

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-023

CHEMISTRY REVIEW(S)

Memorandum to File

Date: January 25, 2008

From: Marie Kowblansky, PhD, Pharmaceutical Assessment Lead, ONDQA, Division 2

Through: Moo-Jhong Rhee, Branch Chief, ONDQA, Division 2

Re: NDA 22-023 Final Labeling

In response to FDA recommendations, Merck has submitted the following revisions to the carton and vial labels and to the package insert. All revisions are as requested, and consequently, acceptable.

Since the last CMC review recommended approval of the NDA pending resolution of labeling issues, from the CMC perspective the NDA may now be approved.

Vial Label:

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2 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Marie Kowblansky
1/28/2008 09:35:53 AM
CHEMIST

Moo-Jhong Rhee
1/28/2008 09:59:29 AM
CHEMIST
Chief, Branch III

NDA/ANDA 22-023

EMEND® IV (Fosaprepitant dimeglumine)

Merck Research Laboratories

Division of Gastroenterology Products

Julia C. Pinto, Ph.D.

**Branch VII, Post Marketing Division IV
Office of New Drug Quality Assessment**

**For
Branch III, Pre-Marketing Division II, ONDQA**



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Chemistry Review Data Sheet

1. NDA 22-023
2. REVIEW #: 2
3. REVIEW DATE: October 25, 2007
4. REVIEWER: Julia C. Pinto, Ph.D.
5. Previous Documents:

Previous Documents

Document Date

Original NDA	March 31, 2006
Amendment	September 29, 2006
Amendment	December 7, 2006
Amendment	December 8, 2006
Amendment	February 21, 2007
Amendment	March 21, 2007

6. SUBMISSION BEING REVIEWED:

Amendment	July 27, 2007
Amendment	September 28, 2007

7. NAME AND ADDRESS OF APPLICANT:

Name: Merck & Co., Inc
Address: 770 Sumneytown Pike
PO Box 4, BL A-20
West Point, PA 19486

Representative: Vijay Tammara, Ph.D., Director Regulatory Affairs-Domestic
Telephone: 484 344 3180

8. Product Drug Code and Name:

- a) Proprietary Name: EMEND (proposed)
- b) Non-Proprietary Name (USAN): Fosaprepitant dimeglumine
- c) Code name/(ONDQA only): MK-0517 and L-00758298
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 2
 - Submission Priority: S

CHEMISTRY REVIEW

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

antiemetic; chemo induced nausea and vomiting (CINV)

11. DOSAGE FORM: lyophilized powder for injection

12. STRENGTH/POTENCY: 115mg/ml

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

a) 1-deoxy-1-(methylamino)-D-glucitol [3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt)

b) D-Glucitol, 1-deoxy-1-(methylamino)-[3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt)

c) bis(1-deoxy-1-(methylamino)-D-glucitol)[3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate

CAS Numbers: 265121-04-8

Molecular Formula: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$

MW = 1004.83

Mass of free base: _____

b(4)

17. RELATED/SUPPORTED DOCUMENTS:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status ²	DATE REVIEW COMPLETE	COMMENTS
14141	V	DSM	Fill Process	1	Adequate	11/20/2006 A. Lolas, Ph.D.	

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-549	EMEND® (Aprepitant) Capsules

18. Status

ONDQAQ:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	May 10, 2006	J. Dambrogio
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Adequate	July 27, 2007	J. Pinto
DMET/DDMAC	NA		
EA	Categorical exclusion satisfactory	March 2007	J. Pinto
Microbiology	NA		

The Chemistry Review for NDA 22023

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the chemistry, manufacturing, and controls, perspective, this application is recommended for approval, pending resolution of the final labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

No post approval commitments are required at the present time.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

Fosaprepitant dimeglumine for injection is a sterile, lyophilized formulation intended for treatment of chemotherapy induced nausea and vomiting (CINV), as a substance P/neurokinin 1 (NK1) antagonist. The active pharmaceutical ingredient (API) is a phosphorylated form of aprepitant (EMEND® Approved NDA 21549), which is a water soluble prodrug. Following intravenous infusion of the reconstituted product, fosaprepitant is rapidly converted to aprepitant. The synthesis of the drug substance begins with the phosphorylation of aprepitant. The manufacture of aprepitant is referenced to NDA 21-549. Fosaprepitant dimeglumine is hygroscopic and must be stored at -20C to avoid degradation to aprepitant. Because of the insolubility of aprepitant in water, a specification has been set for the amount of aprepitant NMT

Since fosaprepitant is hygroscopic and requires _____ was chosen as the reference standard. Up to eighteen months of stability data at 5°C are provided in support of a _____ retest period for the drug substance.

The drug product is a sterile lyophilized formulation that includes polysorbate 80 _____

During the scale-up process, the drug product's moisture content at release, did not meet drug product moisture specification. To address this issue, the applicant made some modifications to the _____ ascribed in more detail, in section P. 3.3). Three of the four batches made with the modified process, did meet the release specification for the moisture. However the applicant noted that there was some process variation from batch to batch which results in lower end of assay results for drug product testing. Thus they have informed the Agency that further modifications to the manufacturing process are needed and the full validation report would not be available until after the PUDFA date of May 3, 2007. As of the Amendment filed July 27, 2007, the manufacturing process and analytical methods are fully validated.

CHEMISTRY REVIEW

Executive Summary Section

B. Description of How the drug is intended to be used:

The currently approved aprepitant is used in a 3 day oral regimen to treat Chemotherapy-Induced Nausea and Vomiting (CINV). Fosaprepitant is to substitute oral aprepitant 125mg on Day 1 of the currently approved 3 day dosing. EMEND-IV, 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

The solution is prepared as follows:

below 25°C).

C. Basis for Approvability or Not-Approval Recommendation

The drug substance manufacturing process, controls are adequate. The specifications for the drug substance and drug product are adequate as are the reference standards and analytical methods. The facility inspections are satisfactory. The manufacturing process and analytical methods are fully validated with sufficient batches and stability data to assure the quality of the drug product and support the proposed expiry of 24 months.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.
Chemistry Team Leader: Marie Kowblansky, Ph.D.
Project Manager: Giuseppe Randazzo

C. CC Block

3 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Julia Pinto
12/12/2007 04:41:34 PM
CHEMIST

Moo-Jhong Rhee
12/13/2007 09:22:50 AM
CHEMIST
Chief, Branch III

NDA/ANDA 22-023

EMEND® IV (Fosaprepitant dimeglumine)

Merck Research Laboratories

Division of Gastroenterology Products

Julia C. Pinto, Ph.D.

**Branch VII, Post Marketing Division IV
Office of New Drug Quality Assessment**

**For
Branch III, Pre-Marketing Division II, ONDQA**

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-023
2. REVIEW #: 1
3. REVIEW DATE: February 21, 2007
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

N/A

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed

Original NDA
Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

March 31, 2006
September 29, 2006
December 7, 2006
December 8, 2006
February 21, 2007
March 21, 2007

7. NAME AND ADDRESS OF APPLICANT:

Name: Merck & Co., Inc
Address: 770 Sumneytown Pike
PO Box 4, BL A-20
West Point, PA 19486

Representative: Vijay Tammara, Ph.D., Director Regulatory Affairs-Domestic
Telephone: 484 344 3180

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. Product Drug Code and Name:

- a) Proprietary Name: EMEND (proposed)
- b) Non-Proprietary Name (USAN): Fosaprepitant dimeglumine
- c) Code name/#(ONDQA only): MK-0517 and L-00758298
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

antiemetic; chemo induced nausea and vomiting (CINV)

11. DOSAGE FORM: lyophilized powder for injection

12. STRENGTH/POTENCY: 115mg/ml

13. ROUTE OF ADMINISTRATION: intravenous infusion

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15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

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Chemical Name:

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

b) D-Glucitol, 1-deoxy-1-(methylamino)-[3-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1) (salt)

c) bis(1-deoxy-1-(methylamino)-D-glucitol)[3-{{(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate

CAS Numbers: 265121-04-8

Molecular Formula: C₂₃H₂₂F₇N₄O₆P · 2(C₇H₁₇NO₅)

MW = 1004.83

Mass of free base: _____

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			Fill Process				

b(4)

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6 – DMF not available

7 – Other (explain under "Comments")

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-549	EMEND® (Aprepitant) Capsules

18. Status

ONDQAQ:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	May 10, 2006	J. Dambrogio
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	To Be Validated		
DMET/DDMAC	NA		
EA	Categorical exclusion satisfactory	March 2007	J. Pinto
Microbiology	NA		



Executive Summary Section

The Chemistry Review for NDA 22023

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability – Pending.

From the Chemistry Perspective, this application is approvable pending resolution of the following deficiencies :

- 1) The Applicant has informed the Agency that the drug product production process is not considered robust and will require further process improvement changes... 2) To date, only 1 month of stability data on three batches of drug product manufactured with the modified lyophilization process, has been submitted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

No Post Approval commitments are required at the present time.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

Fosaprepitant dimeglumine for injection is a sterile, lyophilized formulation intended for treatment of chemotherapy induced nausea and vomiting (CINV). It is a substance P/neurokinin 1 (NK1) antagonist. The active pharmaceutical ingredient (API) is the phosphorylated form which is a water soluble prodrug of aprepitant (EMEND® Approved NDA 21549). Following intravenous infusion of the reconstituted product, fosaprepitant is rapidly converted to aprepitant. The synthesis of the drug substance begins with the phosphorylation of aprepitant. The manufacture of aprepitant is referenced to NDA 21-549. Forsaprepitant dimeglumine is hygroscopic and must be stored at -20C to avoid degradation to aprepitant. Because of the insolubility of aprepitant in water, a specification has been set at — Since Fosaprepitdn is hygroscopic and requires — was chosen as the reference standard. Twenty Four months of stability data are provided in support of a — retest period for the drug substance.

b(4)

The drug product is a sterile lyophilized formulation that includes polysorbate 80 — :

└

b(4)

└

During the scale-up process, the drug product's moisture content at release, did not meet drug product moisture specifications. To address this issue, the Applicant made some modifications to the [redacted] (described in more detail, in section P. 3.3). Three of the four batches made with the modified process, did meet the release specification for moisture. However the Applicant noted that there was some process variation from batch to batch with the assay results for drug product testing being at the lower end of the assay specification. Thus they have informed the Agency that further modifications to the manufacturing process are needed and the full validation report would not be available until after the PUDFA date of May 3, 2007.

b(4)

b(4)

B. Description of How the drug is intended to be used:

The currently approved aprepitant is used in a 3 day oral regimen to treat Chemotherapy-Induced Nausea and Vomiting (CINV). Fosaprepitant is to substitute oral aprepitant 125mg on Day 1 of the currently approved 3 day dosing. EMEND-IV (115 mg) may be substituted for EMEND (125 mg), 30 minutes prior to chemotherapy, on Day 1 only of the CINV regimen as an infusion administered over 15 minutes.

The solution is prepared as follows:

b(4)

below 25°C).

C. Basis for Approvability or Not-Approval Recommendation

The drug substance manufacturing process, controls are adequate. The Specifications for the drug substance and drug product are adequate as are the reference standards and analytical methods. The Facility Inspections are satisfactory. However, the manufacturing process of the drug product is not adequately established with the supporting data. Therefore, this application is Approvable until the manufacturing process is satisfactorily established.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Julia Pinto, Ph.D.
 Chemistry Team Leader: Marie Kowblansky, Ph.D.
 Project Manager: Giuseppe Randazzo

C. CC Block

67 Page(s) Withheld

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Julia Pinto
4/16/2007 10:13:49 AM
CHEMIST

Moo-Jhong Rhee
4/16/2007 10:28:38 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

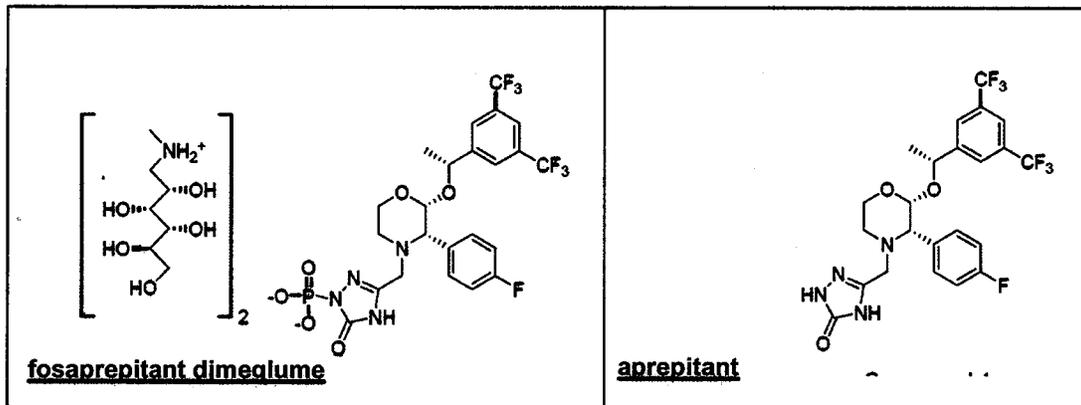
OND Division: Division of Gastroenterology Products
NDA: 22-023
Applicant: Merck
Stamp Date: 3/31/2006
Received by PAL: 4/17/2006
Review Date: 5/11/2006
PDUFA Date: 2/3/2007
Filing Meeting: 6/2/2006
Proposed Trademark: To be determined
Established Name: Fosaprepitant Dimeglumine
Dosage Form: Lyophilized powder
Route of Administration: Intravenous infusion
Indication: antiemetic

PAL: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

Fosaprepitant Dimeglumine for Injection is a sterile, lyophilized formulation intended for treatment of chemotherapy-induced nausea and vomiting (CINV). The active component in this product is fosaprepitant dimeglumine, which is a phosphorylated prodrug of aprepitant (approved for use in EMEND® Capsules, NDA 21-549).



Since aprepitant is the physiologically active moiety in fosaprepitant, a decision has been made by ONDQA that fosaprepitant dimeglumine would not be classified as a new molecular entity, but as a Type II molecule. The considerations that led to this decision are discussed in the e-mail from Dr. Moo-Jhong Rhee that is appended to this document.

2 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

5/11/2006
Date

Moo-Jhong Rhee, PhD
Branch Chief

5/11/2006
Date

Drug Substance:

Manufacture, packaging and release testing:
Laboratories Merck Sharp & Dohme-Chibret
Zone Industrielle de Blavozy
43700 Saint-Germain Laprade
France
ERN 3002195826

Stability testing:
Merck & Co., Inc.
4633 Merck Rd.
Wilson, NC 27893
ERN 1036761

Drug Product

Manufacturing, Primary Packaging
DSM Pharmaceuticals, Inc.
5900 NW Greenville Blvd.
Greenville, NC 27834
DER #1018495

Secondary Packaging:
Merck & Co., Inc.
770 Summeytown Pike
West Point, PA 19486-0004
CFN/DER # 2510592

Release and Stability Testing:
Merck & Co., Inc.
770 Summeytown Pike
West Point, PA 19486-0004
CFN/DER # 2510592

As stated in the application, "Aside from primary packaging at DSM, there are no contract labelers or packagers. There are also no contract laboratories. The facilities listed above will be ready for inspection at the time this application is submitted to the United States Food and Drug Administration (FDA)."

b(4)

From: Rhee, Moo Jhong
Sent: Thursday, March 16, 2006 4:25 PM
To: Harvey, Brian
Cc: Strongin, Brian K; Scroggs, Betsy; Korvick, Joyce A; Gallo Torres, Hugo E; Della'Zanna, Gary; Kowblansky, Marie; Toyer, Denise P; Toyer, Denise P; Thomas, Maria R (CDER/DMETS); Dallas, Scott; Nasr, Moheb M; Chen, Chi-Wan; Poochikian, Guiragos K; Morefield, Elaine; Rhee, Moo Jhong
Subject: RE: IND 48,924 - (fosaprepitant) Tradename meeting issues to resolve by 3/15/2006 PDUFA GOAL DATE

Dear Dr. Harvey,

The distinction between Type I and Type II of a drug substance is based on whether the **active moiety** has ever been approved or not (MAPP 7500.3).

The **active moiety** is defined as a molecule or ion excluding those appended portions of the molecule that cause the drug to be an ester, salt or other noncovalent derivative of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108).

The subject drug substance, fosaprepitant dimeglumine, is a **phosphamide** derivative of the previously approved drug substance, **aprepitant**. It is further appended with dimeglumine to make a salt. However, when this molecule is administered via injection, it undergoes hydrolysis *in vivo* and gives rise to the same active moiety of the previously approved **aprepitant**. Per the MAPP cited above, fosaprepitant diglumine can be classified as Type II.

The dilemma for this prodrug in assigning Type I or Type II, arises from the fact that in the definition of the active moiety in the regulation, the examples of the appended portions do not include **phosphamide**, thereby making it difficult to apply the regulation to this molecule. From a scientific perspective as well as in the spirit of the regulation, any form of the appended portions of the molecule should have been included in the regulation, if the appended portions are known to be removed *in vivo*.

Based on these arguments, ONDQA has decided that fosaprepitant dimeglumine should be classified as Type II.

Moo-Jhong

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Division II
Office of New Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

Marie Kowblansky
5/11/2006 02:34:43 PM
CHEMIST

Moo-Jhong Rhee
5/11/2006 05:26:21 PM
CHEMIST
Chief, Branch III

oc report n22023.txt

Responsibilities:

b(4)

Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-JUN-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9613821 FEI : 3003121602
LABORATOIRES MERCK SHARP AND DOHME CHIBRET
43700 ST GERMAIN LAPRADE, LE PUY EN VALEY, FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile : CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 25-MAY-06

Establishment : CFN : 1036761 FEI : 1036761
MERCK AND CO INC