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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

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