

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207865Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 207865

SUPPL #

HFD #

Trade Name Emend

Generic Name aprepitant

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known December 17, 2015

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 21549 Emend (aprepitant) capsule

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the

application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 2011-000651-16 [Protocol 208]

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation, Study 2011-000651-16 [Protocol 208], was relied upon for NDA 21549/ S-025 Emend (aprepitant) capsule.

The investigation, Study 2011-000651-16 [Protocol 208], demonstrates the effectiveness of the drug product in patients 6 months to 17 years. Under NDA 21549/S-025 Emend (aprepitant) capsule, the investigation was relied upon for demonstration of effectiveness in patients 12 years to 17 years, and children < 12 years who weigh at least 30 kg.

For this NDA 207865 Emend (aprepitant) oral suspension, the investigation was relied upon for demonstration of effectiveness in patients 6 months and older.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 2011-000651-16 [Protocol 208]. Please see response to 3(a).

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 50283            YES             ! NO   
! Explain:

Investigation #2  
IND #                    YES             ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Mary Chung  
Title: Regulatory Project Manager  
Date: 12/12/15

Name of Office/Division Director signing form: Donna Griebel  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H CHUNG  
12/17/2015

DONNA J GRIEBEL  
12/17/2015

# ACTION PACKAGE CHECKLIST

<b>APPLICATION INFORMATION<sup>1</sup></b>		
NDA # 207865 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Emend Established/Proper Name: aprepitant Dosage Form: Oral Suspension		Applicant: Merck Sharpe and Dohme Corp. Agent for Applicant (if applicable):
RPM: Mary Chung		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="text-align: center;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p style="margin-left: 20px;"> <input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:         </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>December 26, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
<b>❖ Application Characteristics<sup>3</sup></b>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 3  
*(confirm chemical classification at time of approval)*

- |                                                           |                                                   |
|-----------------------------------------------------------|---------------------------------------------------|
| <input checked="" type="checkbox"/> Fast Track            | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review        | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |                                                   |

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)**

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

### Action Letters

❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date 12/17/15
---------------------------------------------------------------------------------------	--------------------------

### Labeling

❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
--------------------------------------------------------------------------------------------------	--

- Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*

 Included

- Original applicant-proposed labeling

 Included

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	
------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--

 Medication Guide  
 Patient Package Insert  
 Instructions for Use  
 Device Labeling  
 None

- Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*

 Included

- Original applicant-proposed labeling

 Included

❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
------------------------------------------------------------------------------------------------------------------------------------------------------------------	--

- Most-recent draft labeling

 Included

❖ Proprietary Name	
--------------------	--

- Acceptability/non-acceptability letter(s) *(indicate date(s))*
- Review(s) *(indicate date(s))*

10/3/14 (acceptability letter),  
9/29/14 (review)

❖ Labeling reviews <i>(indicate dates of reviews)</i>	
-------------------------------------------------------	--

RPM:  None 9/24/14  
DMEPA:  None 11/24/15,  
8/11/15, 4/30/15  
DMPP/PLT (DRISK):  
 None 12/4/15,  
11/17/15, 5/15/15  
OPDP:  None 12/3/15  
SEALD:  None  
CSS:  None  
Product Quality  None  
Other:  None DPMH Pediatric:  
12/14/15, 8/14/15. DPMH  
Maternal 12/16/15, 7/2/15

### Administrative / Regulatory Documents

❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	5/18/15
------------------------------------------------------------------------------------------------	---------

❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
----------------------------------------------------------------------------------------	--------------------------------------------------

❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
-----------------------------------------------------------------------	----------------------------------------------

❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
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<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>12/9/2015</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)  (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	12/17/15, 12/15/15, 12/11/15, 12/4/15, 11/30/15, 11/25/15, 11/23/15, 11/20/15, 8/25/15, 7/28/15, 7/22/15, 7/21/15, 6/23/15, 6/23/15, 6/10/15, 5/19/15, 5/18/15, 5/15/15, 5/14/15, 4/30/15, 4/3/15, 3/9/15, 3/4/15, 2/5/15, 11/7/14, 9/5/14, 8/19/14
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/17/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None 2 PMCs
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	8/28/15, 8/17/15
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See clinical review 8/17/15 page 28
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None DMEPA: 11/24/15, 8/11/15, 6/23/15, 5/18/15, 4/30/15.
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 2/25/15 (Letters dated 4/2/15, 3/19/15, 1/26/15)
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/29/15

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/2/15, 8/27/15, 7/20/15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/1/15, 8/19/15, 7/21/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/6/15, 7/20/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharmaceutics 12/7/15, 7/15/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 86 OPQ Review 7/20/15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Page 44 OPQ Review 7/20/15 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

### Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

## Chung, Mary

---

**From:** Chung, Mary  
**Sent:** Thursday, December 17, 2015 7:45 AM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend Oral Suspension - PI  
**Attachments:** N 207865 Emend Oral Suspension FDA Proposed PI 12-17-15 tracked changes.docx; N 207865 Emend Oral Suspension FDA Proposed PI 12-17-15 tracked changes.pdf

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On December 15, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI). We request that you resubmit labeling (PI) that addresses these issues by December 17, 2015.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
12/22/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Tuesday, December 15, 2015 12:55 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) Oral Suspension- PPI  
**Attachments:** NDA 207865 Emend Oral Suspension FDA proposed PPI tracked changes 12-15-15.doc; NDA 207865 Emend Oral Suspension FDA proposed PPI tracked changes 12-15-15.pdf; NDA 207865 Emend Oral Suspension FDA proposed PPI clean 12-15-15.doc; NDA 207865 Emend Oral Suspension FDA proposed PPI clean 12-15-15.pdf

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On December 15, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PPI). We request that you resubmit labeling (PPI) that addresses these issues by December 15, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
12/22/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Friday, December 11, 2015 5:04 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) Oral Suspension- Labeling (PI, PPI, IFU)  
**Attachments:** N 207865 Emend Oral Suspension FDA proposed IFU 12-11-15 clean.doc; N 207865 Emend Oral Suspension FDA proposed IFU 12-11-15 clean.pdf; N 207865 Emend Oral Suspension FDA proposed IFU 12-11-15 tracked changes.doc; N 207865 Emend Oral Suspension FDA proposed IFU 12-11-15 tracked changes.pdf; N 207865 Emend Oral Suspension FDA proposed PPI 12-11-15 clean.doc; N 207865 Emend Oral Suspension FDA proposed PPI 12-11-15 clean.pdf; N 207865 Emend Oral Suspension FDA proposed PPI 12-11-15 tracked changes.doc; N 207865 Emend Oral Suspension FDA proposed PPI 12-11-15 tracked changes.pdf; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-11-15 clean.docx; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-11-15 clean.pdf; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-11-15 tracked changes.docx; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-11-15 tracked changes.pdf

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On December 8, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI, and IFU). We request that you resubmit labeling (PI, PPI, IFU) that addresses these issues by Monday December 14, 2015.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards

Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
12/11/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Friday, December 04, 2015 5:13 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) - Label Comments (PI, PPI, IFU)  
**Attachments:** NDA 207865 Emend Oral Suspension FDA Proposed PI 12-4-15 clean copy.doc; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-4-15 clean copy.pdf; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-4-15 tracked changes.doc; NDA 207865 Emend Oral Suspension FDA Proposed PI 12-4-15 tracked changes.pdf; NDA 207865 Emend Oral Suspension FDA Comments on PPI.docx; NDA 207865 Emend Oral Suspension FDA Comments on PPI.pdf; NDA 207865 Emend Oral Suspension IFU FDA Comments 12-4-15.doc; NDA 207865 Emend Oral Suspension IFU FDA Comments 12-4-15.pdf

Nick,  
Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On December 2, 2015 and October 29, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI, and IFU). We request that you resubmit labeling (PI, PPI, IFU) that addresses these issues by Tuesday December 8, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
12/04/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Friday, December 04, 2015 5:51 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant)- Post Marketing Commitments

Nick,  
Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

We also refer to the proposed Post Marketing Commitments (PMC) for this application indicated to you on July 7, 2015, and your responses and comments provided to the NDA on July 8, 2015. Please see below current list of proposed PMCs for this application. Please confirm your agreement with these commitments, including agreement with the proposed milestone dates.

We request that you provide your response by Tuesday December 8, 2015.

Monitor the particle size distribution (PSD) of commercial drug product in the primary package (at release and on shelf life) and submit the data to support a proposed D<sub>(4)</sub><sup>(b)</sup> specification for the particle size.

Final Report Submission: 06/17 (June 2017)

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

Final Report Submission: 12/16 (December 2016)

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
12/04/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Monday, November 30, 2015 4:35 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) oral suspension- CMC Information Request

Nick,  
Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

We have the following request for additional information. We refer to the November 24, 2015 teleconference, during which the below request was discussed, and the November 25, 2015 clarification provided which indicated the below information request.

Regarding in-use stability testing for 1 mL oral dosing dispenser, we agree with your proposal to perform abbreviated in-use stability testing and only provide the data for assay and degradation products.

We request to receive the above information to the NDA by December 2, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
11/30/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Wednesday, November 25, 2015 12:19 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) oral suspension - Carton/Container Label

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On October 29, 2015, we received your proposed labeling submission to this application, and have the below comments on your proposed carton/container label.

1. Add a statement to the principal display panel of the carton label in (b) (4) bold font, “(b) (4)” to alert the health care provider that reconstitution and measurement of dose must be performed before the product is dispensed to the patient.
2. (b) (4)
3. Add the lot number and expiration date to the drug product immediate container (pouch) label and re-submit.
4. 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.
5. Consider revising the statement (b) (4) to read (b) (4) to minimize risk of the entire reconstituted contents being given as a single dose.
6. Consider including information on post-reconstitution storage on the carton label. These instructions will minimize the risk of administering expired products.

We request that you resubmit to the NDA carton/container labeling that addresses these issues by December 2, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
11/25/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Monday, November 23, 2015 5:38 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) - Label (IFU)  
**Attachments:** NDA 207865 IFU FDA comments 11-23-15.doc; NDA 207865 IFU FDA comments 11-23-15.pdf

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On October 29, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by November 30, 2015, or before. The resubmitted labeling will be used for further labeling discussions.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
11/23/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Friday, November 20, 2015 4:11 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) oral suspension - Label (PI)  
**Attachments:** NDA 207865 Emend FDA Comments 11-20-15 clean copy.doc; NDA 207865 Emend FDA Comments 11-20-15 clean copy.pdf; NDA 207865 Emend FDA Comments 11-20-15 tracked changes.doc; NDA 207865 Emend FDA Comments 11-20-15 tracked changes.pdf

Nick,

Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) oral suspension.

On October 29, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by November 30, 2015, or before. The resubmitted labeling will be used for further labeling discussions.

We note that your plans for the EMEND for oral suspension commercial dosing kit include a single 5 mL oral dispenser that is used both for reconstitution of the suspension and also for withdrawing the dose to be administered to the patient. We recommend you also include in the kit a 1 mL syringe to be used for withdrawing doses of reconstituted suspension that are less than 1 mL (i.e., the 0.6 mL dose for patients 6 to less than 8 kg and the 0.8 mL dose for patients 8 to less than 10 kg, administered on Days 2 and 3). We are concerned that the 5 mL syringe is not accurate enough for these doses and may result in dose variability, which is more significant at these smallest volumes.

Please revise the labeling, as appropriate, to include for the provision of the 1 mL oral dosing dispenser in the kit.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350

Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
11/20/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 207865

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Merck Sharp & Dohme Corp.  
Attention: Nicholas W. Andrew  
Director, Regulatory Affairs  
126 E. Lincoln Avenue  
P.O. Box 2000, RY34-B293  
Rahway, NJ 07065

Dear Mr. Andrew:

Please refer to your New Drug Application (NDA) dated March 26, 2015, received July 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) Powder for Suspension.

On July 1, 2015, we received your July 1, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 26, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 30, 2015.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Project Management Staff

Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
08/25/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Tuesday, June 23, 2015 4:27 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 and NDA 21549 S-025 Emend (aprepitant)- Clinical Information Request

Nick,  
Reference is made to your Supplemental New Drug Application (sNDA) dated and received July 28, 2014 and New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

We have the following request for additional information:

1. In Protocol 208 (cycle 1) only 28.5% of patients received prophylactic dexamethasone. Provide an explanation for such low use of dexamethasone in the pediatric population trial compared to the use of prophylactic dexamethasone in the adult trials. This explanation should include a review of the literature to support the use or non-use of prophylactic dexamethasone in pediatric patients.
2. In patients who received prophylactic dexamethasone, provide the dose that each patient received each day (use a patient line list which should also include patients' ages). Provide this information for both the aprepitant and control groups.
3. Please provide a safety analysis for patients who received dexamethasone, specifically evaluating neuro-psychiatric adverse reactions. Provide this information for both the aprepitant and control groups

We request to receive your response to this information request to both the sNDA and NDA by June 29, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
08/10/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Tuesday, June 23, 2015 4:49 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 and NDA 21549 S-025 Emend (aprepitant)- Clinical Pharmacology Information Request

Nick,

Reference is made to your Supplemental New Drug Application (sNDA) dated and received July 28, 2014 and New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

We have the following request for additional information:

In your base and final population PK model, the effect of age on drug clearance was modeled with fixed values adapted from the publication by Johnson, 2006. It should be noted that the adapted formula refers to the maturation of intestinal/gut CYP3A only. As aprepitant is primarily metabolized by CYP3A4 in the liver, please justify and clarify the physiological rationale of your final model on age effect. Please consider re-evaluating your final popPK model in this regard. One way to account for age effect on clearance is to use the hepatic maturation factor (see the review at Drugs at FDA, page 42, for more details,

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM177428.pdf>).

Your simulation based on final PopPK model should compare the difference of exposure metrics between the dose regimen used in clinical trials (body weight based) versus the nomogram-based dosing regimen (b) (4) and their relative difference to adult and adolescent exposure. Please provide the input dataset, control stream, and codes used for simulation.

We request to receive your response to this information request to both the sNDA and NDA by June 29, 2015.

Regards,

Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
08/10/2015

## Chung, Mary

---

**From:** Chung, Mary  
**Sent:** Tuesday, July 28, 2015 12:31 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865/ NDA 21549 S-025 Emend (aprepitant)- Clinical Information Request

Nick,  
Reference is made to your Supplemental New Drug Application (sNDA) dated and received July 28, 2014 and New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

We have the following request for additional information:

1. Reference is made to explanation provided for *Table 2.7.4: 3 Extent of Exposure of Aprepitant by Dose (cycle 1) All Subjects as Treated Population Protocols 208 and 097 Combined* (provided below), in section 2.7.5 Summary of Clinical Safety. After referencing 1.2.1 Extent of Exposure explanation section, we have the following request for clarification:

Provide further clarification and explanation regarding “Any dose” row and also further explain Column 3 (i.e. why there are no numbers in the rows).

**Table 2.7.4: 3 Extent of Exposure to Aprepitant by Dose <Cycle 1> All Subjects as Treated (ASaT) Population**

**Protocols 208 and 097 Combined**

Aprepitant	1 Day	2 Days	3 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	2	1	181	184	1 to 3	3.0
10 to 20.0 mg	1	16	1	18	days	days
20.1 to 30.0 mg	16	25	0	41	1 to 3	2.0
30.1 to 40.0 mg	16	25	0	41	days	days
40.1 to 50.0 mg	22	10	0	32	1 to 2	1.6
50.1 to 65.0 mg	21	16	0	37	days	days
65.1 to 80.0 mg	10	87	0	97	1 to 2	1.6
80.1 to 125 mg	100	0	0	100	days	days

Each subject could be counted for different dosage categories row.

[\[Ref. 5.3.5.1: P208, P097\]](#)

2. Request related to SAEs:

In Summary of Clinical safety, the table for SAEs list 97 subjects (combined protocols 208 and 091) experienced an SAE, but this differs from totals from each protocol’s CSR. In Protocol 097, 13 subjects had SAEs (10 in aprepitant and 3 in control). In protocol 208, 87 subjects had SAEs (46 subjects in the aprepitant regimen; 41 subjects in the control regimen). Therefore, the total number of SAEs is 100. Please provide clarification on discrepancy and update tables as needed.

We request to receive your response to this information request to both the sNDA and NDA as soon as it could be provided.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products

Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350

Phone: 301-796-0260 /fax: 301-796-9904

[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
08/10/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Wednesday, July 22, 2015 4:58 PM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Emend (aprepitant) - Clinical Information Request

Nick,  
Reference is made to your New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

Reference is made to information sent July 21, 2015, containing your proposal. We have the following request for additional information:

Please submit tabular summary (similar to Table 2 on page 6 of your July 21st submission) for caregiver user errors from the first and second human factor studies. Please include the column titled "impact on dose accuracy". Also include a table that summarizes the percentages of overdose and under dose (0-5%, 5-10%, >10%) stratified by pharmacist, nurse, and caregiver.

We request to receive a response to the above by COB Thursday July 23, 2015 to the NDA.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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/s/  
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MARY H CHUNG  
07/22/2015

## Chung, Mary

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**From:** Chung, Mary  
**Sent:** Tuesday, July 21, 2015 10:30 AM  
**To:** Andrew, Nicholas W. (nicholas\_andrew@merck.com)  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 and NDA 21549 S-025 Emend (aprepitant)- Clinical Information Request

Nick,  
Reference is made to your Supplemental New Drug Application (sNDA) dated and received July 28, 2014 and New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

We have the following request for additional information:

1. What percentage of patients age 6 months to < 12 years receive multi-day chemotherapy, and of that number, what percentage receive chemotherapy for all days at a health care facility?
2. What percentage of patients age 6 months to <12 years in Protocol 208 received multi-day chemotherapy and received the multi-day chemotherapy at a health care facility?

We request to receive your response to this information request to both the sNDA and NDA as soon as it could be provided.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
07/21/2015



NDA 207865

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.  
Attention: Nicholas W. Andrew  
Director, Regulatory Affairs  
126 E. Lincoln Avenue  
P.O. Box 2000, RY 33-200  
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your New Drug Application dated March 26, 2015, received July 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for EMEND (aprepitant) Powder for Suspension.

We also refer to your amendments dated October 31, 2014; January 8, 2015; March 6, 2015; March 11, 2015; March 12, 2015; and April 10, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 26, 2015.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Division Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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DONNA J GRIEBEL  
06/10/2015



NDA 207865

**PRIORITY REVIEW DESIGNATION**

Merck Sharp & Dohme Corp.  
Attention: Nicholas W. Andrew  
Director, Regulatory Affairs  
126 E. Lincoln Avenue  
P.O. Box 2000, RY 33-200  
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your New Drug Application dated March 26, 2015, received July 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for EMEND (aprepitant) Powder for Suspension.

We also refer to your submissions dated October 31, 2014; January 8, 2015; March 6, 2015; March 11, 2015; March 12, 2015; and April 10, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 26, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 2, 2015.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before June 8, 2015.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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DONNA J GRIEBEL  
05/19/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 Emend (aprepitant)- HF Study Protocol  
**Date:** Monday, May 18, 2015 3:54:06 PM  
**Attachments:** [aprepitant \(EMEND for Oral Suspension\) NDA 207865 IFU May-2015 marked.pdf](#)  
[aprepitant \(EMEND for Oral Suspension\) NDA 207865 IFU May-2015 clean.pdf](#)  
[aprepitant \(EMEND for Oral Suspension\) NDA 207865 IFU May-2015 marked.docx](#)  
[aprepitant \(EMEND for Oral Suspension\) NDA 207865 IFU May-2015 clean.docx](#)

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Nick,

Reference is made to your NDA 207865 Emend (aprepitant) Powder for Suspension submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We also refer to your May 12, 2015 human factors study protocol submitted to the referenced IND 50283 Emend (aprepitant) responding to our May 1, 2015 comments and recommendations. We have the following and attached comments and recommendations to your May 12, 2015 submission.

We recommend these comments be implemented prior to the start of the human factor validation study.

**A. Kit:**

Ensure that the 5 mL oral dispenser is calibrated in mL, not in (b) (4) as mentioned in the protocol on page 16 and the (b) (4) marking should be replaced with the 5mL marking.

**B. Instructions for Use: See attached IFU Recommendations and Revisions.**

**C. Study Design:**

1. Ensure that the moderator will document the actual volume of water measured during the reconstitution and solution measured during dosing so the significance of overdose or under dose can be measured. Additionally, document instances when the moderator guides the participant to use the IFU.
2. After the untrained first use simulation, rather than asking the participants to draw up and measure one additional dose, ask them to draw up two additional doses of both 0.6mL and 3.2 mL to ensure the data is robust.
3. Change the “empty the mixing cup” task (Task 1c) from essential to critical. The measuring cup has a 30 mL volume capacity and if this task is not completed, the reconstituted volume could potentially be six times the intended volume, thus changing the final concentration of the product drastically.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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

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/s/

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MARY H CHUNG  
05/18/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 & NDA 21549 Emend (aprepitant) - Information Request/ Clinical Pharmacology  
**Date:** Thursday, May 14, 2015 4:50:09 PM

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Nick,

Reference is made to your NDA 207865 and NDA 21549/S-025 Emend (aprepitant) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We have the following request for additional information:

In your base and final population PK model, the effect of age on drug clearance was modeled with fixed values adapted from the publication by Johnson, 2006. The effect of body weight was also fixed with allometric scaling. Please justify why the parameters describing the effect of age and weight on clearance were fixed. If data allows, you should have data drive these parameter estimates rather than fixing them. In addition, your final model should be evaluated (GOF plots) in each age sub-groups, especially the youngest age subgroup (e.g. 0.5-2 years).

Please provide your response to both applications by May 20, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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/s/  
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MARY H CHUNG  
05/15/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 and NDA 21549 S-025 Emend (aprepitant) - FDA Proposed PI  
**Date:** Friday, May 15, 2015 7:29:06 AM  
**Attachments:** [Emend PI FDA Comments 5-15-15 Clean Copy.pdf](#)  
[Emend PI FDA Comments 5-15-15 Tracked Changes.pdf](#)  
[Emend PI FDA Comments 5-15-15 Clean Copy.doc](#)  
[Emend PI FDA Comments 5-15-15 Tracked Changes.doc](#)

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Nick,

Reference is made to your Supplemental New Drug Application (sNDA) dated and received July 28, 2014 and New Drug Application received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (aprepitant) capsule.

On February 27, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by June 8, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,

Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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

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/s/  
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MARY H CHUNG  
05/15/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](#)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 Emend (aprepitant) Powder for Suspension  
**Date:** Thursday, April 30, 2015 5:00:45 PM

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Nick,

Reference is made to your NDA 207865 Emend (aprepitant) Powder for Suspension submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We have the following comments and recommendations.

**A. Kit- mixing cup:**

Most of the critical use errors observed in the Human Factors Study (HFS) 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 were not intuitive or clear and the IFU was not easy to follow and listed that they read the IFU vertically (i.e., Steps 1, 3, 5). 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 (b)(4) 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. However, on March 6, 2015, you informed us that your proposed commercial product will only include the 5 mL oral dispenser in order to avoid selection errors in measuring out doses. 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 with 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.<sup>[1]</sup> 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 critical tasks under reconstitution, you marked this step as a failure only if the clumps were present in the mixture and the participant did not 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.

[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.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
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[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.

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MARY H CHUNG  
05/01/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 & NDA 21549 Emend (aprepitant) - Information Request/ Clinical Pharmacology  
**Date:** Friday, April 03, 2015 10:24:05 AM

---

Nick,

Reference is made to your NDA 207865 and NDA 21549/S-025 Emend (aprepitant) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We have the following request for additional information:

Reference is made to section 5.3.5.3 of your applications.

1. Please submit the input dataset used for your simulation, which should include the demographic data for the pre-defined age range specified in "Section 5.7. Simulation" of your PopPK study report (Page 29).
2. For Figure 15 of your PopPK study report (Page 146), please overlay the simulated data with observed individual data. Please submit the code for generating the figures for the simulation results.

Please provide this information to both applications by April 9, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
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MARY H CHUNG  
04/03/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 Emend (aprepitant) Powder for Suspension - Clinical Information Request  
**Date:** Monday, March 09, 2015 2:12:20 PM

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Dear Nick,

Reference is made to your NDA 207865 Emend (aprepitant) Powder for Suspension submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We have the following request for additional information:

“You have stated on Page 12 of the Human Factor Study results section that tasks 2f and 2g are critical tasks. However, footnote 4 indicates that only presence of lumps are counted as failures. Please provide the study results related to these two tasks.”

We request to receive a response to the above by Friday March 13, 2015.

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
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MARY H CHUNG  
03/09/2015

**From:** [Bugin, Kevin](#)  
**To:** "[nicholas\\_andrew@merck.com](mailto:nicholas_andrew@merck.com)"  
**Cc:** [Chung, Mary](#); [Bugin, Kevin](#)  
**Subject:** NDA 207865 EMEND (aprepitant) - Request for Information (Human Factors) - March 04, 2015  
**Date:** Wednesday, March 04, 2015 2:59:36 PM

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Hi Nick,

I am covering for Mary Chung this week.

Please refer to New Drug Application for Emend (aprepitant) Powder for Suspension, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We are reviewing your human factors validation information and have the following request for additional information. We request that you respond to this request no later than March 06, 2015.

- Please provide a sample of the oral suspension kit for our review. To clarify, the kit should reflect the commercial product that is intended to be used in the marketplace and the one that was used in the human factors validation testing.

You should mail the kit to Mary at the following address:

10903 New Hampshire Avenue,  
White Oak Bldg. 22, Room 5350  
Silver Spring, Maryland 20903

If you have any questions, please do not hesitate to contact us.

Kind regards,

**Kevin B Bugin, MS, RAC**

Senior Regulatory Health Project Manager | Division of Gastroenterology and Inborn Errors  
Products | Office of Drug Evaluation III | CDER | FDA  
P-301-796-2302 | F-301-796-9904 | 10903 New Hampshire Ave, WO22-RM5232, Silver Spring, MD  
20903 | [kevin.bugin@fda.hhs.gov](mailto:kevin.bugin@fda.hhs.gov) | [www.fda.gov](http://www.fda.gov)

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KEVIN B BUGIN  
03/04/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](#)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 Emend (aprepitant) Powder for Suspension- Clinical Information Request  
**Date:** Thursday, February 05, 2015 12:32:32 PM

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Dear Nick,

Reference is made to your NDA 207865 Emend (aprepitant) Powder for Suspension submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act.

We have the following request for additional information:

Submit safety and efficacy data and analyses for the subset of patients < 12 years of age. The re-analyses should address the following:

1. Analyses of primary and secondary endpoints along with the submission of the programs and datasets used to perform the analyses.
2. Pooled safety analyses from all submitted trials (all cycles) for the subset of patients < 12 years of age, including (but not limited to) the following:
  - a. Overall extent of exposure
  - b. Demographic and other characteristics of study population (efficacy and safety populations)
  - c. Analysis of adverse experiences
  - d. Common adverse events
  - e. Deaths, withdrawals/discontinuations, serious adverse events (narratives for all serious adverse events should be provided whether considered related to the study drug or not)
  - f. Clinical laboratory evaluations

Regards,

Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350

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/s/  
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MARY H CHUNG  
02/05/2015

**From:** [Chung, Mary](#)  
**To:** [Andrew, Nicholas W. \(nicholas\\_andrew@merck.com\)](mailto:nicholas_andrew@merck.com)  
**Cc:** [Chung, Mary](#)  
**Subject:** NDA 207865 Emend (aprepitant) Powder for Suspension  
**Date:** Friday, November 07, 2014 5:09:31 PM

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Dear Nick,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emend (aprepitant) Powder for Suspension, submitted July 25, 2014.

Additional reference is made to the "Instructions for Use" submission. We have the following comments and recommendations:

1. You have not included a systematic evaluation of use-related risk, a determination of the necessity of human factors (HF) validation and, if necessary, how to address the human factors validation. We will need this information to assess if the patients or caregivers can adequately understand the instructions, follow the procedure, and achieve consistent drug delivery without medication error.

This risk analysis of user tasks should include a comprehensive evaluation of all the steps involved in the preparation of the dose, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. In addition, provide summary results of all your formative testing, the modifications that were made, and discuss how these studies informed labeling.

2. Your "Instructions for Use" directs patient caregiver to fill the mixing cup and then measure the required amount of water (4.6 mL) in the syringe dispenser, discard remaining amount and then pour the measured amount back into the mixing up (steps 3 through 6). We recommend you provide a marking of 4.6 mL on the mixing cup for the fill volume to simplify steps 3 through 6 (b) (4).

3. Step 10 states, "(b) (4)". Please clarify what would result, if this step is not performed as recommended.

4. Additional Comments

- a. Applicant should center heading.
- b. Remove the heading and "(b) (4)" from the text boxes. Left justify "(b) (4)" using bullets.
- c. Re-format the Instructions for Use in 1 column, with figures directly following the pertinent text, or in 2 columns with text in the left column and figures in the right column, adjacent to the pertinent text. 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).
- d. We recommend that (b) (4) be referred to as "5 mL oral dosing syringe" throughout the IFU for easier patient understanding.
- e. Include a figure that details each part of the 5mL dispenser (syringe) that is referenced in the IFU, for example the plunger, barrel, syringe tip, and measuring ring. The numbering and markings on the barrel of the syringe, including the 4.6 mL marking, should be identified.

- f. Patient instructions that are sequential should be noted as Step 1, Step 2, etc.
- g. If the IFU will not be attached to the PPI, include the following at the end of the IFU:
  - 1. Storage instructions exactly as written in the PPI
  - 2. “This Instructions for Use has been approved by the U.S. Food and Drug Administration.”
  - 3. Manufacturer’s name and address
  - 4. Issued: Month Year
- h. If the IFU will be attached to the PPI, include the following at the end of the IFU:
  - 1. “This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.”
  - 2. Manufacturer’s name and address
  - 3. Issued: Month Year

Regards,  
Mary

Mary Chung, PharmD.  
Regulatory Health Project Manager  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350  
Phone: 301-796-0260 /fax: 301-796-9904  
[mary.chung@fda.hhs.gov](mailto:mary.chung@fda.hhs.gov)

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MARY H CHUNG  
11/07/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 207865

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corporation  
126 E. Lincoln Avenue  
P.O. Box 2000, RY 33-200  
Rahway, NJ 07065-0900

ATTENTION: Nicholas W. Andrew  
Director, Regulatory Affairs

Dear Mr. Andrew:

Please refer to your New Drug Application (NDA) dated and received July 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aprepitant for Oral Suspension, 125 mg.

We also refer to your correspondence, dated and received August 8, 2014, requesting review of your proposed proprietary name, Emend. We have completed our review of the proposed proprietary name, Emend, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your August 8, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Mary Chung, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0260.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
10/03/2014

**Tran-Zwanetz, Catherine**

---

**From:** Tran-Zwanetz, Catherine  
**Sent:** Tuesday, August 19, 2014 5:54 PM  
**To:** 'Andrew, Nicholas W.'  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 CMC IR

Hello Mr. Andrew,

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please submit a revised FDA Form 356h to include all manufacturers of the (b) (4) (b) (4) that will be used for the manufacture of the drug substance for the manufacture of the to-be-marketed product. Indicate whether each facility is ready for inspection. Provide a statement that DMF (b) (4) is no longer referenced for the said NDA if (b) (4) no longer supplies the (b) (4).
2. Provide the name of the manufacturer for the (b) (4) for the manufacture of all clinical and registration batches of the drug substance.

Please reply by COB Thursday, August 21 and feel free to contact me with any questions.

Cathy

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/s/  
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CATHERINE A TRAN-ZWANETZ  
09/17/2014

## Tran-Zwanetz, Catherine

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**From:** Tran-Zwanetz, Catherine  
**Sent:** Friday, September 05, 2014 2:15 PM  
**To:** 'Andrew, Nicholas W.'  
**Cc:** Chung, Mary  
**Subject:** NDA 207865 Chemistry Information Request

Hello Nick,

Here is a new information request:

You reported that the dissolution occurs instantaneously upon immersion the powder for suspension into the dissolution medium due to the (b) (4) DS (drug substance), however, the dissolution medium employed was the one previously approved for Emend capsules (b) (4). Therefore, the dissolution method employed may not be considered discriminatory.

Since this is a new NDA and a new formulation, you need to submit a dissolution method development report (with or without surfactant) for the proposed new dissolution method with supportive dissolution profile data in the submission for review. Once the discriminatory dissolution method is finalized, provide also the comparative dissolution profiles of the following batches: 2008 clinical batch, 2011 clinical batch, biobatch, FSS 1, FSS 2, and (b) (4) batches using the proposed dissolution method.

Please submit this information as soon as possible and acknowledge the receipt of this email.

Thanks!  
Cathy

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/s/  
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CATHERINE A TRAN-ZWANETZ  
09/17/2014