefit Assessment – Prior to the August 28, 2015 approval of the pediatric sNDA for Emend capsule, no NK-1 inhibitors had been approved for pediatric use. The Emend capsule pediatric indication was limited to patients ≥12 years of age and patients <12 years of age who weighed at least 30kg. 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 adults in the setting of HEC and MEC, when added to a 5HT3 antagonist and dexamethasone. 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 and population PK analysis support that the current adult CINV indication can be extended to the powder for suspension product, to include not only the pediatric population who received the suspension product in the clinical trial (pediatric patients <12 years of age), but also patients (pediatric and adults) ≥ 12 years of age. 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. The data submitted in this sNDA establish that the risk/benefit ratio favors aprepitant's approval for use in the pediatric population for prevention of CINV. Review issues regarding potential for medication errors arising from reconstitution and measurement of suspension doses have been satisfactorily addressed.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None necessary

- Recommendation for other Postmarketing Requirements and Commitments – The approval letter will include two PMCs related to chemistry and manufacturing. Refer to Section 3 CMC of this review or the approval letter for description of these PMCs.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
12/17/2015