

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-032**

**CHEMISTRY REVIEW(S)**



**NDA 22-032**

**Omeprazole Delayed Release Tablets, 20 mg**

**Dexcel Pharma Technologies Limited**

**Maria Ysern, MSc.**

**Pre-marketing Assessment Division II, Branch III**

NDA 22-032

Delayed Release Tablets

Dexcel Pharma Technologies Limited

Maria Ysern, MSc.

Pre-marketing Assessment Division II

NDA 22-032

Delayed Release Tablets

Dexcel Pharma Technologies Limited



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**Chemistry Review Data Sheet**

1. NDA 22-032
2. REVIEW: # 3
3. REVIEW DATE: October 29, 2007
4. REVIEWER: Maria Ysern, MSc
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	FEB 8, 2006
BZ Amendment	JUN 20, 2006
BC Amendment	JUL 21, 2006
BC Amendment	DEC 07, 2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC Amendment	JUL 19, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Dexcel-Pharma Technologies Limited  
Southern Industrial Zone  
Address: Or Kiva 30600  
Israel  
John D. Franolic, PhD  
Lachman Consultant Services, Inc  
Representative: 1600 Stewart Avenue  
Westbury, New York  
Telephone: Telephone : (516) 222-6222



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Omeprazole Delayed Release Tablets, 20 mg
- b) Non-Proprietary Name (USAN): Omeprazole
- c) Code Name/# (ONDQA only): n/a
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: Standard review.

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

10. PHARMACOL. CATEGORY: Proton Pump inhibitor

11. DOSAGE FORM: Delayed Release Tablets  
(The dosing regimen is one tablet per day for a 14-day course of treatment).

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

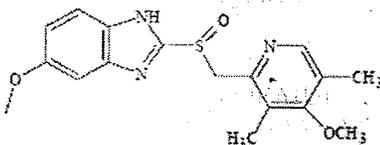
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



Compendial/International Non-Proprietary Name: Omeprazole

IUPAC Nomenclature: 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl] sulfinyl]-benzimidazole.

CAS #: [73590-58-6]

Molecular formula : C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S

Relative Molecular mass: 345.42

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT S
b(4)	II	[REDACTED]	[REDACTED]	1	Adequate	Nov 06, 2003	Dr. Basaram
b(4)	III			4			
b(4)	III			4			

<sup>1</sup> 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")

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



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

**B. Other Documents: N/A**

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Dec 5, 2006	
Pharm/Tox	No unresolved toxicology issues. Should be approved:	October 03, 2006	Dr. David Joseph
Biopharm	Done		Dr. Abimbola Adebowale
LNC	OTC will review labeling section		
Methods Validation	after approval		
OPDRA/DMETS	N/A		
EA	N/A		
Microbiology	N/A		

**OGD: N/A**

19. ORDER OF REVIEW N/A



## CHEMISTRY REVIEW



### Executive Summary Section

#### The Chemistry Review for NDA 22-032

#### The Executive Summary

##### I. Recommendations

###### A. Recommendation and Conclusion on Approvability

Previously this NDA was tentatively approved due to patent infringement issues. Meanwhile, the sponsor submitted a CMC amendment (July 19, 2007) with new CMC information. This information is reviewed and this NDA is recommended for approval from the standpoint of CMC.

###### 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:

Omeprazole, USP is the active ingredient in this delayed release formulation. The chemical name is 5-methoxy-2-((4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl) sulfinyl)-1H-benzimidazole. CAS number: [7390-58-6]. It is a white to off white powder with a melting range of 150-156°, very slightly soluble in water.

Omeprazole undergoes rapid degradation to cationic sulfonamide when exposed to acidic environments. The manufacturer of Omeprazole is \_\_\_\_\_

The production and manufacturing controls for the drug substance are detailed in DMF \_\_\_\_\_

This DMF has been reviewed and it is now adequate. The specifications for omeprazole drug substance are based on the US Pharmacopoeia (USP) monograph.

The drug substance is \_\_\_\_\_. The proposed specifications also include tests for particle size, additional impurities and residual solvents.

###### Drug Product:

Omeprazole delayed release tablets, 20 mg, is a brownish capsule-shaped, film coated tablet. Each film coated tablet weighs approximately 307 mg. The components of the drug product include:



# CHEMISTRY REVIEW



## Executive Summary Section

The two non compendial ingredients are not novel excipients; the ingredient itself or the components of the ingredients are listed in the FDA's inactive ingredient data base for oral solid dosage forms.

b(4)

Omeprazole Delayed Release Tablets 20 mg is produced as a \_\_\_\_\_ with an enteric coating and the production size batch is \_\_\_\_\_. In the amendment dated July 19, 2007 the sponsor increased the production scale to \_\_\_\_\_ with validation data which is deemed acceptable.

b(4)

Omeprazole is a weak base, very slightly soluble in acidic media. It is essential to have the tablets coated with enteric coating during the formulation in order to prevent release of the active in the stomach.

b(4)

Physical compatibility studies were designed to determine the interaction of the drug substance with the excipients in direct contact with Omeprazole and no incompatibility was observed.

Omeprazole should be kept at sufficiently high pH value to maintain the stability of the product. The sodium stearate,

b(4)

The analytical method for detection of impurities in the drug product is an USP method capable of detecting and separating the impurities.

The specification for Omeprazole Delayed-Release Tablets, 20 mg is based on the requirements of the Omeprazole Delayed Release Capsules monograph in the USP. According to the amendment dated July 19, 2007 the proposed drug product will be debossed with "20" on one side and comparative dissolution data indicate that debossment would not affect the quality of the tablets. They are packaged in unit-dose, child resistant blister trays comprised of an aluminate base foil which is molded into blisters on the packaging line, and a paper based aluminum, child resistant peel/push lidding foil. The blister tray has seven cavities and is designed to hold one tablet in each cavity.

The to-be market formulation is the same formulation used in the BE/BA studies and registration stability batches. Stability data provided in the initial submission to support an expiry period of 24 months includes six months at 25°C/60% RH, 30° C/ 65% RH and 40°C/75% RH from three production scale batches. Additional supporting stability data of 24 months (25°C/ 60% RH) are provided for two large development batches of the same formulation.

Updated stability data was also submitted in the above mentioned amendment for the 500,000 tablets NDA batches # B0415, # B0515 and # B0615. The stability data at 25°C/60% RH for 24 months for the proposed shelf life meet specification.



## CHEMISTRY REVIEW



### Executive Summary Section

Stability testing for the validation batches 06447, 06G77 and 06J97 is in progress according to the NDA stability testing protocol, and will be submitted to the annual report.

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

This product is to be used once a day (every 24 hours), everyday for 14 days. One tablet will be swallowed with a glass of water before eating in the morning. The tablets (delayed release) should not be chewed or crushed, nor crushed on food. This product should not be used for more than 14 days unless directed by the doctor, and is to be used by adults 18 years and older.

#### B. Basis for Approvability or Not-Approval Recommendation

Previously this NDA was recommended for approval based on reasons described in Review #1 of this application. However, Dexcel Pharma has submitted a Chemistry, Manufacturing and Controls BC Amendment, dated July 19, 2007 which provided for supporting data for the tablet debossment (number "20" on one side of the tablet), supporting data for CMC for the increased batch size of \_\_\_\_\_, and \_\_\_\_\_ and in process dosage units, stratified sampling and assessment.

b(4)

Updated stability data was generated for the \_\_\_\_\_ tablet NDA batches # B0415, # B0515 and # B0615. The stability data at 25°C/60% RH for 24 months for the proposed shelf life meet the requirements of the stability specifications. Stability testing for the undebossed batch # 060707 and for debossed validation batches 06447, 06G77 and 06J97 is in progress according to the NDA stability testing protocol, and will be submitted to the annual report.

b(4)

The additional information provided in this amendment has been reviewed and found acceptable.

### III. Administrative

#### A. Reviewer's Signature in DFS

#### B. Endorsement Block

Maria Ysern/ Review Chemist/  
Moo-Jhong Rhee/ Brach Chief/Date  
Keith Olin / Project Manager/Date  
Linda Athey/ Project Manager



**C. CC Block in DFS**

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**  
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/s/

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Maria Ysern  
10/30/2007 08:46:12 AM  
CHEMIST

Moo-Jhong Rhee  
10/30/2007 09:02:27 AM  
CHEMIST  
Chief, Branch III



**NDA 22-032**

**Omeprazole Delayed Release Tablets, 20 mg**

**Dexcel Pharma Technologies Limited**

**Maria Ysern, MSc.**

**Pre-marketing Assessment Division II, Branch III**

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Chemistry Review Data Sheet

**Chemistry Review Data Sheet**

- 1. NDA 22-032
- 2. REVIEW: # 2
- 3. REVIEW DATE: Jan 26, 2007
- 4. REVIEWER: Maria Ysern, MSc.
- 5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	FEB 8, 2006
BZ Amendment	JUN 20, 2006
BC Amendment	JUL 21, 2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC Amendment	DEC 7, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Dexcel Pharma Technologies Limited  
Address: Southern Industrial Zone  
Or Kiva 30600  
Israel  
John D. Franolic, PhD  
Lachman Consultant Services, Inc  
Representative: 1600 Stewart Avenue  
Westbury, New York  
Telephone: Telephone : (516) 222-6222

8. DRUG PRODUCT NAME/CODE/TYPE:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- a) Proprietary Name: Omeprazole Delayed Release Tablets, 20 mg  
b) Non-Proprietary Name (USAN): Omeprazole  
c) Code Name/# (ONDQA only): n/a  
d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5
  - Submission Priority: Standard review.

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

10. PHARMACOL. CATEGORY: Proton Pump inhibitor

11. DOSAGE FORM: Delayed Release Tablets  
(The dosing regimen is one tablet per day for a 14-day course of treatment).

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

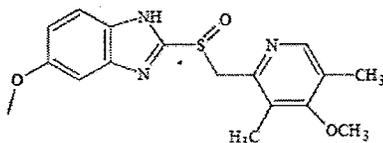
14. Rx/OTC DISPENSED: \_\_\_ Rx \_\_\_ x \_\_\_ OTC

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

\_\_\_ SPOTS product – Form Completed

\_\_\_ x \_\_\_ Not a SPOTS product

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



**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

Compendial/International Non-Proprietary Name: Omeprazole  
 IUPAC Nomenclature: 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-benzimidazole.

CAS #: [73590-58-6]  
 Molecular formula : C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S  
 Relative Molecular mass: 345.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT S
b(4)	II	/	/	1	Adequate	Nov 06, 2003	Dr. Basaram
	III			4			
	III			4			

<sup>1</sup> 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")

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

B. Other Documents: N/A

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Dec 5, 2006	
Pharm/Tox	No unresolved toxicology issues. Should be approved.	October 03, 2006	Dr. David Joseph
Biopharm	Done		Dr. Abimbola Adebawale
LNC	OTC will review labeling section		
Methods Validation	after approval		
OPDRA/DMETS	N/A		
EA	N/A		
Microbiology	N/A		

OGD: N/A

19. ORDER OF REVIEW N/A

APPEARS THIS WAY ON ORIGINAL

Executive Summary Section

**The Chemistry Review for NDA 22-032**

**The Executive Summary**

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

This NDA can be approved from the standpoint of CMC.

**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:**

Omeprazole, USP is the active ingredient in this delayed release formulation. The chemical name is 5-methoxy-2-((4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl sulfinyl)-1H-benzimidazole. CAS number: [7390-58-6]. It is a white to off white powder with a melting range of 150-156° very slightly soluble in water.

Omeprazole undergoes rapid degradation to cationic sulfonamide when exposed to acidic environments. The manufacturer of Omeprazole is \_\_\_\_\_

The production and manufacturing controls for the drug substance are detailed in DMF \_\_\_\_\_

— This DMF has been reviewed and it is now adequate. The specifications for omeprazole drug substance are based on the US Pharmacopoeia (USP) monograph.

The drug substance is \_\_\_\_\_ The proposed specifications also include tests for particle size, additional impurities and residual solvents.

b(4)

b(4)

**Drug Product:**

Omeprazole delayed release tablets, 20 mg, is a brownish capsule-shaped, film coated tablet. Each film coated tablet weighs approximately 307 mg. The components of the drug product include:

✓

\_\_\_\_\_

b(4)

\_\_\_\_\_ , calcium wax  
The two non compendial ingredients are not novel excipients; the ingredient itself or the components of the ingredients are listed in the FDA's inactive ingredient data base for oral solid dosage forms.



Executive Summary Section

Omeprazole Delayed Release Tablets 20 mg is produced as a [redacted] with an enteric coating and the production size batch is [redacted]

b(4)

Omeprazole is a weak base, very slightly soluble in acidic media. It is essential to have the tablets coated with enteric coating during the formulation in order to prevent release of the active in the stomach.

b(4)

Physical compatibility studies were designed to determine the interaction of the drug substance with the excipients in direct contact with Omeprazole and no incompatibility was observed.

Omeprazole should be kept at sufficiently high pH value to maintain the stability of the product. The sodium stearate, [redacted]

b(4)

The analytical method for detection of impurities in the drug product is an USP method capable of detecting and separating the impurities.

The specifications for Omeprazole Delayed-Release Tablets, 20 mg are based on the requirements of the Omeprazole Delayed Release Capsules monograph in the USP.

The proposed drug product is packaged in unit-dose, child resistant blister trays comprised of an aluminate base foil which is molded into blisters on the packaging line, and a paper based aluminum, child resistant peel/push lidding foil. The blister tray has seven cavities and is designed to hold one tablet in each cavity.

The to-be market formulation is the same formulation used in the BE/BA studies and registration stability batches. Stability data provided in the initial submission to support an expiry period of 24 months includes six months at 25°C/60% RH, 30° C/ 65% RH and 40°C/75% RH from three production scale batches. Additional supporting stability data of 24 months (25°C/ 60% RH) are provided for two large development batches of the same formulation.

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

This product is to be used once a day (every 24 hours), everyday for 14 days. One tablet will be swallowed with a glass of water before eating in the morning. The tablets (delayed release) should not be chewed or crushed, nor crushed on food. This product should not be used for more than 14 days unless directed by the doctor, and is to be used by adults 18 years and older.

**B. Basis for Approvability or Not-Approval Recommendation**

The basis for approvability was described in review #1 of this application.

**Executive Summary Section**

The cGMP inspection of all the manufacturing facilities was completed and found acceptable by the Office of Compliance.

The sponsor had committed to revise some of the analytical methods as recommended by the inspector and these were submitted as an amendment (Dec 7, 2006), reviewed and found satisfactory.

**III. Administrative****A. Reviewer's Signature in DFS****B. Endorsement Block**

Maria Ysern/ Review Chemist /Feb 16, 2006

Moo-Jhong Rhee/ Brach Chief/Date

Keith Olin / Project Manager/Date

Linda Athey/ Project Manager.

**C. CC Block in DFS**

9 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Maria Ysern  
2/22/2007 01:44:09 PM  
CHEMIST

Moo-Jhong Rhee  
2/22/2007 02:38:22 PM  
CHEMIST  
Chief, Branch III

## MEMORANDUM

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

**DATE:** Dec. 6, 2006

**TO:** NDA 22-032 CMC Review #1

**FROM:** Shulin Ding, Ph.D., Pharmaceutical Assessment Lead  
(ONDQA Division of Pre-Marketing assessment II)

**THROUGH:** Moo-Jhong Rhee, Ph.D., Chief, Branch III  
(ONDQA Division of Pre-Marketing assessment II)

**SUBJECT:** **Change in CMC Recommendation for NDA 22-032 due to Recent Notification of Revisions in Analytical methods and others**

### Background

The PUDUFA goal date of NDA 22-032 is Dec. 10, 2006. CMC Review #1 was closed on Dec. 5 with a recommendation of Approval upon the receipt of the establishment evaluation report through EES (Establishment Evaluation System). The overall recommendation from the Office of Compliance regarding facility cGMP status is "Acceptable" for this NDA.

Electronic mails (see attached) have recently been forwarded to ONDQA, indicating that the NDA applicant is attempting to submit a CMC amendment to NDA 22-032 for revisions in analytical methods and perhaps other CMC aspects. The amendment has not been received as of the date of this memorandum.

### Reviewer's evaluation

According to the information available at this time (see the attached emails), the "Acceptable" recommendation from the Office of Compliance appears to be based on the sponsor's commitment to revising some analytical methods, which we have not known until the last minutes of this review cycle and therefore have not been incorporated in our review.

Because of uncertainty of the validity of the revised analytical methods, until we fully review the changes and the revised methods are deemed acceptable, "Approvable" action is recommended for the NDA from the CMC perspective.

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this page is the manifestation of the electronic signature.**

/s/

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Shulin Ding  
12/7/2006 02:36:14 PM  
CHEMIST

Moo-Jhong Rhee  
12/7/2006 02:47:31 PM  
CHEMIST  
Chief, Branch III



**CHEMISTRY REVIEW**



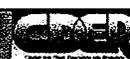
**NDA 22-032**

**Omeprazole Delayed Release Tablets, 20 mg**

**Dexcel Pharma Technologies Limited**

**Maria Ysern, MSc.**

**Pre-marketing Assessment Division II, Branch III**



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III. Administrative.....9

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    B. Endorsement Block ..... 9

    C. CC Block ..... 9

**Chemistry Assessment**..... 10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....10

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    P DRUG PRODUCT [Name, Dosage form]..... 15

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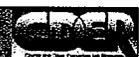
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    B. Environmental Assessment Or Claim Of Categorical Exclusion..... 57

III. List Of Deficiencies To Be Communicated.....57



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. NDA 22-032
2. REVIEW: # 1
3. REVIEW DATE: December 5, 2006
4. REVIEWER: Maria Ysern, MSc.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	FEB 8, 2006
BZ Amendment	JUN 20, 2006
BC Amendment	JUL 21, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Dexcel Pharma Technologies Limited  
Southern Industrial Zone  
Address: Or Kiva 30600  
Israel  
John D. Franolic, PhD  
Lachman Consultant Services, Inc  
Representative: 1600 Stewart Avenue  
Westbury, New York  
Telephone: Telephone : (516) 222-6222

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Omeprazole Delayed Release Tablets, 20 mg
- b) Non-Proprietary Name (USAN): Omeprazole
- c) Code Name/# (ONDQA only): n/a



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: Standard review.

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

10. PHARMACOL. CATEGORY: Proton Pump inhibitor

11. DOSAGE FORM: Delayed Release Tablets  
(The dosing regimen is one tablet per day for a 14-day course of treatment).

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

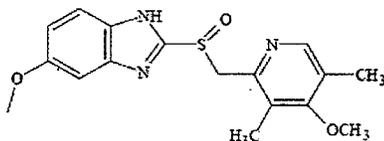
14. Rx/OTC DISPENSED: \_\_\_ Rx \_\_\_ x \_\_\_ OTC

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

\_\_\_\_\_ SPOTS product – Form Completed

x  Not a SPOTS product

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



Compendial/International Non-Proprietary Name: Omeprazole

IUPAC Nomenclature: 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-benzimidazole.



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

CAS #: [73590-58-6]  
Molecular formula :  $C_{17}H_{19}N_3O_3S$   
Relative Molecular mass: 345.42

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
●	II	[REDACTED]	[REDACTED]	1	Adequate	Nov 06, 2003	Dr. Basaram
●	III			4			
●	III			4			

b(4)

<sup>1</sup> 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")

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

B. Other Documents: N/A

### 18. STATUS:

ONDQA:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Acceptable		
Pharm/Tox	No unresolved toxicology issues. Should be approved.	October 03, 2006	Dr. David Joseph
Biopharm	N/A		
LNC	OTC will review labeling section		
Methods Validation	N/A		
OPDRA/DMETS	N/A		
EA	N/A		
Microbiology	N/A		

**OGD: N/A**

19. ORDER OF REVIEW N/A

**APPEARS THIS WAY ON ORIGINAL**



Executive Summary Section

The Chemistry Review for NDA 22-032

The Executive Summary

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

This NDA is recommended for approval from a CMC perspective.

**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:**

Omeprazole, USP is the active ingredient in this delayed release formulation. The chemical name is 5-methoxy-2-((4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl) sulfinyl)-1H-benzimidazole. CAS number: [7390-58-6]. It is a white to off white powder with a melting range of 150-156° very slightly soluble in water.

Omeprazole undergoes rapid degradation to cationic sulfonamide when exposed to acidic environments. The manufacturer of Omeprazole is

The production and manufacturing controls for the drug substance are detailed in DMF

This DMF has been reviewed and it is now adequate. The specifications for omeprazole drug substance are based on the US Pharmacopoeia (USP) monograph.

The drug substance is. The proposed specifications also include tests for particle size, additional impurities and residual solvents.

b(4)

b(4)

**Drug Product:**

Omeprazole delayed release tablets, 20 mg, is a brownish capsule-shaped, film coated tablet. Each film coated tablet weighs approximately 307 mg. The components of the drug product include:

T

↓

b(4)

The two non compendial ingredients are not novel excipients; the ingredient itself or the components of the ingredients are listed in the FDA's inactive ingredient data base for oral solid dosage forms.



## CHEMISTRY REVIEW



### Executive Summary Section

Omeprazole Delayed Release Tablets 20 mg is produced as a \_\_\_\_\_ with an enteric coating and the production size batch is \_\_\_\_\_

b(4)

Omeprazole is a weak base, very slightly soluble in acidic media. It is essential to have the tablets coated with enteric coating during the formulation in order to prevent it from releasing the active ingredient in the stomach.

Physical compatibility studies were done to determine the interaction of the drug substance with the excipients in direct contact with Omeprazole and no incompatibility was observed.

Omeprazole should be kept at sufficiently high pH value to maintain the stability of the product. The sodium stearate, \_\_\_\_\_

b(4)

b(4)

The analytical method for the detection of impurities in the drug product is the USP method

capable of detecting and separating the impurities.

The specifications for Omeprazole Delayed-Release Tablets, 20 mg are based on the requirements of the Omeprazole Delayed Release Capsules monograph in the USP.

The proposed drug product is packaged in unit-dose, child resistant blister trays comprised of an aluminate base foil which is molded into blisters on the packaging line, and a paper based aluminum, child resistant peel/push lidding foil. The blister tray has seven cavities and is designed to hold one tablet in each cavity.

The to-be market formulation is the same formulation used in the BE/BA studies and registration stability batches. Stability data provided in the initial submission to support an expiry period of 24 months include six months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH from three production scale batches. Additional supporting stability data of 24 months (25°C/60% RH) are provided for two large development batches of the same formulation.

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

This product is to be used once a day (every 24 hours), everyday for 14 days. One tablet will be swallowed with a glass of water before eating in the morning. The tablets (delayed release) should not be chewed or crushed, nor crushed on food. This product should not be used for more than 14 days unless directed by the doctor, and is to be used by adults 18 years and older.



## CHEMISTRY REVIEW



### Executive Summary Section

#### B. Basis for Approvability or Not-Approval Recommendation

The manufacturing information on the drug substance, Omeprazole, has been provided in the DMF (Type II) and is deemed satisfactory.

The manufacturing of the drug product comprises ( ) and they are deemed robust.

b(4)

The specifications for Omeprazole Delayed Release tablets, 20 mg are based on the requirements for Omeprazole Delayed Release Capsules and they are deemed acceptable. The dissolution specification is adequate to ensure the product quality.

The tablets are packaged in unit dose, child resistant blister trays and they are deemed adequate. The second packaging consists of two blister trays, each containing seven tablets, and packed into a 14-count printed carton. Two and three 14-count cartons are packaged into 28-count and 42 count printed carton respectively.

The facility inspection reports are satisfactory.

### III. Administrative

A. Reviewer's Signature in DFS

#### B. Endorsement Block

Maria Yserri/ Review Chemist /October 19, 2006

Moo-Jhong Rhee/ Brach Chief/Date

Keith Olin / Project Manager/Date

Linda Athey/ Project Manager.

C. CC Block in DFS

48 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**  
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/s/

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Shulin Ding  
12/5/2006 03:54:55 PM  
CHEMIST  
On behalf of Maria Ysern

Moo-Jhong Rhee  
12/5/2006 04:11:26 PM  
CHEMIST  
Chief, Branch III

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Nonprescription Clinical Evaluation  
**NDA:** 22-032  
**Applicant:** Dexcel Pharma Technologies Limited  
**Stamp Date:** Feb. 10, 2006  
**PDUFA Date:** Dec. 10, 2006  
**Trademark:** Omeprazole Delayed Release Tablets 20 mg  
**Established Name:** Omeprazole  
**Dosage Form:** Tablet  
**Route of Administration:** Oral  
**Indication:** Frequent heartburns (occurs two or more days a week)

**PAL:** Shulin Ding

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

**Summary and Critical Issues:**

**A. Summary**

Dexcel Pharma Technologies Limited (Dexcel) is submitting a 505(b) (2) New Drug Application (NDA) for Omeprazole Delayed Release Tablets, 20 mg with proposed labeling for OTC marketing. The proposed indication is frequent heart burns which occurs two or more days a week, and the listed reference drug is Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets).

The applicant references \_\_\_\_\_ DMF \_\_\_\_\_ for the drug substance, omeprazole USP. The DMF has been reviewed multiple times, most recently in December 2005, and found adequate. To facilitate drug dissolution, \_\_\_\_\_ omeprazole is used in the manufacture of drug product.

b(4)

The proposed drug product is an enteric coating tablet with a delayed drug-release profile. The formulation contains the following excipients: \_\_\_\_\_

b(4)

\_\_\_\_\_ These two non-compendial ingredients are not novel excipients because either the ingredient itself or the components of the ingredient is listed in the FDA's inactive ingredient data base for oral solid dosage forms.

The proposed drug product is packaged in unit-dose, child resistant blister trays comprised of (a) aluminum base foil which is molded into blisters on the packaging line, and (b) paper based

#### Drug Product

- **Related Substance Specification:** The proposed specification does not include known impurities/degradants. No justification is provided by the applicant for the exclusion. The entire set of specification for related substances will need to be critically reviewed because the accelerated stability study failed to meet the proposed specification at 3 and 6 month time points. b(4)
- **Sodium Stearate and Monoethanolamine:** The two excipients are present in the formulation at an amount greater than the maximum amount listed in the FDA's inactive ingredient data base. The issue was discussed in the pre-IND meeting dated May 20, 2005 (PIND 63,799, p. 172, Module 1). The applicant was told in the meeting that toxicology studies were required to qualify the formulation levels of these two excipients. The applicant's response (amendment dated July 25, 2005 under PIND 63799) to this issue is provided in Module 1 of this NDA (pp. 186-228) where expert toxicology reports on these two excipients are presented.

#### Foreign Inspection

- EER has been submitted for the manufacturing sites of drug substance and drug product. Both facilities are located overseas. The drug substance manufacturing site has been deemed acceptable by the Office of Compliance. The inspection of the drug product manufacturing site is pending. The site is located in Israel.

#### C. Comments for 74-Day Letter

None.

#### D. Recommendation:

This NDA is fileable from a CMC perspective. It has a few issues which need to be critically evaluated during the review.

Shulin Ding  
Pharmaceutical Assessment Lead

## Filing Checklists

### A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

### B. Technical Checklists

#### 1. Drug Substance Full information for the drug substance is referenced to DMF 12827.

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

#### 2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

### C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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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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Shulin Ding  
3/29/2006 01:36:28 PM  
CHEMIST

Moo-Jhong Rhee  
3/29/2006 02:16:16 PM  
CHEMIST  
Chief, Branch III