Application Type	NDA
Application Number(s)	207,865
Priority or Standard	Priority
Submit Date(s)	March 26, 2015
PDUFA Goal Date	December 26, 2015 (with 3-month extension due to a major amendment)
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Aisha P. Johnson, MD, MPH, MBA
Review Completion Date	02 December 2015
Established Name	aprepitant
(Proposed) Trade Name	Emend
Therapeutic Class	NK-1 antagonist
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	Powder for oral suspension
Dosing Regimen	EMEND is given orally for 3 days, 1 hour prior to chemotherapy treatment on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning
Indication(s)	In combination with other antiemetic agents in patients 6 months of age and older for 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
Intended Population(s)	Children 6 months to <12 years of age

NDA 207,865
Emend Oral Suspension Brief Clinical Review

I. Recommendation on Regulatory Action

In the opinion of this reviewer, EMEND FOR ORAL SUSPENSION should be approved for marketing in the United States for the prevention of chemotherapy induced nausea and vomiting (CINV). With the approval of the oral suspension, Emend for oral use (as tablets and oral suspension) can be used for the prevention of CINV in patients as young as 6 months of age.

Current EMEND CINV Indication (excerpt from 8/2015 version of label)

1 INDICATIONS AND USAGE
1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND, in combination with other antiemetic agents, is indicated in patients 12 years of age and older and patients less than 12 years who weigh at least 30 kg for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin *[see Dosage and Administration (2.1)]*.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.1)]*.

Proposed EMEND CINV Indication

1 INDICATIONS AND USAGE

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND®, 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).

II. Background

On July 28, 2014, the Applicant submitted a Prior Approval Supplement to NDA 21,549 (Supplement-025) providing non-clinical and clinical data to support the use of EMEND (aprepitant oral formulations) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in patients 6 months to 12 years of age (EMEND capsules are currently approved for use in patients 12 years of age and greater). Simultaneous to the prior approval supplement submission, the Applicant submitted an NDA (207,865) to support the use of a powder for suspension pediatric formulation of EMEND. The final necessary information to complete the submission of NDA 207,865 was received March 26, 2015 and the PDUFA clock for this NDA began on that date.

To support sNDA 21,549 and NDA 207,865 a single phase 3 efficacy and safety study was submitted. The clinical study and supporting information was reviewed and the supplemental NDA for the EMEND capsule was approved on 28 August 2015. See the full clinical review for sNDA 21,549/S-025 in DARRTS by Dr. Karyn Berry (17 August 2015) and subsequent clinical addendums in DARRTS (28 August 2015). Given that NDA 207,865 relied upon the same clinical information as sNDA 21,549/S-025, the clinical review and addendum are also in DARRTS under NDA 207,865 to provide details regarding the determination of efficacy and safety for Emend tablets and the powder for oral suspension for pediatric patients <12 years of age. The approval of sNDA 21,549/S-025 occurred on August 28, 2015.

The review clock for NDA 207,865 (EMEND for oral suspension) was extended in order to receive additional information to support appropriate labeling instructions for reconstitution and measurement of doses. The results of a Human Factors Study submitted with NDA 207,865 were found to be unacceptable by FDA's Division of Medication Error Prevention and Analysis (DMEPA). During the review cycle, the Applicant conducted an additional HF validation study using a revised protocol based on FDA recommendations. Sherly Abraham, R. PH, DMEPA reviewer, concluded the following:

> *The repeat human factors validation study was unable to show that the intended user population is able to use the product safely and effectively. Participants were only able to perform critical task functions safely and effectively 36/67 instances. Most of the task failures noted in the study would result in pediatric patients receiving either an under-dose, overdose or not receiving the medication at all.*

Given that two HF studies showed that lay caregivers were unable to reconstitute and measure accurate doses without an unacceptable rate of critical failures, FDA recommended that an additional HF study in HCP using revised instructions for use

(IFU) and incorporating redesigns recommended by DMEPA be conducted by the Applicant. These study results were submitted as a major amendment.

See the full HF Study Reviews in DARRTS (11 August 2015) by Sherly Abraham, R. Ph and section 4.5 of Dr. Karyn Berry's Clinical Review (17 August 2015).

The current review focuses on the additional information received to support the safe use and administration of EMEND powder for suspension.

III. Review Issues

a. Human Factor Study Results

Based on failed HF study results and discussion with FDA, the Applicant proposed revising their labeling to restrict reconstitution and preparation of Emend oral suspension to health care providers (HCPs) and administration of the pre-measured doses by lay patient caregivers. To support this proposed labeling change, the Applicant conducted two human factor studies with 21 oncology nurses and 16 patient caregivers.

Sherly Abraham DMEPA concluded the following:

> *The repeat human factors validation study results were generally acceptable since most of the intended user population was able to use the product safely and effectively. Participants were able to perform critical task functions safely and effectively in 64/76 instances. Most of the remaining use error tasks can be managed through improvements in the label and labeling.*

See the full HF Study Review by Sherly Abraham, R. Ph, in DARRTS (24 November 2015).

MO Comment:
This reviewer agrees that based on two failed HF studies in lay caregivers and an acceptable HF study in HCP, restricting reconstitution and preparation of EMEND for oral solution to health care professionals is appropriate. The first dose of EMEND oral suspension will be given by the HCP prior to chemotherapy. Syringes with subsequent pre-measured doses of Emend oral suspension will be prepared by the HCP and given to the lay caregiver for dosing on Days 2 and 3.

b. Contents of Emend for Oral Suspension Kit

In the human factor studies, the Applicant used an oral suspension kit that included the following:

- One pouch containing powder for suspension
- A 5-mL oral dispenser with a cap
- One mixing cup
- Instructions for Use (IFU) dosing instructions
- Prescribing Information (PI/PPI)
- Dosing of Emend for Oral Suspension

The FDA recommended that the Applicant add a 1 mL oral dispenser with cap to the EMEND for oral suspension kit. This recommendation was made in an effort to increase the accuracy of the doses can be measured by the oral dispenser. For example, the lowest dose is 0.6 mL which can best be measured using a 1 mL dispenser. In addition, other weight based doses can best be measured using a 5 mL dispenser (for the integer mL portion of the dose) in combination with a 1 mL oral dispenser (for the sub-mL portion of the dose).

The Applicant agreed to include a 1 mL oral dispenser with cap. To support the adequacy of this dispenser, the Applicant proposed to perform abbreviated in-use stability testing and only provide the data for assay and degradation products. The FDA agreed that the Applicant's proposal was acceptable.

MO Comment:
This reviewer agrees with the inclusion of both the 5 mL and 1 mL oral dispensers with caps in each Emend for oral suspension kit in an effort to increase dosing accuracy.

c. Weight-based Dosing

With the initial submission of NDA 207,865, the Applicant proposed to include a nomogram of weight bands in the label to assist lay caregivers in determining the correct dose. However, given the current plan to limit reconstitution of EMEND powder for suspension to HCP, the FDA recommended that the Applicant place mg/kg dosing in the label as was used in the clinical trial. The Sponsor agreed and submitted revised labeling on 01 December 2015.

MO Comment:
This reviewer agrees that the label should include weight-based dosing in lieu of a nomogram given that the labeling will restrict reconstitution and preparation of EMEND for oral solution to health care professionals.

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

/s/

AISHA P JOHNSON
12/14/2015

ANIL K RAJPAL
12/14/2015
I concur with Dr. Johnson.