

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207865Orig1s000

OTHER REVIEW(S)

During the review of the application, it was noted that the applicant monitored and reported the drug substance particle size distribution (D₍₄₎^(b)) in the ^{(b)(4)} suspension. However, the particle size of the finished drug product (powder for suspension) had not been routinely monitored as a product manufacturing in-process control and quality measure. It was assessed that the finished drug product particle size distribution can affect the time required for the powder to dissolve and produce an appropriate suspension for dosing. The Agency requested that the applicant start monitoring the particle size distribution of the finished drug product (D₍₄₎^(b)) and include testing and acceptance criterion for this attribute in the release and stability specification. Although the applicant agreed and updated the specification, sufficient data had not been generated to allow the applicant to propose a valid acceptance criterion. Therefore, the acceptance criterion for the final drug product particle size distribution in the specification has been set as “to be determined” until adequate amount of data is generated. Based on the t-con discussion with the applicant on 07/07/15, and the assessment of the potential risk to product quality, the Agency agreed with the applicant’s proposal (see amendment dated 07/08/2015) to generate the relevant data, an appropriate acceptance criterion, and updated specification postapproval.

2. Describe the particular review issue and the goal of the study.

Applicant should monitor the particle size distribution of the final drug product and generate statistically meaningful particle size distribution data from multiple batches of product manufactured after the approval of this application. Based on the data generated postapproval, the applicant should propose an appropriate acceptance criterion for D₍₄₎^(b) and update the drug product release and stability specification.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

As discussed during the teleconference on 07/07/2015, as a post-marketing commitment, the Applicant agreed to monitor the particle size distribution (PSD) of commercial drug product in the primary package (at release and on stability testing) and propose a D₍₄₎^(b) specification when appropriate amount of data has been generated (see quality amendment dated 07/08/2015).

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?

- Are the objectives clear from the description of the PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

Sponsor needs to generate new dissolution data using the new dissolution method proposed during the review cycle, and acceptance criterion as they agreed prior to approval on July 8, 2015.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

To generate new in vitro dissolution data using the new dissolution method and acceptance criterion: USP Apparatus II (Paddle) with 50 rpm in water (with 1.2% Tween 80), 900 mL at 37°C.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

MARY H CHUNG
12/16/2015

DONNA J GRIEBEL
12/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Addendum to the File

Date: December 15, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Emend (aprepitant) capsules and powder for suspension

NDA: 21549/S-025 & 207865

Subject: Maternal Health Labeling Recommendations

Applicant Merck Sharp & Dohme Corp.

INTRODUCTION

On July 24, 2014, Merck submitted NDA 207865 for a new powder formulation of Emend (aprepitant) for oral suspension with the proposed indication in pediatric patients 6 months to 12 years of the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV), prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC) and treatment of nausea and vomiting associated with CINV highly emetogenic cancer chemotherapy (HEC). On July 28, 2014, Merck submitted NDA 20529/S-025 which is an already approved capsule formulation with the proposed indication in pediatric 12 to 17 years of the prevention of acute and delayed CINV, prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC), and treatment of nausea and vomiting associated with CINV highly emetogenic cancer chemotherapy (HEC). These submissions are being reviewed simultaneously. DGIEP consulted DPMH to review and update the Emend labeling subsections related to the Pregnancy and Lactation Labeling Rule (PLLR) (specifically Subsections 8.1, 8.2 and 8.3).

This document is an addendum to the July 2, 2015, DPMH review by Carrie Ceresa, for additional recommendations to the labeling for Emend.

BACKGROUND

As per Clinical Pharmacology, Emend was evaluated in drug interaction studies with oral contraceptives. When Emend was administered as a 3-day regimen (125-mg/80-mg/80-mg) with ondansetron and dexamethasone, and coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment compared to the trough levels following administration of the oral contraceptive alone.¹

Reviewer Comment

While the current labeling warns of the clinically important drug interaction between Emend and hormonal contraceptives in subsection 5.3 and 7.1, per PLLR, subsection 8.3 is a newly dedicated subsection for placement of recommendations pertaining to females and males of reproductive potential. This includes recommendations on contraception use. DPMH suggests language for 8.3 to briefly mention the drug interaction and cross-reference the other areas of the labeling containing the more detailed information.

During treatment with Emend, patients using oral contraceptives should switch to an effective alternative method that is not susceptible to the drug-contraceptive interaction and which is effective in preventing pregnancy. Otherwise, a back-up method in addition to the current oral contraceptive should be used for one month, the time until the drug-contraceptive interaction is believed to resolve and the patient's usual method of contraception would have regained effectiveness.

RECOMMENDATIONS

DPMH recommends the addition of subsection 8.3 and other minor edits to the Emend labeling. DPMH recommended language is below in ***bolded italics***. The reader is referred to the final NDA action for final labeling.

¹ Emend Capsules labeling, approved August 28, 2015, accessed at Drugs@FDA website http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021549s025lbl.pdf.

- **HIGHLIGHTS OF PRESCRIBING INFORMATION**
WARNINGS AND PRECAUTIONS

Hormonal Contraceptives: Efficacy of contraceptives may be reduced during administration of and for 28 days following the last dose of EMEND. Use **effective** alternative or back-up methods of contraception. (5.3, 7.1, 8.3)

- **FULL PRESCRIBING INFORMATION**
5 WARNINGS AND PRECAUTIONS

5.3 Risk of Reduced Efficacy of Hormonal Contraceptives Upon coadministration with EMEND, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of EMEND [see Clinical Pharmacology (12.3)]. Advise patients to use **effective** alternative or back-up methods of contraception during treatment with EMEND and for 1 month following the last dose of EMEND [see Drug Interactions (7.1), Use in Specific Populations (8.3)].

7 DRUG INTERACTIONS

Hormonal Contraceptives.

<i>Hormonal Contraceptives</i>	
<i>Clinical Impact</i>	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of EMEND [see <i>Warnings and Precautions (5.3), Use in Specific Populations (8.3), Clinical Pharmacology (12.3)</i>].
<i>Intervention</i>	Effective alternative or back-up methods of contraception (such as condoms and spermicides) should be used during treatment with EMEND and for 1 month following the last dose of EMEND
<i>Examples</i>	birth control pills, skin patches, implants, and certain IUDs

8 USE IN SPECIFIC POPULATIONS

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 (12.3)].

17 PATIENT COUNSELING INFORMATION

Drug Interactions

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)*].

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/s/

CHRISTOS MASTROYANNIS
12/16/2015

TAMARA N JOHNSON
12/16/2015

LYNNE P YAO
12/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
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MEMORANDUM TO FILE

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health

NDA Numbers: 207865

Sponsor: Merck Sharp & Dohme Corporation

Drug: Emend[®] (aprepitant)

Dosage form and route of administration: oral suspension

Emend[®] is also available as oral capsules and intravenous injection.

Approved Indication: In combination with other antiemetic agents for the:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

For the prevention of postoperative nausea and vomiting (PONV)

- Proposed Indication:** 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)

Consult request: The Division of Gastroenterology and Inborn Errors Products requests continued DPMH input on the proposed labeling change for Emend[®] for oral suspension.

Emend[®] capsules for oral use was originally approved on March 27, 2003. The sponsor submitted an assessment for CINV in patients 6 month to 17 years. Labeling for Emend[®] capsules was approved on August 28, 2015. At that time, the oral suspension was not ready for approval due to concerns about preparation and administration. Labeling recommendations for the oral capsule labeling were provided by DPMH in a labeling review (DARRTS reference number 3806081). The sponsor revised the instructions and amended the application. The oral suspension will now be prepared by pharmacists and/or oncology nurses. The first dose will be administered by healthcare providers and patients/families will be given prepared doses to administer on Days 2 and 3.

This NDA has the following post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA):

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

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.

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

Of note, these studies are included as part of a Written Request (WR) issued on February 2, 2009 for Emend (aprepitant). The WR was amended (b) (4). The studies requested include:

(b) (4)

(b) (4)

The sponsor has indicated that they will not be able to meet the deadline for this WR (b) (4)

Now that the oral suspension is ready to be approved, DPMH agrees with expanding the indication down to 6 months of age. Labeling for the oral suspension will be combined with the capsule. The currently approved oral labeling allows for the use of Emend® oral capsule in patients 12 years and older and in patients less than 12 years who are at least 30 kg. The minimum weight was derived from comparing median clearance levels in patients aged 12 to 17 years and patients less than 12 years and weighing at least 30 kg.

(b) (4)

The weight-based dosing administered in the clinical trial with the oral suspension is 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3. Based on this weight-based dosing, the minimum weight for use of the oral capsule would be 42 kg. This represents 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. Because there would be fewer children less than 12 years who meet the minimum weight of 42 kg and the oral suspension would be available, DPMH concurs with DGIEP's decision not to include a minimum weight as part of the dosing of the oral capsule.

DPMH assisted the Division in preparing for review of the assessment by PeRC. DPMH continues to work with DGIEP on labeling while labeling changes are negotiated with the sponsor. See approved final labeling, which reflects DPMH input.

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/s/

AMY M TAYLOR
12/10/2015

HARI C SACHS
12/14/2015
I agree with these recommendations.

LYNNE P YAO
12/14/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 4, 2015

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): EMEND (aprepitant)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 207865

Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On March 26, 2015, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted for the Agency's review the final portion of a rolling submission for New Drug Application (NDA) 207865 for EMEND (aprepitant) Powder for Suspension, with the proposed indication for the use in patients ages 6 months to less than 12 years, in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

The naming convention for EMEND (aprepitant) "Powder for Suspension" was revised to EMEND (aprepitant) "for oral suspension" during the review process and will be referred to as such throughout the memo.

NDA 021549 EMEND (aprepitant) capsules was approved on March 27, 2003. NDA 022023 EMEND (fosaprepitant dimeglumine) for injection was approved on January 25, 2008.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by DGIEP on July 30, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EMEND (aprepitant) for oral suspension. Our review of the IFU was submitted in DARRTS on May 15, 2015 in response to a request by the Division of Medication Error Prevention and Analysis (DMEPA) on May 13, 2015, for DMPP to review the Applicant's proposed IFU for EMEND (aprepitant) for oral suspension.

2 MATERIAL REVIEWED

- Draft EMEND (aprepitant) for oral suspension PPI received on October 29, 2015 and received by DMPP and OPDP on December 1, 2015.
- Draft EMEND (aprepitant) for oral suspension Prescribing Information (PI) received on July 25, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 4, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. The PPI document is formatted using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
12/04/2015

MEETA N PATEL
12/04/2015

MARCIA B WILLIAMS
12/04/2015

LASHAWN M GRIFFITHS
12/04/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: December 3, 2015

To: Mary Chung
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207865
OPDP Comments for draft Emend (aprepitant) for oral suspension PI and PPI

OPDP has reviewed the proposed draft PI for Emend (aprepitant) for oral suspension PI and PPI. We have reviewed the draft PI, retrieved from SharePoint on December 2 2015, and have no additional comments. Comments on the draft PPI will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/03/2015

HUMAN FACTORS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: November 24, 2015

Requesting Office or Division: Division of Gastrointestinal and Inborn Error Products (DGIEP)

Application Type and Number: NDA 207865

Product Name and Strength: Emend (aprepitant) for Oral Suspension, 125 mg per pouch

Product Type: Single

Rx or OTC: Rx

Applicant/Sponsor Name: Merck & Co. Inc.

Submission Dates: October 29, 2015
July 28, 2014

OSE RCM #: 2015-157

DMEPA Primary Reviewer: Sherly Abraham, R.Ph

DMEPA Team Leader: Kendra Worthy, Pharm.D.

DMEPA Associate Director: Lubna Merchant, M.S., Pharm.D.

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review the human factor study results submitted for the new pediatric NDA. Based on the feedback from the Agency, Merck conducted two human factor validation studies restricting reconstitution and preparation of Emend oral suspension to oncology nurses and administration of the premeasured doses by lay patient caregivers.

2 REGULATORY HISTORY

Merck and Co. submitted a new pediatric NDA on July 25, 2014, to provide an age appropriate formulation (Emend for Oral Suspension) for pediatric patients 6 months to 12 years of age. Merck had submitted human factor study results conducted in 35 participants (12 Pharmacists, 12 nurses, and 11 lay caregivers) with the submission. Due to multiple failures in the study, we did not find that the results of the study supported safe and effective use of product in the actual use environment.¹ Based on agency feedback in a teleconference on May 4, 2015, between FDA and Merck, Merck revised their protocol and conducted a supplementary human factor validation study involving 17 untrained lay caregivers. However, we had similar concerns with the second study due to similar task failures.² Based on discussion between the agency and Merck, Merck revised their labeling restricting reconstitution and preparation of Emend oral suspension to health care providers and administration of the pre-measured doses by lay patient caregivers. Thus, Merck conducted two additional human factor studies with 21 oncology nurses and 16 patient caregivers.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Human Factor and Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

¹Abraham, A. Label and Labeling Review for Emend (NDA 207865) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 04 30. 32 p. OSE RCM No: 2015-15.

²Abraham, A. Label and Labeling Review for Emend (NDA 207865) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 08 11. 32 p. OSE RCM No: 2015-15.

FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E
Other	F-N/A
Labels and Labeling	G
Patient Labeling Recommendations	H

N/A=not applicable for this review

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Based on discussion between the Agency and Merck, Merck revised their labeling restricting reconstitution and preparation of Emend oral suspension to health care providers and administration of the pre-measured doses by lay patient caregivers. Merck conducted two additional human factor studies with 21 oncology nurses and 16 patient caregivers.

Proposed Emend for Oral Suspension Kit:

In the last two human factor studies, Merck used the proposed oral suspension kit that will be used for commercialization and included a cap for the 5 mL oral dispenser so that reconstituted medication can be transported and stored by the lay patient care giver. Each kit contains the following:



There are two parts to the IFU: an IFU for health care provider and an IFU for the patient caregiver. The IFU for the health care provider describes steps to measure 4.6 mL water with the 5 mL oral dosing dispenser, prepare the mixture by swirling and inverting, and measure the prescribed dose. The IFU for the patient caregiver describes how to store and administer the reconstituted Emend suspension.

Human Factor Study Design:

The applicant conducted two simulated-use usability testing with 21 healthcare providers and 16 untrained lay caregivers. These studies were IFU mandatory with one an hour-long session. In order to assess whether participants could find the IFU during the medication preparation and administration scenarios, the moderator did not initially provide any instructions on whether or not to use the IFU. However, in the event the participant began drug preparation or administration without referring to the IFU, the moderator instructed the participant to utilize the IFU. Merck proposed this approach to support the assessment of the effectiveness of the IFU changes. We agreed with this approach in general but noted that this was the best case scenario since all end users may not use the IFU.

Human Factor Study Results:

See Table 2 and 3 for summaries of critical task failures by oncology nurses and lay patient caregivers.

Table 2: Summary of Critical Task Failures by Oncology Nurses

Use Error Tasks	Occurrences	Root Causes Reported by Participants
Left 5-10% of the powder in the medication pouch	1/42	Packet felt light and patient didn't realize that medication was left inside the pouch.
Withdrew 0.7mL of dose instead of 0.6 mL	1/42	Presence of air bubbles.
Withdrew 4.6 mL of dose instead of 0.6 mL (self corrected at the second trial)	1/42	Confusion between reconstitution volume and dose volume.

Table 3: Summary of Critical Task Failures by Patient Caregivers

User Error Tasks	Occurrences	Root Causes Reported by Participants
Didn't read or understand IFU	1/32	Patient was confused by the two parts of the IFU on one sheet. (One for health care provider and the other for patient care giver)

Administered medication in the middle of the mouth rather than to the side of the cheek.	7/32	Didn't read the IFU and relied on previous methods of medication administration.
Pushed the plunger before inserting the dropper into patient's mouth	1/32	Confusion between the Health care provider IFU and Patient caregiver IFU and was experimenting with the new device.

We note that the failures noted in previous studies were not identified in the most recent human factor study. The most significant error in this study was a nurse withdrawing 4.6 mL of medication when the prescribed dose was 0.6 mL in the first of two trials; the user self-corrected for the second trial. She had recalled the reconstitution volume of 4.6 mL volume of water in the previous step rather than the prescribed volume of medication since she skipped step 9 which states to refer to the PI for dose volume. Other two errors involving health care provider study were leaving a small amount powder in the medication pouch (as she thought it was empty) and withdrawing 0.7 mL of dose volume instead of 0.6 mL (due to the presence of air bubbles). In both instances the participants self-corrected on the second trial.

In the patient caregiver study, there were seven instances of patient caregivers administering medication in the middle of the mouth rather than to the side of the cheek. These use errors can occur with any other oral solution and the risks involved in these use errors are not unique to this product. Additionally, these errors are not clinically significant if the patient swallows the medication. However, to address this failure we recommend the sponsor revise the figure depicting the tip of the oral dosing dispenser placed along the inner cheek of the mouth rather to the middle of the mouth. The other use errors involve confusion of having two different IFUs one for the healthcare provider and one for the patient caregiver are managed by improvements in label and labeling such as including health care provider IFU in section 2.3 and 2.4 and having a separate IFU for patient caregiver. The 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 risks associated with this product.

We reviewed the proposed prescribing information and carton and container labels and identified areas that can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide the recommendations in Section 4. We defer to the Division for the appropriateness of the pediatric dosing information in the label.

5 CONCLUSION & RECOMMENDATIONS

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.

Additionally, we consulted the patient labeling team (PLT) on October 29, 2015, to review the proposed Instructions for Use (IFU) that Merck submitted on October 29, 2015. PLT made recommendations to clarify the Chemistry, Manufacturing and Control changes made to the product including stability, storage and inclusion of a cap since reconstitution is restricted to health care providers and patient caregivers are only administering the premeasured dose. We agree with PLT's recommendations on IFU for patient caregivers included in their review.³ See Appendix H for IFU recommendations and revisions.

5.1 RECOMMENDATIONS TO THE DIVISION:

A. Full Prescribing Information- Dosage and Administration section:

1. Table 3 - We recommend the addition of the word "reconstituted" to the heading of table 3 to clarify that the dose volume refers to the reconstituted suspension.
2. We recommend including preparation and administration directions with corresponding pictures in section 2.3 and 2.4 since preparation and reconstitution will be restricted to the healthcare providers. This will eliminate the need for the separate IFU for health care providers. Sponsor should retain the IFU for the patient caregiver so that the storage and administration directions are clear to the patient caregiver.

5.2 RECOMMENDATIONS FOR MERCK AND CO.

A. Carton and Container Labels:

1. Add a statement to the principal display panel of the carton label in red bold font, "This product must be reconstituted and dose must be measured by a health care provider" to alert the health care provider that reconstitution and measurement of dose must be performed before the product is dispensed to the patient.
2. Allow space for healthcare providers to write post-reconstitution expiration date on the label. We recommend, "Discard after __/__/__" since "Discard after" is an affirmative

³ Dowdy, K. Patient Labeling Review for Emend (NDA 207865) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Medical Policy, Division of Medical Policy Programs, (US); 2015 11 20. 32 p.

statement, and has been shown to result in the desired action. Additionally, the “_/_/” statement will alert the healthcare provider to write a complete date (month, day, and year) on the container label.

3. Consider adding the statement, “For Oral Administration Only” to the principal display panel. Post-marketing experiences have indicated that wrong route of administration errors have occurred when oral liquid products have been inadvertently administered as injections. Because this product is an oral suspension and the product is supplied with a syringe, we recommend the addition of the route “For Oral Administration Only” statement to minimize the risk of wrong route of administration.

4. Consider revising the statement “^{(b) (4)}” to read “Single-Dose Kit– Discard Unused Portion” to minimize risk of the entire reconstituted contents being given as a single dose.

5. Consider including information on post-reconstitution storage on the carton label. These instructions will minimize the risk of administering expired products.

B. Instructions for Use for Patient Caregivers:

See Appendix H for IFU Recommendations and Revisions.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Emend Oral Suspension that Merck and Co. submitted on October 29, 2015.

Table 4: Comparison of Emend Products.

Products:	Emend for Oral Suspension Proposed	Emend Capsules Approved 3/2003	Emend for Intravenous Injection Approved 1/2008
Active Ingredient:	Aprepitant	aprepitant	fosaprepitant dimeglumine
Indication:	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy) including high-dose Cisplatin.  (b) (4)	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin. For prevention of postoperative nausea and vomiting.	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin.
Route of Administration:	Oral	Oral	Intravenous
Dosage Form:	Powder for Oral Suspension	Capsule	Injection
Strength:	125 mg	40 mg, 80 mg, and 125 mg	115 mg and 150 mg
Dose and Frequency	Adults and adolescents: The recommended dose is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. Children (aged 6 months to less than	The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3.	<u>HEC (Single Dose Regimen)</u> : EMEND for Injection (150 mg) is administered on Day 1 only as an infusion over 20-30 minutes initiated approximately 30 minutes prior to

	<p>12 years): The recommended dose for oral suspension is based on weight as shown below:</p> <p>less than 6 kg: Not recommended</p> <p style="text-align: right;">(b) (4)</p>		<p>chemotherapy. No capsules of EMEND are administered on Days 2 and 3.</p> <p><u>HEC and MEC (3-Day Dosing Regimen):</u> EMEND for Injection (115 mg) is administered on Day 1 as an infusion over 15 minutes initiated approximately 30 minutes prior to chemotherapy. EMEND capsules (80 mg) are given orally on Days 2 and 3.</p>
How Supplied:	Pink to light pink powder, in a single-	80 mg Cap: Unit-of-use bipack of 2, unit-	Single dose vial: 1 vial per carton.

	use pouch, packaged as a kit with one 5 mL dispenser and one mixing cup.	dose package of 6. 125 mg: unit-dose package of 6, unit of use Tripack containing one 125 mg cap and two 80 mg capsules. 40 mg: unit-of-use package of 1 and unit-dose package of 5.	
Storage:	Storage: Store at 20 25°C (68-77°F); excursions permitted between 15 30°C (between 59 86°F). Store in the original container. Do not open pouch until ready for use. Use within 30 minutes of preparation of suspension.	Storage: Store at 20 25°C (68 -77°F). See USP Controlled Room Temperature.	Store at 2-8°C (36-46°F).
Container and Closure System:	Single-use pouch.	White Plastic [REDACTED] (b) (4) Closure.	Glass vial closed by a rubber stopper and capped with an aluminum seal and a flip-off plastic cap.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 10, 2015, using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter⁴.

Table 4: FAERS Search Strategy	
Date Range	June 1, 2015-November 1, 2015
Product	Emend [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

B.2 Results

Our search identified 17 cases, of which none described errors relevant for this review.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

We searched the L drive on November 10, 2015, using the term “Emend” to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified nine previous reviews⁵, and we confirmed that our previous recommendations were implemented or considered.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

⁵Abraham, S. Label and Labeling Review for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 08 11. 32 p. OSE RCM No.: 2015-157

Abraham, S. Human Factor Study Final Protocol MEMO for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 06 23. 32 p. OSE RCM No.: 2015-157

Abraham, S. Human Factor Study Protocol for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 05 12. 32 p. OSE RCM No.: 2015-157

Abraham, S. Label and Labeling Review for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 04 30. 32 p. OSE RCM No.: 2015-157

Owens, Lissa C. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 5 8. 32 p. OSE RCM No.: 2013-931.

Mena-Grillasca, C. Label and Labeling Review for Emend (NDA 21549). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 01 31. 32 p. OSE RCM No.: 2012-2897.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 8 4. 32 p. OSE RCM No.: 2009-1348.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 8. 32 p. OSE RCM No.: 2008-1414.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 5. 32 p. OSE RCM No.: 2008-1414.

Holmes, L. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2008 7 1. 32 p. OSE RCM No.: 2008-698.

Merck and Co. they conducted two human factors validation studies with 21 oncology nurses and 16 lay patient caregivers restricting reconstitution and preparation of Emend oral suspension to oncology nurses and administration of the premeasured doses by lay patient caregivers.

The oncology nurses participant demographics included:

- 21 oncology nurses
- 18 females and 3 males
- 8 pediatric nurses and 13 others

The lay patient caregiver participant demographics included:

- 16 lay patient caregivers
- 7 males and 9 females

D.2. Results

Table 5 below shows the summary of oncology nurses user errors and close calls by tasks presented by the Applicant:

Table: 5 Summary of Oncology Nurses User Errors and Close Calls

Task	Critical/Essential	Performance in Trial #1 (N=21)	Performance in Trial #2 (N=21)	Risk Acceptability
1. Read IFU	Essential	All successful	All successful	No Residual Risk
2. Open mixing cup	Essential	All successful	All successful	No Residual Risk
3. Fill mixing cup with room temperature drinking water	Essential	All successful	All successful	No Residual Risk
4. Using dispenser, measure volume of water required	Critical	All successful	All successful	No Residual Risk
5. Empty mixing cup	Critical	All successful	All successful	No Residual Risk
6. Fill mixing cup with measured amount of water	Critical	All successful	All successful	No Residual Risk
7. Fill mixing cup with medicine	Essential	One use error occurred	All successful	Residual Risk is Acceptable
8. Close/seal mixing cup	Essential	All successful	All successful	No Residual Risk
9. Reconstitute	Critical	All successful	All successful	No Residual Risk
10. Withdraw dose/volume to administer	Critical	2 use errors and 3 close calls occurred	All successful	Residual Risk is Acceptable
11. Store dose in refrigerator	Critical	All successful	All successful	No Residual Risk
Task #12 Tested One Time (N=21)				
12. Administer dose	Critical	All successful	All successful	No Residual Risk

Table 6 below shows the summary of lay patient caregivers user errors and close calls by tasks presented by the Applicant:

Table: 6 Summary of Lay Patient Caregivers User Errors and Close Calls

Task	Critical/Essential	Performance in Trial #1 (N=16)	Performance in Trial #2 (N=16)	Risk Acceptability
1. Read IFU	Essential	1 Use Error ¹ and 3 Close Calls Occurred	1 Use Error ¹	Residual Risk is Acceptable
2. Store dose in refrigerator	Critical	All Successful	All Successful	No Residual Risk
3. Administer dose	Critical	5 Use errors ² and 1 close call occurred	3 Use errors ² and 1 close call occurred	Residual Risk is Acceptable

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on November 10, 2015, using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Emend

E.2 Results

Our search identified one case; this case was excluded because it was regarding the difficulty to tell the difference between the various strengths of Emend in Merck's unit-dose packages. Merck addressed this issue and it was confirmed by the presentation in the container labels in the previous DMEPA review (RCM: 2012-2897).

APPENDIX G. LABELS AND LABELING

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APPENDIX H. Patient Labeling Recommendations

H.1 List of Labels and Labeling Reviewed

DMPP reviewed the following Emend Oral Suspension labels and labeling submitted by Merck and Co. on October 29, 2015.

- Instructions for Use for Patient Care Givers (not pictured)

H.2 Labeling Images



11-20-15
DMPP-aprepitant (EM)

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/s/

SHERLY ABRAHAM
11/23/2015

KENDRA C WORTHY
11/24/2015

LUBNA A MERCHANT
11/24/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 17, 2015

To: Todd Bridges, PharmD
Director
**Division of Medication Error Prevention and Analysis
(DMEPA)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): EMEND (aprepitant)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 207865

Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On July 25, 2014, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted for the Agency's review New Drug Application (NDA) 207865 for EMEND (aprepitant) Powder for Suspension, with the proposed indication for the use in pediatrics, ages 6 months to less than 12 years, in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

On October 29, 2015, the Applicant submitted revised labeling for the Instructions for Use (IFU) for EMEND (aprepitant) for oral suspension in accordance with their agreement with the Agency on July 29, 2015, to develop a procedure whereby the medication is prepared by a healthcare provider for administration directly to the patient in a hospital/clinic setting or provided to the caregiver for administration in an out-patient setting. This agreement is in response to the Agency's concern that lay caregivers could not safely and effectively prepare the medication.

EMEND (aprepitant) capsules was originally approved on March 27, 2003. EMEND (fosaprepitant dimeglumine) for Injection was originally approved on January 25, 2008.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Medication Error Prevention and Analysis (DMEPA) on May 13, 2015, for DMPP to review the Applicant's proposed Instructions for Use (IFU) for EMEND (aprepitant) for oral suspension.

2 MATERIAL REVIEWED

- Draft EMEND (aprepitant) for oral suspension IFU received on October 29, 2015 and received by DMPP on October 29, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
11/17/2015

MARCIA B WILLIAMS
11/17/2015

LASHAWN M GRIFFITHS
11/17/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 021549/ S-025

Application Type: Efficacy Supplement

Name of Drug/Dosage Form:

NDA 21549/S-025 Emend (aprepitant) Capsules

Applicant: Merck Sharp & Dohme Corp

Receipt Date: July 28, 2014

Goal Date: May 28, 2015

1. Regulatory History and Applicant's Main Proposals

On July 25 and July 28, 2014, Merck submitted a new NDA and sNDA (efficacy supplement) to fulfill their PREA PMRs (PMR#1395-7 and 331-1). NDA 207865 Emend (aprepitant) is a new dosage form, powder for suspension, for use in younger children as young as 6 months. NDA 21549/S-025 Emend (aprepitant) proposes to expand the indication of the already approved capsule for use in pediatric patients 12 to 17 years. These applications are supported by the following studies: 1] Protocol 097: pharmacokinetic data in patients 12 to 17 years of age, 2] Protocol 134: pharmacokinetic data for patients 6 months to 12 years of age, and 3] Protocol 208: Single phase 3 efficacy/safety data in CINV in patients 6 months to 17 years of age.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 28, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:**
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:**
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:**
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
- Comment:**
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:**
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

MARY H CHUNG
09/24/2014

BRIAN K STRONGIN
09/24/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Linda L. Lewis, MD, Acting Deputy Director
Division of Pediatric and Maternal Health

NDA Numbers: 21549

Sponsor: Merck Sharp & Dohme Corporation

Drug: Emend (aprepitant)

Dosage form and route of administration: oral capsule (125 mg, 80 mg and 40 mg)

Approved Indication: In combination with other antiemetic agents for the:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

For the prevention of postoperative nausea and vomiting (PONV)

Proposed Indication: In combination with other antiemetic agents in patients 12 years 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)

Consult request: The Division of Gastroenterology and Inborn Errors Products requests DPMH's input on the proposed labeling change for Emend® capsules for oral use.

Background

Emend® capsules for oral use was originally approved on March 27, 2003. The sponsor submitted an assessment for CINV in patients 6 month to 17 years. At this time, DGIEP is ready to take a regulatory action for the Emend® capsules. This NDA has the following post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA):

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

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.

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

Of note, these studies are included as part of a Written Request (WR) issued on February 2, 2009 for Emend (aprepitant). The WR was amended (b) (4). The studies requested include:



(b) (4)

The sponsor has indicated that they will not be able to meet the deadline for this WR (b) (4)

For patients less than 12 years, the sponsor studied an oral suspension. However, the oral suspension is not ready for approval at this time. The preparation and administration of the oral suspension is complicated and caregivers as well as some healthcare workers did not perform well during the human factors studies. The sponsor is working to simplify the preparation and to test the stability of the oral suspension to see if it is feasible to have pharmacists and/or oncology nurses prepare the suspension and allow families to administer the product at home on Days 2 and 3. Thus, additional time is needed for DGIEP to complete its review. This review will focus on the Emend® oral capsules. DPMH's review of the oral suspension labeling will be conducted at a later time.

Pediatric specific labeling (as of July 30, 2015)

Highlights

Indications and Usage

EMEND® is a substance P/neurokinin 1 (NK₁) receptor antagonist (b) (4):

- in combination with other antiemetic agents in patients 12 years 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)

Dosage and Administration

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) (2.1)

- (b) (4) EMEND in adults and pediatric patients 12 years of age and older is 125 mg on Day 1 and 80 mg on Days 2 and 3
- Administer EMEND (b) (4) 1 hour prior to chemotherapy on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND in morning.
- See Full Prescribing Information for recommended dosages of concomitant dexamethasone and 5-HT₃ antagonist for HEC and MEC.

Reviewer comment: DPMH agrees with specifying that the indication (b) (4)

(b) (4)



Full Prescribing Information

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 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 (b) (4)
- Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) (b) (4)

Reviewer comment: See previous comment under the Highlights section.

2 Dosage and Administration

2.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Adults and Pediatric Patients 12 Years of Age and Older

(b) (4) the recommended oral dosage of EMEND capsules, dexamethasone, and a 5-HT₃ antagonist in adults and pediatric patients 12 years of age and older for the prevention of nausea and vomiting associated with administration of HEC. (b) (4)



Table 1: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with HEC

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

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemo therapy is given on Days 2 and 3, administer EMEND capsules in the morning (b) (4)

[†]Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. (b) (4) a 50% dosage reduction to account for a drug interaction with EMEND [see Clinical Pharmacology (12.3)].

Table 2: Recommended Dosing for the Prevention of Nausea and Vomiting Associated with MEC

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

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemo therapy is given on Days 2 and 3, administer EMEND capsules in the morning (b) (4).

[†]Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. (b) (4) a 50% dosage reduction to account for a drug interaction with EMEND [see Clinical Pharmacology (12.3)].

Reviewer comment:

(b) (4)

6 Adverse Reactions

6.1 Clinical Studies Experience

Adverse Reactions in (b) (4) the Prevention of Nausea and Vomiting Associated with HEC or MEC

(b) (4)

Table 6: Most Common Adverse Reactions in HEC and MEC (b) (4)

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

[†]Reported in ≥3% of patients treated with the EMEND regimen and at a greater incidence than control regimen.
(b) (4)

Reviewer comment: (b) (4)

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, (b) (4) 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)].

(b) (4)

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.

Prevention of Postoperative Nausea and Vomiting (PONV)

The safety and effectiveness of EMEND have not been established for the prevention of postoperative nausea and vomiting in pediatric patients.

Juvenile Animal Study

A study was conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended pediatric human dose and exposure in female rats equivalent to the pediatric human exposure) from the early postnatal period (Postnatal Day 10) through Postnatal Day 58. Slight changes in the onset of sexual maturation were observed in female and male rats. (b) (4) however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

Reviewer comment: DPMH recommends that Subsection 8.4 be (b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Specific Populations

Age: Pediatric Population

(b) (4)

Reviewer comment: DPMH has no comment on this section.

14 CLINICAL STUDIES

14.3 Prevention of Nausea and Vomiting Associated with HEC or MEC in Pediatric

Patients (b) (4)

In a randomized, double-blind, active comparator-controlled clinical study that included (b) (4) 302 pediatric patients aged (b) (4) 6 months to 17 years receiving HEC or MEC, EMEND in combination with ondansetron was compared to ondansetron alone (control regimen) for the prevention of CINV (Study 5). Intravenous dexamethasone was permitted as part of the antiemetic regimen in both treatment groups, at the discretion of the physician. A 50% dose reduction of dexamethasone was required for patients in the EMEND group, reflecting a dosage adjustment to account for a drug interaction [see *Clinical Pharmacology* (12.3)]. No dexamethasone dose reduction was required for patients who received the control regimen.

(b) (4)

Eligible patients had documented malignancy at either an original diagnosis or relapse and were scheduled to receive emetogenic chemotherapy or a chemotherapy regimen not previously tolerated due to vomiting along with ondansetron as part of their antiemetic regimen.

Of the 152 pediatric patients randomized to receive the EMEND regimen, 55% were male, 45% female, 78% White, 7% Asian, 0% Black, 24% Hispanic, and 13% Multi-Racial. The most common primary malignancies in subjects receiving the EMEND regimen were osteosarcoma (11%), Ewing's sarcoma (11%), neuroblastoma (9%) and rhabdomyosarcoma (8%).

The treatment regimens in Study 5 for pediatric patients (b) (4) are defined in Table 17. Of the pediatric patients, 29% in the EMEND regimen and 28% in the control regimen used dexamethasone as part of the antiemetic regimen in Cycle 1.

Comment [TA1]: To the Division... These data would need to be recalculated for (b) (4) only

Table 17: HEC and MEC Treatment Regimens* for Pediatric Patients (b) (4) to 17 Years of Age — Study 5

	Day 1	Day 2	Day 3
CINV EMEND Regimen			
(b) (4)	125 mg	80 mg	80 mg
Ondansetron	Per standard of care [†]	none	none
CINV Control Regimen*			
Ondansetron	Per standard of care [†]	none	none

* Intravenous dexamethasone was permitted at the discretion of the physician. A 50% dose reduction of dexamethasone was

required for patients in the EMEND group, reflecting a dosage adjustment to account for a drug interaction [see *Clinical*

Pharmacology (12.3)]. No dexamethasone dose reduction was required for patients in the control regimen

**EMEND placebo was used to maintain blinding

[†]EMEND was administered 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy was given on Days 2 and 3, EMEND was administered in the morning.

*Ondansetron was administered 30 minutes prior to chemotherapy on Day 1.

The antiemetic activity of EMEND was evaluated over a 5-day (120 hour) period following the initiation of chemotherapy on Day 1. The primary endpoint in Study 5 was complete response in the delayed phase (25 to 120 hours following chemotherapy) in Cycle 1. Patients had the opportunity to receive open-label EMEND in subsequent cycles (Optional Cycles 2-6); however efficacy was not assessed in these optional cycles. Overall efficacy was based on the evaluation of the following endpoints:

Primary endpoint:

- complete response (no vomiting, retching and no use of rescue medication) in the delayed phase (25 to 120 hours following initiation of chemotherapy)

Other prespecified endpoints:

- complete response in the acute phase (0 to 24 hours following initiation of chemotherapy)
- complete response in the overall phase (up to 120 hours following initiation of chemotherapy)
- no vomiting (defined as no emesis, retching or dry heaves, regardless of use of rescue medication) in the overall phase
- safety and tolerability

A summary of the key study results (b) (4)

re shown in Table 18.

Table 18: Percent of Patients Who Responded to Treatment by Treatment Group and Phase – Cycle 1 of Study 5

	EMEND Regimen n/m (%)	Control Regimen n/m (%)
(b) (4)		
PRIMARY ENDPOINT		
Complete Response – Delayed phase	77/152 (50.7) [†]	30/150 (20.0)
OTHER PRESPECIFIED ENDPOINTS		
Complete Response – Acute phase	401/152 (66.4)	78/150 (52.0)
Complete Response – Overall phase	61/152 (40.1) [†]	30/150 (20.0)
(b) (4)		

Complete Response = No vomiting or retching and no use of rescue medication.
[†]n<0.01 when compared to Control Regimen

(b) (4)

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.

(b) (4)

Reviewer comment: The description of the study should include (b) (4)

DPMH Recommendations:

If scientifically reasonable, dosing of the capsule (b) (4)

(b) (4)

(b) (4)



These recommendations were communicated to the DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

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/s/

AMY M TAYLOR
08/13/2015

HARI C SACHS
08/14/2015

I agree with these recommendations. If appropriate, the product should be labeled for pediatric patients (b) (4)

LINDA L LEWIS
08/14/2015

HUMAN FACTORS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 11, 2015

Requesting Office or Division: Division of Gastrointestinal and Inborn Error Products (DGIEP)

Application Type and Number: NDA 207865

Product Name and Strength: Emend (aprepitant) for Oral Suspension, 125 mg per pouch

Product Type: Single

Rx or OTC: Rx

Applicant/Sponsor Name: Merck & Co. Inc.

Submission Date: July 1, 2015
July 28, 2014

OSE RCM #: 2015-1513
2014-1470

DMEPA Primary Reviewer: Sherly Abraham, R.Ph

DMEPA Team Leader: Kendra Worthy, Pharm.D.

DMEPA Associate Director: Lubna Merchant, M.S., Pharm.D.

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review the human factor study results submitted under this pediatric NDA. Merck and Co. previously submitted a human factor study results report for this NDA. DMEPA reviewed this study and found it to be unacceptable¹. Merck conducted a supplementary human factor validation study with 17 lay patient caregivers focusing on evaluating changes to the IFU. Merck submitted the study results on July 1, 2015.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Human Factor and Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E
Other	F-N/A
Labels and Labeling	G-N/A
Patient Labeling Recommendations	H

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck and Co. submitted a human factor study results report with this NDA on July 25, 2014, and we reviewed the study results and found it to be unacceptable¹. After a teleconference on May 4, 2015, between FDA and Merck, Merck revised their protocol based on our recommendations and they agreed to conduct a supplementary human factors validation study

¹Abraham, A. Label and Labeling Review for Emend (NDA 207865) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 04 30. 32 p. OSE RCM No: 2015-157

with lay patient caregivers. During the teleconference, we also recommended that they make changes to their product and IFU based on the previous failed human factor study.

Proposed Emend for Oral Suspension Kit:

In this study, as per our recommendation, Merck used the proposed oral suspension kit that will be used for commercialization. Each kit contains the following:



The IFU has (b) (4) total steps and four subsections: (b) (4)
(b) (4) giving the prescribed dose, and disposing the trash.

Human Factor Study Design:

The applicant conducted a supplementary simulated-use usability testing with 17 untrained lay caregivers. This repeat study had one hour-long session that was IFU mandatory. If the participant intends to perform tasks without reading the IFU, the moderator reminded them to use the IFU. Merck proposed this approach to support the assessment of the effectiveness of the IFU changes. We agreed with this approach in general but noted that this was “best case scenario” for this patient group since in real life scenarios; all end users may not use the IFU.

Human Factor Study Results:

The task failures for Merck’s repeat human factor study were very similar to the original study. See Table 2 for a summary of critical task failure.

Table 2: Summary of Critical Task Failures

Critical Task	Subtasks	Total Critical User Errors
---------------	----------	----------------------------

Failure to measure correct volume for reconstitution	Over-filling with water Under-filling with water	11/19
Failure to correctly prepare solution	Pour powder into the mixing cup Gently swirl 20 times Invert the cup slowly five times	6/17
Failure to withdraw correct dose volume	Over-filling with medicine Under-filling with medicine	*First dose-10/18 Second dose-6/15 Third dose-4/15

***In addition to preparing the full dose, each participant was required to draw up two additional doses.**

Failure to measure correct volume for reconstitution:

The most critical task failures involved incorrect measuring of the reconstitution volume of water (4.6 mL) with the dispenser. Eleven of 19 instances of measuring out the required reconstitution volume (4.6 mL) were critical use errors of either under-filling or overfilling. Five out of seven instances had significant under-filling differences varying from 1.2 mL to 1.6 mL. All four overfilling cases involved patient caregivers filling the full cup with 18 mL instead of the required 4.6 mL (four times the required amount). The root causes of these errors that the participants reported are as follows:

- Confused by IFU and therefore missed or skipped reconstitution steps (3)
- Presence of air bubbles (2)
- Mistaken the dose for reconstitution volume (2)
- Misinterpreted markings (2)
- Measured the plastic rib (1)

- Large amount of text in IFU and missed important information (1)

Failure to correctly prepare the solution:

There were six of 17 instances had critical use errors in correctly preparing the solution. These involved pouring the powder from the pouch into the mixing cup, swirling the mixture at least 20 times and slowly inverting the mixing cup five times in order to prevent foaming and presence of clumps. The root causes of these errors that the participants reported are as follows:

- Misinterpreted, misunderstood or missed the step and the diagram associated with step 10 (3)
- Didn't read the directions regarding reconstitution (2)
- Shook the medicine vigorously instead of slowly swirly due to previous experience (1)

Failure to withdraw correct dose:

The other most common critical task failure involved withdrawing the correct dose to administer. In this study, we requested Merck to repeat measuring of two additional doses to ensure robust data. First instance of dosing had 10 out of 17 critical use errors, second instance had six out of 15 critical use errors, and third instance had four out of 15 critical use errors. Although measurements were improved with the third dosing, the overall number of use errors are concerning. The root causes of these tasks as reported by the participants include:

- Presence of air bubbles and lack of understanding of proper resolution of air bubbles (7)
- IFU confusion and misinterpreted 4.6 mL to be the dose (3)
- Not understanding each gradation on the 5 mL dispenser is 0.2 mL (3)
- Didn't realize the dose was incorrectly measured or misunderstanding how to measure or misunderstood IFU (3)
- Didn't see or read instructions and missed steps (3)
- Misinterpreted 0.6 mL dose as 6 mL dose and administered until cup was empty (1)

The root causes reported by participants in the failure of measuring of dose volume were very similar to the critical task failure in measuring out reconstitution volume. One of the main root causes of concern in both measuring tasks is getting the reconstitution volume confused with dose volume which resulted in significant overage in both cases. In general, there was a lack of comprehension among end users in the purpose of a two-step process to measure out the reconstitution volume and then the dose volume.

In the repeat study, the task failures were very similar to the task failures in the original study with no improvements from the IFU changes and other mitigation strategies. It is concerning

that all the use errors involved in measurements of reconstitution volume and/or dose volume. Dosing of this product is for pediatric patients 6 months to 12 years of age. Although the lowest (0.6 mL) and highest (3.2 mL) dose volumes were studied, significant overages of up to eight-fold were observed. Merck has proposed several minor changes to text, layout, and fold pattern of IFU and carton to mitigate some of these errors, but it is difficult to assess if these revisions will mitigate the failures observed in the study.

Merck has acknowledged that there are user errors in measuring the reconstitution volume of 4.6 mL and measuring the prescribed dose, however, they state that most of these errors are not clinically significant. They state that although some of these errors could in principle lead to clinically significant dosing errors, the potential clinical significance of overdosing and under dosing does not represent an unacceptable risk. Merck believes that the risk of adverse outcomes resulting from overdosing using the current dosing algorithm, even in the worst-case scenario, is acceptable.

Based on the results of both human factor studies, we do not believe the minor changes to text, layout, and fold pattern of IFU and carton as proposed by Merck would mitigate the errors observed in the studies. We believe the root causes for most of the use errors were confusion, misinterpretations and lengthy directions in the IFU and not comprehending the two-step process of reconstitution and dosing.

The Agency met with Merck via teleconference on July 20th and July 29th to discuss our comments on the second Human Factors Study results. Based on the lack of improvement in the second study, the Agency recommended the following:

- Conduct stability/compatibility studies to support a process whereby a health care professional (e.g., oncology pharmacist or nurse) can prepare and provide the reconstituted PFS to the caregiver for administration in an out-patient setting.
- In order to support limiting preparation by health care professionals, conduct an additional Human Factors study involving oncology nurses who are experienced in preparing chemotherapy drugs prior to approval.

4 CONCLUSION & RECOMMENDATIONS

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.

The Agency met with Merck via teleconference on July 20th and July 29th to discuss our comments on the second Human Factors Study results. Based on the lack of improvement in the second study, the Agency recommended Merck revise the labeling to include directions for the health care provider to prepare the dose to be administered to the patient and transfer it to a container for administration by the caregiver at home with no further preparation or measurement required. We recommend a repeat human factor study involving oncology nurses who are experienced in preparing chemotherapy drugs prior to approval to validate these revisions. We provide recommendations to the Division and the Applicant below.

Additionally, we consulted the patient labeling team (PLT) on July 1, 2015 to review the proposed Instructions for Use (IFU) that Merck submitted on July 1, 2015, and we agree with PLT's recommendations included in their review.² The IFU will remain in labeling for patients not able to receive the reconstituted solution from a healthcare professional. See Appendix H for IFU recommendations and revisions.

4.1 RECOMMENDATIONS FOR MERCK AND CO.

Instructions for Use: See Appendix H for IFU Recommendations and Revisions.

²Dowdy, K. Patient Labeling Review for Emend (NDA 207865) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Medical Policy, Division of Medical Policy Programs, (US); 2015 07 06. 32 p.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Emend Oral Suspension that Merck and Co. submitted on July 1, 2015.

Table 3: Comparison of Emend Products.

Products:	Emend for Oral Suspension Proposed	Emend Capsules Approved 3/2003	Emend for Intravenous Injection Approved 1/2008
Active Ingredient:	Aprepitant	aprepitant	fosaprepitant dimeglumine
Indication:	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy) including high-dose Cisplatin. 	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin. For prevention of postoperative nausea and vomiting.	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin.
Route of Administration:	Oral	Oral	Intravenous
Dosage Form:	Powder for Oral Suspension	Capsule	Injection
Strength:	125 mg	40 mg, 80 mg, and 125 mg	115 mg and 150 mg
Dose and Frequency	Adults and adolescents: The recommended dose is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3.	The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once	<u>HEC (Single Dose Regimen)</u> : EMEND for Injection (150 mg) is administered on Day 1 only as an infusion over 20-30 minutes

	<p>Children (aged 6 months to less than 12 years): The recommended dose for oral suspension is based on weight as shown below:</p> <p>less than 6 kg: Not recommended</p>	<p>daily in the morning on Days 2 and 3.</p>	<p>initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3.</p> <p><u>HEC and MEC (3-Day Dosing Regimen):</u> EMEND for Injection (115 mg) is administered on Day 1 as an infusion over 15 minutes initiated approximately 30 minutes prior to chemotherapy. EMEND capsules (80 mg) are given orally on Days 2 and 3.</p>
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(b) (4)

<p>How Supplied:</p>	<p>Pink to light pink powder, in a single-use pouch, packaged as a kit with one 5 mL dispenser and one mixing cup.</p>	<p>80 mg Cap: Unit-of-use bipack of 2, unit-dose package of 6.</p> <p>125 mg: unit-dose package of 6, unit of use Tripack containing one 125 mg cap and two 80 mg capsules.</p> <p>40 mg: unit-of-use package of 1 and unit-dose package of 5.</p>	<p>Single dose vial: 1 vial per carton.</p>
<p>Storage:</p>	<p>Storage: Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F). Store in the original container.</p> <p>Do not open pouch until ready for use. Use within 30 minutes of preparation of suspension.</p>	<p>Storage: Store at 20-25°C (68-77°F). See USP Controlled Room Temperature.</p>	<p>Store at 2-8°C (36-46°F).</p>
<p>Container and Closure System:</p>	<p>Single-use pouch.</p>	<p>White Plastic (b) (4) Closure.</p>	<p>Glass vial closed by a rubber stopper and capped with an aluminum seal and a flip-off plastic cap.</p>

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on June 29, 2015, using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter³.

Table 4: FAERS Search Strategy	
Date Range	April 1, 2015 - June 1, 2015
Product	Emend [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

B.2 Results

Our search identified five cases, of which none described errors relevant for this review.

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L drive on June 29, 2015, using the term “Emend” to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified eight previous reviews⁴, and we confirmed that our previous recommendations were implemented or considered.

⁴Abraham, S. Human Factor Study Final Protocol MEMO for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 06 23. 32 p. OSE RCM No.: 2015-157

Abraham, S. Human Factor Study Protocol for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 05 12. 32 p. OSE RCM No.: 2015-157

Abraham, S. Label and Labeling Review for Emend (NDA 207865). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 04 30. 32 p. OSE RCM No.: 2015-157

Owens, Lissa C. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 5 8. 32 p. OSE RCM No.: 2013-931.

Mena-Grillasca, C. Label and Labeling Review for Emend (NDA 21549). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 01 31. 32 p. OSE RCM No.: 2012-2897.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 8 4. 32 p. OSE RCM No.: 2009-1348.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 8. 32 p. OSE RCM No.: 2008-1414.

Oleszczuk, Z. Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 5. 32 p. OSE RCM No.: 2008-1414.

Holmes, L. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2008 7 1. 32 p. OSE RCM No.: 2008-698.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

Merck and Co. they conducted a supplementary human factors validation study with 17 lay patient caregivers focusing on evaluating the IFU changes.

The participant demographics included:

- 17 lay patient caregivers
- 6 males and 11 females
- The average age is 42.2

Methods:

1. Background questions
2. Untrained, first time use simulation
3. Measure 2nd and 3rd dose
4. IFU comprehension questions
5. Root cause probe
6. Subjective feedback

D.2. Results

Table 3 below shows the summary of user errors and close calls by tasks presented by the Applicant:

Table: 3 Summary of user errors and close calls by task

Task	<i>n</i>	OK	Close Calls	Use Errors
Task 1—Measure water				
1a. Open mixing cup, fill mixing cup with room temperature drinking water.	17	17	0	0
1b. Fill the 5mL oral dispenser with 4.6mL of water.	17	8	0	10 ¹
1c. Pour out remaining water from mixing cup.	14	13	0	1
1d. Add the 4.6mL of water from the oral dispenser back into the empty mixing cup.	13	13	0	0
Task 2—Prepare solution				
2a. Open and pour all contents from medicine pouch into the mixing cup containing water.	17	17	0	0
2b. Close the lid on the mixing cup and gently swirl approximately 20 times.	17	12	1	4
2c. Invert the cup slowly 5 times.	14	12	0	2
Task 3—Administer the dose				
3a. Inspect the liquid. If there are clumps, repeat swirling and inverting until there are none. If there is foam, wait for foam to disappear.	17	17	0	0

Task	<i>n</i>	OK	Close Calls	Use Errors
3b. Open the mixing cup and pull back the amount of medication to the mL line that matches the child's prescribed dose.	17	7	0	10
3c. Place the tip of dosing dispenser into the child's mouth, point toward either cheek and push plunger slowly to give the medication.	16	16	0	0
3d. Place all supplies in the trash.	17	17	0	0
Task 4—Measure 2nd and 3rd doses				
4a. Pull back on the plunger to withdraw medication to the mL line that matches the child's prescribed dose.	15	8	0	7
4b. Pull back on the plunger to withdraw medication to the mL line that matches the child's prescribed dose.	15	11	0	4

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on June 29, 2015, using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Emend

E.2 Results

Our search identified one case; this case was excluded because it was regarding the difficulty to tell the difference between the various strengths of Emend in Merck's unit-dose packages. Merck addressed this issue and it was confirmed by the presentation in the container labels in the previous DMEPA review (RCM: 2012-2897).

APPENDIX H. Patient Labeling Recommendations

H.1 List of Labels and Labeling Reviewed

DMPP reviewed the following Emend Oral Suspension labels and labeling submitted by Merck and Co. on July 1, 2015.

- Instructions for Use (not pictured)

H.2 Labeling Images



7-6-2015 DMPP
proposed comments t

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

/s/

SHERLY ABRAHAM
08/11/2015

KENDRA C WORTHY
08/11/2015

LUBNA A MERCHANT
08/11/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: July 2, 2015

From: Carrie Ceresa, Pharm D, MPH
Clinical Analyst, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Emend (aprepitant) capsules and powder for suspension

NDA: 21549/S-025 & 207865

Subject: Maternal Health Labeling Recommendations

Applicant Merck Sharp & Dohme Corp.

Materials Reviewed:

- Merck submission dated 7/25/14 for NDA 207865 & 7/28/14 for NDA 20529

Consult Question: DGIEP requests assistance with review of maternal health labeling subsections 8.1 and 8.2.

INTRODUCTION

On July 24, 2014, Merck submitted NDA 207865 for a new powder formulation of Emend (aprepitant) for oral suspension with the proposed indication in pediatric patients 6 months to 12 years of the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV), prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC) and treatment of nausea and vomiting associated with CINV highly emetogenic cancer chemotherapy (HEC). On July 28, 2014, Merck submitted NDA 20529/S-025 which is an already approved capsule formulation with the proposed indication in pediatric 12 to 17 years of the prevention of acute and delayed CINV, prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC), and treatment of nausea and vomiting associated with CINV highly emetogenic cancer chemotherapy (HEC). These submissions are being reviewed simultaneously and are intended to fulfill the PREA PMRs and partially respond to the Written Request.

DGIEP consulted DPMH to review and update the subsections related to Pregnancy and Lactation (8.1-8.2).

BACKGROUND

Product Background

Emend (aprepitant) is a substance P/neurokinin 1 (NK₁) receptor antagonist.¹ The capsule formulation was originally approved on March 27, 2003, to be used in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin.

Emend (aprepitant) capsule formulation (NDA 21549) was originally approved on March 27, 2003, to be used in combination with other antiemetics, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin. Emend capsules are currently approved for the following:

- in combination with other antiemetic agents for the:
 - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
 - prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
- for the prevention of postoperative nausea and vomiting (PONV)

Of note, on January 25, 2008, Emend (fosaprepitant dimeglumine) injection was approved under NDA 22023 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin; and, the prevention of nausea and vomiting associated with initial and repeat courses of MEC.

¹ 8/12/2014. Emend approved package insert.

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”² also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule³ format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015. In the meantime, conversion to the PLLR format is voluntary. The recommendations in this review are consistent with the PLLR format.

DISCUSSION

Review of Data & Labeling recommendations

Pregnancy

A search of published literature was performed on the use of Emend (aprepitant and fosaprepitant) during pregnancy and no information was found; therefore, there is no safety information in humans to inform the drug associated risk with use during pregnancy

In animal reproduction studies, there is no evidence of fetal harm in rats at exposures 1.6 times the exposure at the recommended adult human dose and in rabbits at 1.4 times the exposure at the recommended adult human dose of 125 mg/day.

Lactation

The Drugs and Lactation Database (LactMed)⁴ was searched for available lactation data with the use of Emend, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

The presence of Emend in rat milk was identified in the original animal reproduction studies. (DPMH refers to the March 12, 2003 nonclinical review).

² *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

³ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

⁴ United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

Therefore, because there is no current safety information to recommend against breastfeeding, the following regulatory statement has been added to 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.

Females and Males of Reproductive Potential

Infertility

There are no human data available regarding the effects of Emend on fertility. In animal reproduction studies, no effects were observed on infertility in male and female rats at dose exposures at about 1.6 times the adult human exposure at the recommended dose of 125 mg/day. Subsection 8.3 Females and Males of Reproductive Potential will be omitted from the Emend label as there is no adequate data to inform this subsection.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR. DPMH refers to the NDA action for final labeling. The sponsors draft labeling recommendation can be found in Appendix A.

DPMH LABELING RECOMMENDATIONS HIGHLIGHTS

[REDACTED] (b) (4)

Reviewer comment: DPMH recommends deleting the above statement from HIGHLIGHTS as no information is available on the use of Emend [REDACTED] (b) (4) therefore this information is not needed in this section.

8.1 Pregnancy

Risk Summary

There [REDACTED] (b) (4) data on EMEND [REDACTED] (b) (4) in pregnant women to inform the drug associated risk. In animal reproduction studies, no [REDACTED] (b) (4) in rats [REDACTED] (b) (4) rabbits [REDACTED] (b) (4) during organogenesis [REDACTED] (b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively..

Data

Animal Data

[REDACTED] (b) (4)

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. 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.

Appendix A – Merck prior approved labeling for capsule formulation

(b) (4)



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/s/

CARRIE M CERESA
07/02/2015

TAMARA N JOHNSON
07/02/2015

LYNNE P YAO
07/02/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207865 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: EMEND Established/Proper Name: aprepitant Dosage Form: powder for suspension Strengths: Not applicable (NA)		
Applicant: Merck Sharpe & Dohme Corp. Agent for Applicant (if applicable): NA		
Date of Application: 3/26/15 Date of Receipt: 3/26/15 Date clock started after UN: NA		
PDUFA/BsUFA Goal Date: 9/26/15		Action Goal Date (if different): 8/28/15
Filing Date: 5/25/15		Date of Filing Meeting: 4/30/15
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Proposes the addition of following indication in pediatric patients ages 6 months to less than 12 years- 1] Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy including high-dose cisplatin. 2] Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i><i>The product is a Qualified Infectious Disease Product (QIDP)</i><i>A Tropical Disease Priority Review Voucher was submitted</i><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s):

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>		<input type="checkbox"/>	<input type="checkbox"/>		
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested: 3 years					
Note: An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	On 4/10/15, sponsor submitted an updated 356h form to include all facilities used for the commercial product
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DMPP/Patient Labeling Team was consulted 7/30/14.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DPMH consulted 7/29/15
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Sponsor refers to a type B meeting which was canceled by the sponsor upon receipt of the preliminary comments on 6/4/12 as the Pre-NDA meeting. Although the outstanding aprepitant CINV PREA requirements were discussed, this was not a meeting solely dedicated to discuss submission plans for this application.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2015

BACKGROUND:

On July 25 and July 28, 2014, Merck submitted a new NDA and sNDA (efficacy supplement) to fulfill their PREA PMRs (PMR#1395-7 and 331-1). NDA 207865 Emend (aprepitant) is a new dosage form, powder for suspension, for use in younger children 6 months to less than 12 years of age. NDA 21549/S-025 Emend (aprepitant) proposes to expand the indication of the already approved capsule for use in pediatric patients 12 to 17 years. These applications are supported by the following studies: 1] Protocol 097: pharmacokinetic data in patients 12 to 17 years of age, 2] Protocol 134: pharmacokinetic data for patients 6 months to 12 years of age, and 3] Protocol 208: Single phase 3 efficacy/safety data in CINV in patients 6 months to 17 years of age.

On October 29, 2014, NDA 207865 Emend (aprepitant) powder for suspension was granted Fast Track/ Rolling Review status. On March 26, 2015, remaining CMC components of the application was received constituting a complete NDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Chung	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Division Director/Deputy	Donna Griebel/ Joyce Korvick (Deputy Director for Safety)		Y
Office Director/Deputy			N
Clinical	Reviewer:	Karyn Berry	Y
	TL:	Anil Rajpal	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Elizabeth Shang	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	Wen Jen Chen	Y
	TL:	Yeh Fong Chen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Not applicable (NA)	
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Danuta Gromek-Woods	N
	RBPM:	Kerri-Ann Jennings	Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:	Hamid Shafiei	Y
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:	Vapul Dhalakia / Grace McNally	Y
• Biopharmaceutics	Reviewer:	Albert (Tien Mien) Chen/ Tapash Ghosh	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	James Laurenson		N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Sherly Abraham/ Kendra Worthy & Lubna Merchant	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Joette Meyer/ DGIIEP, Denise Pica-Branco/ DPMH		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	

PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<u>New Molecular Entity (NDAs only)</u>	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Facility Inspection</u>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? 	
Comments:	
<u>Facility/Microbiology Review (BLAs only)</u>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	

<p>CMC Labeling Review (BLAs only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Donna Griebel</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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/s/

MARY H CHUNG
05/18/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 15, 2015

To: Kellie Taylor PharmD, MPH
Acting Director
**Division of Medication Error Prevention and Analysis
(DMEPA)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): EMEND (aprepitant)

Dosage Form and Route: for Oral Suspension

Application Type/Number: NDA 207865

Applicant: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On July 25, 2014, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted for the Agency's review New Drug Application (NDA 207865) for EMEND (aprepitant) Powder for Suspension, with the proposed indication for the use in pediatrics, ages 6 months to less than 12 years, in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

Merck also included the results of the human factors study for EMEND for the Agency's review in this submission. The results of the study provided an overview of the end users' comprehension of the EMEND Instructions for Use. EMEND (aprepitant) capsules was approved on March 27, 2003. EMEND (fosaprepitant dimeglumine) for Injection was approved on January 25, 2008.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Medication Error Prevention and Analysis (DMEPA) on May 13, 2015, for DMPP to review the Applicant's proposed Instructions for Use (IFU) for EMEND (aprepitant) for Oral Suspension.

2 MATERIAL REVIEWED

- Draft EMEND (aprepitant) for Oral Suspension IFU received on May 12, 2015 and received by DMPP on May 12, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the draft IFU to determine if further revisions need to be made.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KAREN M DOWDY
05/15/2015

MARCIA B WILLIAMS
05/15/2015

LASHAWN M GRIFFITHS
05/15/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 30, 2015

Requesting Office or Division: Division of Gastrointestinal and Inborn Error Products (DGIEP)

Application Type and Number: NDA 207865

Product Name and Strength: Emend (aprepitant) for Oral Suspension, 125 mg per pouch

Product Type: Single

Rx or OTC: Rx

Applicant/Sponsor Name: Merck & Co. Inc.

Submission Date: July 25, 2014

OSE RCM #: 2015-157

DMEPA Primary Reviewer: Sherly Abraham, R.Ph

DMEPA Team Leader: Kendra Worthy, Pharm.D.

DMEPA Associate Director: Lubna Merchant, M.S., Pharm.D.

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review the human factor study results report that is submitted with this pediatric supplemental NDA. With this supplement, Merck and Co. is proposing a new dosage form (For Oral Suspension) for Emend. The capsule formulation of Emend (aprepitant) in 40 mg, 80 mg, and 125 mg was approved on March 27, 2003 and the intravenous injection formulation of Emend (fosaprepitant dimeglumine) was approved on January 25, 2008.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This review is in response to a request by DGIEP to review human factor study results report that is submitted with this pediatric supplemental NDA. Merck is currently marketing oral capsules and powder for intravenous injection for Emend. In this supplemental NDA, Merck and Co. is proposing to expand the approved indications to pediatric patients 6 months to 12 years of age. To support dosing in pediatric patients less than 12 years of age, an age appropriate new dosage form (Emend for Oral Suspension) is proposed for this product. Below is the description of the proposed product.

Proposed Emend for Oral Suspension Kit:

The Applicant initially proposed and tested the tri-pack carton with three mono-pack kits. Each kit contains the following (see Appendix F for an illustration of the kit):

- 1) One pouch containing powder for suspension
- 2) A 1-mL oral dispenser (required for doses 1 mL or less)- (b) (4)
- 3) A 5-mL oral dispenser (required for doses greater than 1 mL)
- 4) One mixing cup
- 5) Instructions for Use (IFU) dosing instructions
- 6) Prescribing Information (PI/PPI)

The human factor validation study tested two oral dispensers (1 mL and 5 mL) to measure out the dose volume. The 1 mL oral dispenser was used to measure out small dose volumes of less than 1 mL. However, on March 6, 2015, Applicant informed us that their proposed commercial product will only include the 5 mL oral dispenser in order to avoid selection errors in measuring out doses.

The IFU has (b) (4) total steps and four subsections; (b) (4) administering the dose and disposing the trash.

Human Factor Study Design:

The applicant conducted a simulated-use testing and the study design included 35 participants: 12 pharmacists, 12 nurses, and 11 lay caregivers. There were two different testing sessions, first one was Instructions for Use (IFU)-optional and second one was IFU mandatory. The applicant has tested six critical functions (see Appendix D for study design details).

Human Factors Study Results:

Participants: We note that the participant numbers included in the study were inadequate because they did not include sufficient number of lay caregiver participants. Studies demonstrate that enrolling lower than 15 participants per arm could cause a percentage of the problems that they may experience with the proposed product go undetected.¹ Although the

¹ Faulkner, Laura. Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. (2003). Behav. Research Methods, Instruments and Computers. 35 (3): 379-383. ² Faulkner, Laura. Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. (2003).

representation of the health care participants in the study was not optimal, we can still draw some conclusions based on the study because overall there were sufficient numbers of health care practitioners (12 pharmacists + 12 nurses) to allow for a sound human-factors evaluation of the product usability in a health care provider population.

Twenty-eight critical use failures occurred during the study as follows. See table 2 for the summary of critical task failures.

Table 2: Summary of Critical Task Failures

Critical Task	Subtasks	Number of Participants	Total Critical Use Errors	
			IFU Optional	IFU Mandatory
Failure to determine correct dose/volume to administer using patient weight and PI *Pharmacists only	Determined incorrect dose	24	1	1
Failure to measure correct volume for reconstitution	Over-filling with water Under-filling with water	69	8	6
Failure to withdraw correct dose volume	Under-filling with medicine Over-filling with medicine Didn't administer the correct dose Administered all the contents of the pouch	69	5	7

Failure to determine correct dose/volume to administer using patient weight and PI:

The first critical task failure involved a pharmacist in both the IFU optional and mandatory arms that misinterpreted the pre-determined dose volume (mL) for dose weight concentration (mg/kg) to calculate the dose. The participant reported that doses are typically given in mg/kg on other medications requiring reconstitution. Emend powder for oral suspension does not conform to this standard, but provides doses in mL for weight range in kilograms. The Applicant reported that the root cause of this error was negative transfer from pharmacist's previous experience reconstituting medication. We note that most PI list the dosing information in mg/kg or mg. Pharmacists and other health care providers are more familiar with the dosing information presented as mg/kg or mg rather than mL. Therefore to minimize the medication error concerns, we recommend addition of the dosing information in mg/kg in the dosing table.

Failure to measure correct volume for reconstitution:

The second critical task failure involved incorrect measuring of the reconstitution volume of water (4.6 mL) with a 5 mL dispenser. There were 14/69 use errors and 4/69 close calls. This critical task failure involved either over-filling or under-filling the syringe with water. The root causes of these errors that the participants reported are as follows:

- Measuring steps were not intuitive and clear (8)
- Difficulty reading the volume marks on the dispenser (3)
- Presence of air bubbles (2)
- Misinterpreted markings (2)
- Did not read IFU(1)
- Read the IFU vertically (i.e., Steps 1, 3, 5) (1)
- Measured the plastic rib (1)

The Instructions for Use (IFU) has with ^(b)₍₄₎ steps; four steps involve the critical task of measuring out reconstitution volume to 4.6mL. These four critical steps can be removed from the IFU if the applicant were to provide a marking on the medicine cup for reconstitution volume of 4.6 mL rather than having the user measure the reconstitution volume. If the steps are cumbersome, there is a greater risk that the intended user may not read them. The readability of the IFU can be improved by:

- Reformatting the two-sided format into a single column with figures directly following the pertinent text or in two columns with text in the left column and figures in the right column, adjacent to the pertinent text. This will also avoid errors involving reading the IFU out of order.

- IFU should be more focused on measuring steps clearly indicating to the user how to resolve air bubbles and specifying that black marking should be the measuring line instead of the white plunger line and include a diagram to clearly indicate this. Failure of this task may be of concern in the vulnerable pediatric population since under-filling or over-filling the reconstitution volume leads to incorrect concentration of the oral suspension. The difference in dosing volume for infants is as little as 0.2 mL; even slight changes in the reconstitution volume may adversely impact the safety of the pediatric population and result in medication errors.

Failure to withdraw correct dose:

The third critical task failure involved withdrawing the dose to administer; 12/69 use errors and 3/69 close calls occurred. Failures involved under-filling or over-filling the oral dispenser with medication, not administering the correct dose, and administering all the contents of the pouch. The root causes of these tasks as reported by the participants include:

- Lack of knowledge of proper resolution of air bubbles and sacrificed dose accuracy (3)
- Participant didn't read instructions (2)
- Not administering the correct dose as participant didn't see dosing information (2)
- Dispensers are not sufficiently intuitive and markings on dispensers not sufficiently clear (2)
- Dose measuring steps were not sufficiently intuitive and clear (1)
- Misinterpretation on how to use syringe (measuring white dome on the plunger) (1)
- Participant looked at drops measurement instead of mL (1)
- Didn't read instructions at top of IFU (1)
- IFU confusion and misinterpreted 4.6 mL to be the dose (1).
- Participant didn't see dose on the box and guessed how to proceed (1)

The root causes reported by participants in the failure of measuring of dose volume were very similar to the critical task failure in measuring out reconstitution volume. Thus, all the recommendations noted above to improve the IFU into a more focused, clear, and concise document for end users should be followed.

Tasks not tested in the Study:

Another concern with the study is that some of the critical tasks were not tested. There are two steps in the IFU during the reconstitution that involve swirling the mixture at least 20 times and slowly inverting the mixing cup five times in order to prevent foaming and presence of clumps. Although these tasks were considered as critical tasks under reconstitution, Merck marked this step as a failure only if the clumps were present in the mixture and the participant didn't address them. Merck did not provide the results of whether all participants completed the mixing as per the reconstitution instructions. These tasks should be considered critical tasks

since the presence of air bubbles due to foaming caused critical use errors in measuring dose volumes.

As noted previously, the human factor validation study tested two oral dispensers (1 mL and 5 mL) to measure out the dose volume. The 1 mL oral dispenser was used to measure out small dose volumes of less than 1 mL. [REDACTED] (b) (4)

[REDACTED] This scenario was not addressed or studied in the human factor validation study. Given that most of the critical use errors involved measuring the reconstitution and dose volume either by under-filling or over-filling, it is critical that the applicant test the proposed commercial product without the 1 mL oral dispensers to determine whether the critical task failure results would be different.

Additionally, the preparation of this product involves a two-step process of measuring out reconstitution volume and dose volume which is neither common nor intuitive for the end users. We note that Merck's Isentress oral powder for suspension has a similar preparation and administration steps; however, the reconstitution volume for Isentress is 5 mL, which is easier to measure out compared to 4.6 mL of Emend. Dosing for Isentress is also more straightforward, as the smallest dose is 1 mL and additional smaller doses are at 1.5 mL, 2 mL, and 3 mL. Due to these differences, many critical errors that were observed with this product in measuring the 4.6 mL reconstitution volume and dose volumes of 0.2 mL increments may not occur in the reconstitution and administration of Isentress. We recommend the IFU for Emend Oral Suspension be similar to the IFU for Isentress which is more user-friendly, focused, and clear.

4 CONCLUSION & RECOMMENDATIONS

The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. Participants were only able to perform critical task functions safely and effectively 41/69 instances. Most of the task failures noted in the study would result in pediatric patients receiving either an under-dose, over-dose or not receiving the medication at all. Additionally, we note that there are differences between the kit studied in the HFS and the proposed commercial product. Thus, we recommend the Applicant implement corrective and preventative measures to address the failures and validate these changes in another human factors study prior to approval. We provide recommendations to the Division and the Applicant below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. Out of 24 attempts performed by pharmacists in calculating the correct dose, two attempts by one pharmacist failed to determine the correct dose or volume to administer using patient weight in the PI. In 14 of 69 trials, participants failed to measure the correct volume for reconstitution and in 12 of 69 trials, participants failed to withdraw correct dose or volume. All of these task failures would result in patients receiving either an under-dose or overdose resulting in treatment failures. Most of the task failures noted in the study would result in pediatric patients receiving either an under-dose, over-dose or not receiving the medication at all. Additionally, we note that there are differences between the kit studied in the HFS and the proposed commercial product.

We recommend the Applicant revise the Instructions for Use (IFU) based on our recommendations in section 4.2 and submit a revised protocol for our review. We recognize the tight timelines associated with this supplement and will take that into consideration and provide a quick turnaround on the review of the revised protocol if submitted by the Applicant. We also recommend the Applicant conduct their revised human factors validation study and submit the results to us by June 25, 2015 to give us adequate time for our review.

4.2 RECOMMENDATIONS FOR MERCK AND CO.

DMEPA recommends the following comments to be implemented to prior to approval.

A. Kit- mixing cup:

Most of the critical use errors observed in the HF study occurred with measuring the reconstitution volume. We recommend you provide a marking on the medicine cup for reconstitution volume of 4.6 mL rather than having the user measure the reconstitution volume using an oral syringe. This will eliminate (b) (4) steps from the IFU. If the steps are cumbersome, there is a greater risk that the intended user may not read them.

B. Instructions for Use:

1. Some of the participants in your HFS noted that the measuring steps in the IFU weren't intuitive or clear and the IFU was not easy to follow and listed that they read the IFU vertically ((b) (4) We recommend you reformat the Emend IFU (see IFU for Isentress (NDA 205786) as an example) to improve clarity and conciseness by revising into a single column with figures directly following the pertinent text or in two columns with text in the left column and figures in the right column, adjacent to the pertinent text similar to the Isentress IFU. The figures

should be labeled as Figure A, Figure B, etc. and should be appropriately referenced in the text. For example, at the end of Step 1, say (See Figure A). This will also avoid errors involving reading the IFU out of order if the user were to read it vertically as done by one of the participants.

2. Some of the participants also reported difficulty reading volume marks, misinterpreting the marking, and reading the white plunger line. Revise your IFU to clearly indicate to the user how to read the black marking for dose volume. Include a full diagram of the dispenser and describe how to read the black marking so that the white plunger line is not confused as the measuring line.
3. Participants also noted the lack of clear instructions on how to properly resolve air bubbles. Clearly indicate to the user how to resolve air bubbles if they are present with an illustration and clear, concise instructions.

C. Human Factors Study:

1. Your Human Factor Study (HFS) tested two oral dispensers (1 mL and 5 mL) to measure out the dose volume. (b) (4)

The smallest pediatric dose is as little as 0.6 mL and measuring that dose with a 5 mL oral dispenser may be difficult and may not be precise. Given that some of the critical use errors involved incorrect measuring of the dose volume either by under-filling or over-filling, we recommend you repeat the HF study the proposed commercial product without the 1 mL oral dispensers to determine whether the critical task failure results would be different and how it would impact the safety of the pediatric population. Repeat the HF study using the proposed commercial product and the revised IFU.

2. Studies demonstrate that enrolling lower than 15 participants per arm could cause a percentage of the problems that they may experience with the proposed product go undetected.² Please ensure that at least 15 lay caregivers are included in the revised protocol.
3. There are two steps in the IFU during the reconstitution that involve swirling the mixture at least 20 times and slowly inverting the mixing cup five times in order to prevent foaming and presence of clumps. Although these tasks were considered as

² Faulkner, Laura. Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. (2003). *Behav. Research Methods, Instruments and Computers*. 35 (3): 379-383.

critical tasks under reconstitution, you marked this step as a failure only if the clumps were present in the mixture and the participant didn't address them. Repeat the HF study including these as critical tasks and test them since the presence of air bubbles due to foaming resulted in errors in measurement of reconstitution volume and dose volume.

4. Submit the revised IFU and revised protocol for our review prior to conducting the study. We also request that you submit the human factor study results to us by June 25, 2015, to allow adequate time for our evaluation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Emend Oral Suspension that Merck and Co. submitted on.

Table 3: Comparison of Emend Products.

Products:	Emend for Oral Suspension Proposed	Emend Capsules Approved 3/2003	Emend for Intravenous Injection Approved 1/2008
Active Ingredient:	Aprepitant	aprepitant	fosaprepitant dimeglumine
Indication:	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy) including high-dose Cisplatin. 	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin. For prevention of postoperative nausea and vomiting.	For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic cancer chemotherapy including high-dose Cisplatin.
Route of Administration:	Oral	Oral	Intravenous
Dosage Form:	Powder for Oral Suspension	Capsule	Injection
Strength:	125 mg	40 mg, 80 mg, and 125 mg	115 mg and 150 mg
Dose and Frequency	Adults and adolescents: The recommended dose is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3.	The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once	<u>HEC (Single Dose Regimen)</u> : EMEND for Injection (150 mg) is administered on Day 1 only as an infusion over 20-30 minutes

	<p>Children (aged 6 months to less than 12 years): The recommended dose for oral suspension is based on weight as shown below:</p> <p>less than 6 kg: Not recommended</p>	<p>daily in the morning on Days 2 and 3.</p>	<p>initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3.</p> <p><u>HEC and MEC (3-Day Dosing Regimen):</u> EMEND for Injection (115 mg) is administered on Day 1 as an infusion over 15 minutes initiated approximately 30 minutes prior to chemotherapy. EMEND capsules (80 mg) are given orally on Days 2 and 3.</p>
	<p>(b) (4)</p>		

<p>How Supplied:</p>	<p>Pink to light pink powder, in a single-use pouch, packaged as a kit with one 5 mL dispenser and one mixing cup.</p>	<p>80 mg Cap: Unit-of-use bipack of 2, unit-dose package of 6.</p> <p>125 mg: unit-dose package of 6, unit of use Tripack containing one 125 mg cap and two 80 mg capsules.</p> <p>40 mg: unit-of-use package of 1 and unit-dose package of 5.</p>	<p>Single dose vial: 1 vial per carton.</p>
<p>Storage:</p>	<p>Storage: Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (between 59-86°F). Store in the original container.</p> <p>Do not open pouch until ready for use. Use within 30 minutes of preparation of suspension.</p>	<p>Storage: Store at 20-25°C (68-77°F). See USP Controlled Room Temperature.</p>	<p>Store at 2-8°C (36-46°F).</p>
<p>Container and Closure System:</p>	<p>Single-use pouch.</p>	<p>White Plastic (b) (4) Closure.</p>	<p>Glass vial closed by a rubber stopper and capped with an aluminum seal and a flip-off plastic cap.</p>

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 10, 2015, using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter³

Table 4: FAERS Search Strategy	
Date Range	September 15, 2014-April 1, 2015
Product	Emend [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

B.2 Results

Our search identified 22 cases, of which none described errors relevant for this review.

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L drive on April 7, 2015, using the terms, Emend, to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified five previous reviews⁴, and we confirmed that our previous recommendations were implemented or considered.

⁴ Owens, Lissa C. Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 5 8. 32 p. OSE RCM No.: 2013-931.

Oleszczuk, Z . Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 8 4. 32 p. OSE RCM No.: 2009-1348.

Oleszczuk, Z . Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 8. 32 p. OSE RCM No.: 2008-1414.

Oleszczuk, Z . Label and Labeling Review for Emend (NDA 22371). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2009 5 5. 32 p. OSE RCM No.: 2008-1414.

Holmes, L . Label and Labeling Review for Emend (NDA 22203). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2008 7 1. 32 p. OSE RCM No.: 2008-698.

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

Merck and Co. evaluated reconstitution and administration of the Emend Oral suspension completion of a Task Analysis and Use Error Analysis (TAUEA) and a Human Factor Study. TAUEA identified critical and essential tasks associated with the successful intended use of the product. The Human Factors Study was conducted to identify and mitigate potential hazards, and optimize the instructions for use (IFU).

The participant demographics included:

- 35 participants (12 Pharmacists, 12 Oncology Nurses and 11 Patient caregivers)
- 16 males and 19 females

The average age varied across the different groups from 45 to 47.8.

Table 5 below outlines the critical and essential tasks that were tested in this study:

Table 5: Summary of Critical and Essential Tasks.

Task	Critical/Essential
Use patient weight to determine dose/volume to administer	Critical
Read IFU	Essential
Using 5mL dispenser, measure volume of water required	Critical
Empty mixing cup	Essential
Fill mixing cup with measured amount of water	Critical
Fill mixing cup with medicine	Essential
Close/seal mixing cup	Essential
Reconstitute ⁴	Critical
Withdraw dose/volume to administer	Critical
Administer dose	Critical

⁴ The IFU states that the user must inspect for clumps. During the human factors testing, the inspection task was only marked as a failure if the clumps were present in the mixture but the participant did not address them.

In the human factor validation study, the tri-pack carton with three mono-pack kits was used. Each kit contained the following (see Appendix F for an illustration of the kit):

1. One pouch containing powder for suspension
2. A 1-mL oral dispenser (required for doses 1 mL or less)
3. A 5-mL oral dispenser (required for doses greater than 1 mL)

4. One mixing cup
5. Instructions for Use (IFU) dosing instructions
6. Prescribing Information (PI/PPI)

D.2 Results

- There were two different testing sessions, IFU-optional and IFU mandatory. Each participant participated in both sessions except one nurse was only able to attend the IFU optional session due to time constraints. The critical use errors are summarized below:
- 8/35 participants failed to correctly fill the 5 mL dispenser with 4.6 mL of water in the IFU optional trial and 6/35 failed to correctly fill the 5 mL dispenser with 4.6 mL of water in the IFU mandatory trial.
- 2/35 participants didn't fill the correct dispenser with the correct dose in the IFU optional trial and 7/35 participants didn't fill the correct dispenser with the correct dose in the IFU mandatory trial.
- 5/35 participants did not successfully open and pour all contents from the medication pouch into the mixing cup on the IFU optional trial and 2/35 participants did not successfully open and pour all contents from the medication pouch into the mixing cup on the IFU mandatory trial.
- 2/35 participants were not able locate the prescribed dose and administered the wrong dose in the IFU optional trial.
- 1/35 participants didn't understand the prescribed dose and administered the entire contents of the mixing cup.
- 2/35 participants failed to empty the mixing cup or reconstitute medication and dispensed water directly to the patients in the IFU optional trial. One participant repeated this error in the IFU mandatory trial.
- 1/35 participants failed to empty the mixing cup prior to reconstituting the medication and therefore produced medication at an incorrect concentration on the IFU optional trial.
- 1/12 Pharmacist failed to correctly determine dose/volume to administer using patient weight and PI in both trials.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on April 7, 2015, using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Emend

E.2 Results

Our search identified one case; this case was excluded because it was regarding the difficulty to tell the difference between the various strengths of Emend in Merck's unit-dose packages. Merck addressed this issue already and it was confirmed by the presentation in the container labels in the previous DMEPA review (RCM: 2012-2897).

Appendix F:

Table 6: Merck’s Table of Use Error Summary:

Task	Use Errors	IFU Optional				IFU Mandatory			
		Pharmacist (12)	Nurse (12)	Caregiver (11)	Total (35)	Pharmacist (12)	Nurse (11) ⁵	Caregiver (11)	Total (34)
[Task 1a] Determine dose/volume to administer using patient weight and PI	[UE-A] Determined incorrect dose by misinterpreting the pre-determined dose volume (mL) for dose weight concentration (mg/kg) to calculate the dose.	1	0	0	1	1	0	0	1
[Task 2b] Fill the 5 mL dispenser with 4.6 mL of water.	[UE-B] Overfilled the dispenser with water.	1	1	0	2	0	0	1	1
	[UE-C] Under-filled the dispenser with water.	0	2	4	6	0	3	2	5
[Task 2c] Pour out remaining water from mixing cup.	[UE-D] Did not empty mixing cup prior to dispensing 4.6 mL of water for reconstitution.	0	1	0	1	0	0	0	0
	[UE-E] Did not add medicine into mixing cup during dose preparation	0	1	1	2	0	0	1	1
	[UE-H] Confused the reconstitution volume (4.6 mL water) for the dosing volume (3.2 mL).	0	0	0	0	0	0	1	1

Task	Use Errors	IFU Optional				IFU Mandatory			
		Pharmacist (12)	Nurse (12)	Caregiver (11)	Total (35)	Pharmacist (12)	Nurse (11) ⁵	Caregiver (11)	Total (34)
[Task 2e] Open and pour all contents from medication pouch into mixing cup.	[UE-F] Small spill of powder on table.	1	1	2	4	0	0	1	1
	[UE-G] Did not completely empty all contents from pouch.	1	0	0	1	1	0	0	1
[Task 3a] Withdraw dose/volume to administer.	[UE-K] Under-filled dispenser with medication.	0	0	2	2	1	0	3	4
	[UE-L] Overfilled dispenser with medication.	0	0	0	0	0	1	2	3
	[UE-M] Did not find prescribed dose and did not administer correct dose.	0	1	1	2	0	0	0	0
	[UE-N] Did not understand the weight based dose concept and administered all the content of the pouch.	0	0	1	1	0	0	0	0

- 1) One pouch containing powder for suspension
- 2) A 1-mL oral dispenser (required for doses 1 mL or less)
- 3) A 5-mL oral dispenser (required for doses greater than 1 mL)
- 4) One mixing cup
- 5) Instructions for Use (IFU) dosing instructions
- 6) Prescribing Information (PI/PPI)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarketing medication error data, we reviewed the following Emend Oral Suspension labels and labeling submitted by Merck and Co. on July 25, 2014.

- Instructions for Use

G.2 Label and Labeling Images

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
04/30/2015

LUBNA A MERCHANT on behalf of KENDRA C WORTHY
04/30/2015

LUBNA A MERCHANT
04/30/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 23, 2014

TO: Mary Chung, Regulatory Project Manager
Karyn Berry, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21549-S25 and 207865

APPLICANT: Merck Sharp & Dohme Corp.

DRUG: aprepitant (EMEND®)

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic chemotherapy including high-dose cisplatin in patients 6 months of age and older.

CONSULTATION REQUEST DATE: August 13, 2014
 INSPECTION SUMMARY GOAL DATE: February 28, 2015
 DIVISION ACTION GOAL DATE: August 28, 2015
 PDUFA DATE: August 28, 2015

I. BACKGROUND:

Under the Pediatric Research Equity Act (PREA), Merck Sharp & Dohme (MSD) Corp., is required to conduct pediatric studies for EMEND[®] (aprepitant) approved on March 26, 2003 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. MSD Corp. submitted NDA 207865 for EMEND[®] (aprepitant) 125 mg Powder for Suspension and also an amendment to NDA 21-549 for EMEND[®] to revise the labelling to include pediatric dosing for the tablets.

The sponsor submitted Protocol 0869-208 entitled “A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, to Examine the Efficacy and Safety of Aprepitant for the Prevention of CINV in Pediatric Patients” in support of the application. Sites were chosen based on high enrollment, efficacy outcome, geographic distribution, and previous inspectional history. There are not adequate domestic data.

II. RESULTS (by Site):

Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
Anna Balcerska, M.D. Debinki 7, Kl. Pediatri, Hematologii, Onkologii I Endokrynologii Gdansk, 80-211, Poland	0869-208 Site 52/ 13 Subjects	November 3 to 7, 2014	NAI
Juan L. Garcia, M.D. Avenida Angamos Este 2520, Surquillo Lima, 34, Peru	0869-208 Site 44/ 10 Subjects	November 10 to 13, 2014	NAI
C. M. Zwaan, M.D. Dr. Molewaterplein 60 Rotterdam, 3015 GJ Netherlands	0869-208 Site 32/ 13 Subjects	November 10 to 13, 2014	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

**1. Anna Balcerska, M.D.
Gdansk, 80-211, Poland**

- a. **What was inspected:** At this site, 13 subjects were screened, 13 subjects were enrolled, and 13 subjects completed the study. All subject records were reviewed.
- b. **General Observations/Commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data submitted in the NDA and the source data.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Juan L. Garcia, M.D.
Lima, 34, Peru**

- a. **What was inspected:** At this site, 11 subjects were screened, 10 subjects were enrolled, and 10 subjects completed the study. All records for enrolled subjects were reviewed.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. Inclusion and exclusion criteria were met. IEC initial approval and regulatory agency approvals and acknowledgements were present. There was no apparent unblinding noted. Labs, ECGs, and subject diaries were completed. Drug accountability was accurate. Site monitoring by sponsor was documented. No regulatory violations were noted and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

**3. C. M. Zwaan, M.D.
Rotterdam, 3015 GJ, Netherlands**

- a. **What was inspected:** At this site, 14 subjects were screened, 13 subjects were enrolled, and 13 subjects completed the study. All 14 subject records were reviewed.

- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. No regulatory violations were noted and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected for this application. All clinical sites had the classification of NAI. The studies appear to have been conducted adequately, and the data generated by this study appears acceptable in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Medical Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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/s/

SUSAN LEIBENHAUT
02/24/2015

SUSAN D THOMPSON
02/24/2015

KASSA AYALEW
02/25/2015