

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-106

CHEMISTRY REVIEW(S)

NDA 22-106

Doribax (doripenem for injection, 500mg)

**Johnson & Johnson Pharmaceutical Research &
Development, L.L.C**

Lin Qi, Ph.D.
Office of New Drug Quality Assessment
for
Division of Anti-Infective and Ophthalmology Product

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A APPENDICES.....	Error! Bookmark not defined.
R REGIONAL INFORMATION	Error! Bookmark not defined.
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	Error! Bookmark not defined.
A. Labeling & Package Insert.....	Error! Bookmark not defined.
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III. List Of Deficiencies To Be Communicated	Error! Bookmark not defined.

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 22-106
2. REVIEW #: 2
3. REVIEW DATE: October 9, 2007
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

Dec 12, 2006

Amendment

May 30, 2007

Amendment

July 2, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson Pharmaceutical Research & Development, L.L.C

Address: 920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Representative: George Marchesini (CMC issues)

Telephone: 908-704-5389

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Doribax
b) Non-Proprietary Name (USAN): Doripenem for Injection
Code Name/#: JNJ-38174942-ZAF, S-4661
c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Antibiotics

11. DOSAGE FORM: Powder for Injection

12. STRENGTH/POTENCY: 500 mg (anhydrous basis)/vial

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

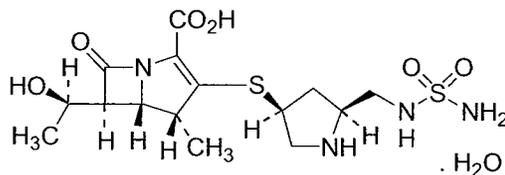
Not a SPOTS product

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

Chemical Name (IUPAC): (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-[[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate

Chemistry Review Data Sheet

Structural formula:

Molecular formula: C₁₅H₂₄N₄O₆S₂·H₂O

Relative molecular mass/molecular weight: 438.52

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	4			
	III	/	--	3	Adequate	07-Feb-2006	

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
IND	64,416	Doripenem for Injection, filed on Dec 2, 2002
Orphan	04-1881	Doripenem for Injection, filed on Apr 16, 2004

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	10/9/07	EES report
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	A Categorical Exclusion Claimed	10/9/07	Lin Qi
Sterility Assurance	Acceptable	9/28/07	John Metcalfe

The Chemistry Review for NDA 22-106

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the quality assessment, this application is recommended for an approval action.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Doripenem drug substance is a sterile white to slightly yellowish, off-white crystalline powder synthesized using an _____ technique. The drug substance exists in the form of monohydrate with _____

_____. Doripenem monohydrate is soluble in _____

_____. The pH of its 10 mg/mL aqueous solution is _____. _____ is not hygroscopic. The specific optical rotation of doripenem in water (10 mg/mL on anhydrous basis) at 20°C is +34.9° - +36.1°.

The structure of doripenem was elucidated by _____

_____. The attributes controlled in release testing include appearance, identification by _____ specific rotation, clarity and color of solution, _____ assay of doripenem, chromatographic purity (specified impurities, unspecified impurities, and total impurities), residual solvents, _____, water content, particulate matter test for injections, _____, bacterial endotoxins, and sterility.

The drug substance is stored inside two containers. The primary product-contact container is a _____, bag that is then placed inside a secondary container, a _____ container.

An expiry dating period of 24 months when stored at 2–8 °C is proposed, and is acceptable for doripenem drug substance based on 24 months stability data.

Executive Summary Section

Drug Product:

Doripenem for injection (500 mg) is provided as single-use vials containing 500 mg of sterile powder for constitution. It is manufactured by filling bulk drug substance powder into clear Type I glass vials. The drug product does not contain excipients.

The attributes controlled in release testing include appearance, identification by clarity and color of solution, assay of doripenem, specified degradation products, individual degradation products, total degradation products, water content, weight variation, particulate matter test for injections, bacterial endotoxins, and sterility.

The drug product will be packaged in a glass vial, stoppered with an closure, and sealed with an aluminum crimp seal with a plastic flip-off cap.

A shelf life of 24 months at room temperature is proposed for the drug product based on 12 months stability data. Based on this data, the proposal is acceptable.

B. Description of How the Drug Product is Intended to be Used

The recommended dose of the drug product is 500 mg administered every 8 hours by intravenous infusion over one hour.

At the time of administration, the drug product is constituted with 10 mL of Water for Injection, USP or Sodium Chloride Injection, USP, and is shaken to form a suspension. The suspension is then withdrawn using a 21-gauge needled syringe and added to a polyvinylchloride (PVC) infusion bag containing 100 mL of Sodium Chloride injection, USP, or Dextrose Injection, USP to achieve a final dosing concentration of mg/mL. The Baxter Minibag Plus® delivery system may alternatively be used to prepare doripenem for injection (500 mg) solution.

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, the drug product suspension in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

The infusion solution is stable in PVC and Baxter Minibag Plus® infusion bags for at controlled room temperature and at refrigerated temperature in Sodium Chloride for Injection, USP, and 4 hours at controlled room temperature and at refrigerated temperature in Dextrose Injection, USP, respectively.

Constituted drug product suspension or drug product infusion should not be frozen.

C. Basis for Approvability or Not-Approval Recommendation

The sterilized drug substance is synthesized through . Adequate information is provided on the synthesis and process controls, drug substance characterization, characterization of impurities, specification, container closure system, and stability studies.

Executive Summary Section

Issues regarding inappropriate starting material controls were resolved during the review process.

The drug product is manufactured by _____ of the bulk _____ drug substance. Adequate information is provided on manufacturing process and process controls, container closure system, and stability studies. Additional information on specification justification and the dissolution time during constitution were provided during the review process. The results demonstrated that the drug product is appropriately controlled.

The microbiological processes and process controls were found acceptable by Dr. John Metcalfe in his product quality microbiological review dated September 28, 2007.

The overall recommendation for establishment inspection is acceptable in October 9, 2007. See the inspection report in the chemistry assessment section.

III. Administrative

A. Reviewer's Signature

Lin Qi (Signed and dated in DFS)

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryBranchChiefName/Date
ProjectManagerName/Date
(Information in DFS)

C. CC Block

Information in DFS

6 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

Lin Qi
10/10/2007 12:49:51 PM
CHEMIST

Norman Schmuff
10/11/2007 06:32:16 AM
CHEMIST

MEMORANDUM

Date: October 5, 2007

To: NDA 22-106

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-106 Doribax (Doripenem for injection, 500 mg)

I have assessed the ONDQA review of NDA 22-106 and concur with the approval recommendation from a CMC perspective.

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/s/

Elaine Morefield
10/10/2007 10:20:42 AM
CHEMIST

NDA 22-106**Doribax (doripenem for injection, 500mg)****Johnson & Johnson Pharmaceutical Research &
Development, L.L.C****Lin Qi, Ph.D.**
Office of New Drug Quality Assessment
for
Division of Anti-Infective and Ophthalmology Product

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R REGIONAL INFORMATION	92
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A. Labeling & Package Insert	92
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III. List Of Deficiencies To Be Communicated	96

Chemistry Review Data Sheet

1. NDA 22-106
2. REVIEW #: 1
3. REVIEW DATE: September 6, 2007
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

Dec 12, 2006

Amendment

May 30, 2007

Amendment

July 2, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Johnson & Johnson Pharmaceutical Research & Development, L.L.C

Address: 920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Representative: George Marchesini (CMC issues)

Telephone: 908-704-5389

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Doribax
b) Non-Proprietary Name (USAN): Doripenem for Injection
Code Name/#: JNJ-38174942-ZAF, S-4661
c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Antibiotics

11. DOSAGE FORM: Powder for Injection

12. STRENGTH/POTENCY: 500 mg (anhydrous basis)/vial

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

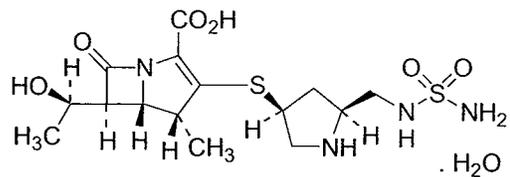
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

Chemical Name (IUPAC):

(4*R*,5*S*,6*S*)-3-(((3*S*,5*S*)-5-
[[[(aminosulfonyl)amino]methyl]-3-
pyrrolidinyl]thio]-6-[(1*R*)-1-
hydroxyethyl]-4-methyl-7-oxo-
1-azabicyclo[3.2.0]hept-2-ene-
2-carboxylic acid monohydrate

Chemistry Review Data Sheet

Structural formula:

Molecular formula: C₁₅H₂₄N₄O₆S₂·H₂O

Relative molecular mass/molecular weight: 438.52

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
✓	III	/		4			
	III	/		3	Adequate	07-Feb-2006	

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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
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Orphan	04-1881	Doripenem for Injection, filed on Apr 16, 2004

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending	9/6/07	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Sterility Assurance	Pending	9/6/07	John Metcalfe

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 22-106

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the quality assessment, this application is recommended for an approval action pending adequate sterility assurance observed in the product quality microbiology review and acceptable establishments inspection results.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Doripenem drug substance is a sterile white to slightly yellowish, off-white crystalline powder synthesized using an _____ g technique. The drug substance exists in the form of monohydrate with

_____. The pH of its 10 mg/mL aqueous solution is _____. It is not hygroscopic. The specific optical rotation of doripenem in water (10 mg/mL on anhydrous basis) at 20°C is +34.9° - +36.1°.

The structure of doripenem was elucidated by _____. The attributes controlled in release testing include appearance, identification by _____, specific rotation, clarity and color of solution, _____, assay of doripenem, chromatographic purity (specified impurities, unspecified impurities, and total impurities), residual solvents, _____, water content, particulate matter test for injections, _____, bacterial endotoxins, and sterility.

The drug substance is stored inside two containers. The primary product-contact container is a _____ container, a _____ bag that is then placed inside a secondary _____ container.

An expiry dating period of 24 months when stored at 2–8 °C is proposed, and is acceptable for doripenem drug substance based on 24 months stability data.

Executive Summary Section

Drug Product:

Doripenem for injection (500 mg) is provided as single-use vials containing 500 mg of sterile powder for constitution. It is manufactured by filling bulk drug substance powder into clear Type I glass vials. The drug product does not contain excipients.

The attributes controlled in release testing include appearance, identification by clarity and color of solution, assay of doripenem, specified degradation products, individual degradation products, total degradation products, water content, weight variation, particulate matter test for injections, bacterial endotoxins, and sterility.

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B. Description of How the Drug Product is Intended to be Used

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At the time of administration, the drug product is constituted with 10 mL of Water for Injection, USP or Sodium Chloride Injection, USP, and is shaken to form a suspension. The suspension is then withdrawn using a 21-gauge needled syringe and added to a polyvinylchloride (PVC) infusion bag containing 100 mL of Sodium Chloride injection, USP, or Dextrose Injection, USP to achieve a final dosing concentration of 5 mg/mL. The Baxter Minibag Plus® delivery system may alternatively be used to prepare doripenem for injection (500 mg) solution.

Upon constitution with sterile water for injection or 0.9% sodium chloride (normal saline) injection, the drug product suspension in the vial may be held for 1-hour prior to transfer and dilution in the infusion bag.

The infusion solution is stable in PVC and Baxter Minibag Plus® infusion bags for at controlled room temperature and at refrigerated temperature in Sodium Chloride for Injection, USP, and 4 hours at controlled room temperature and at refrigerated temperature in Dextrose Injection, USP, respectively.

Constituted drug product suspension or drug product infusion should not be frozen.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is synthesized through Adequate information is provided on the synthesis and process controls, drug substance characterization, characterization of impurities, specification, container closure system, and stability studies.

Executive Summary Section

Issues regarding inappropriate starting material controls were resolved during the review process.

The drug product is manufactured by _____ of the bulk _____ drug substance. Adequate information is provided on manufacturing process and process controls, container closure system, and stability studies. Additional information on specification justification and the dissolution time during constitution were provided during the review process. The results demonstrated that the drug product is appropriately controlled.

The microbiological processes and process controls are evaluated in the product quality microbiological review by Dr. John Metcalfe.

III. Administrative

A. Reviewer's Signature

Lin Qi (Signed and dated in DFS)

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryBranchChiefName/Date
ProjectManagerName/Date
(Information in DFS)

C. CC Block

Information in DFS

44 Page(s) Withheld

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Draft Labeling

Deliberative Process

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/s/

Lin Qi
9/7/2007 08:56:01 AM
CHEMIST

Norman Schmuff
9/9/2007 05:12:01 PM
CHEMIST

NDA 22-106, Doripenem for Injection, 500 mg/Vial

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information. Your response should be submitted as an amendment to the submission and a copy via facsimile to the reviewer.

CMC COMMENTS

- The gauge of the needle used to withdraw the suspension during constitution (21-gauge) should be included in the constitution direction in the package insert to ensure a complete suspension transfer.

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/s/

Lin Qi
7/16/2007 12:59:03 PM
CHEMIST

Norman Schmuff
7/17/2007 07:00:49 AM
CHEMIST

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division:	Division of Anti-Infectives and Ophthalmic Drug Products		
NDA:	22-106		
Applicant:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C		
Stamp Date:	Dec-13-2006		
PDUFA Date:	Oct-13-2007		
Trademark:	Not given		
Established Name:	Doripenem monohydrate		
Dosage Form:	Powder for injection		
Route of Administration:	Injection, intravenous		
Indication:	Complicated Intra-Abdominal Infections (cIAI), Complicated Urinary Tract Infections (cUTI), including Complicated and Uncomplicated Pyelonephritis		
PAL:	Rapti D. Madurawe, Ph.D.		
	YES	NO	
ONDQA Fileability:	<input type="checkbox"/>	<input type="checkbox"/>	To be determined by primary reviewer
Comments for 74-Day Letter:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Summary and Critical Issues:

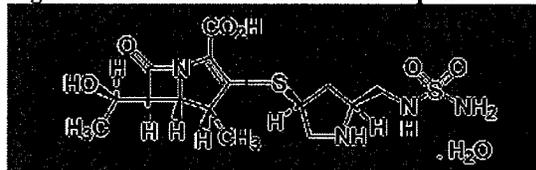
A: Summary

NDA 22-106 provides for doripenem for injection, a sterile lyophilized powder for intravenous injection. The corresponding IND number is 64,416. Doripenem is a New Molecular Entity (NME) belonging to the β -lactam class of antibiotics. The drug substance is obtained by chemical synthesis. The drug product is supplied 500 mg doripenem anhydrous base per vial. The drug product does not contain any inactive ingredients. A 250-mg doripenem drug product is marketed in Japan.

Drug Substance (DS)

The drug substance is doripenem monohydrate. It is an NME. Its chemical structure is given below.

Figure 1: Chemical Structure of Doripenem Monohydrate



The DS is manufactured at Shinogi & Co., Ltd., Kanegasaki, Japan as an enantiomerically pure monohydrate. The DS is a slightly yellowish, off-white crystalline powder. It has 6 chiral centers. The applicant

The DS

The DS is soluble in

The applicant states that in correspondences dated 07-Mar-06 and 26-Feb-04, respectively, the Agency agreed to the designate _____ as starting materials and accepted the proposed specifications for _____. There is no record of the 07-Mar-06 e-mail in DFS, but the applicant has provided a copy of this email. The 26-Feb-04 letter accepting _____ as a starting material is in DFS. The reviewer based acceptance on the commercial availability of _____ and reference to DMF _____ with the designation of these starting materials, DS synthesis is simplified to _____

Over product development, the DS synthetic method has undergone many changes. Toxicology studies were done on batches made per early synthetic methods (i.e., methods _____). Clinical studies (phase not identified) used DS made per methods _____. The commercial DS and registration stability DS (and DP) batches are made per method _____. Changes from _____ to the commercial _____ method are: _____

The proposed DS specifications are given in Table 1.

4 Page(s) Withheld

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/s/

Rapti Madurawe
1/29/2007 11:41:41 AM
CHEMIST

Norman Schmuff
1/30/2007 08:35:22 AM
CHEMIST