CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050824Orig1s000

CHEMISTRY REVIEW(S)

NDA 50-824

Copackage consisting of:
Omeprazole Delayed-Release Capsules USP **20 mg,**
Clarithromycin Tablets USP, **500 mg,**
Amoxicillin Capsules USP, **500 mg**

DAVA Pharmaceuticals', Inc.

Jeffrey B. Medwid, PhD
ONDQA
Division of Pre-Marketing Assessment II
Branch IV

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See review #2

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1. Attachment 1 EER Report Feb 7, 2011, 2010

Chemistry Review Data Sheet

1. NDA 50-824

2. REVIEW: #3

3. REVIEW DATE: February 7, 2011

4. REVIEWER: Jeffrey B. Medwid, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Quality Review #1 and #2	08-Jul-2010 and 16-Jul-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 50-824, (Original assigned as NDA (b) (4))	Sept 22, 2009
NDA 50-824 (withdrawn due to Patent issues)	
NDA 50-824 (Resubmitted)	Nov 20, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: **DAVA Pharmaceuticals, Inc.**

Address: Parker Plaza, 400 Kelby Street. loth FI.
Fort Lee, New Jersey 07024

Representative: Susan F. Hamet
Vice President Regulatory Affairs

Telephone: Phone (Direct): (201) 592-4476
Phone (Main): (201) 947-7442
Fax: (201) 592-4640
Email: shamt@dava~hm.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be Determined

b) Non-Proprietary Name (USAN): Omeprazole Delayed-Release Capsules USP **20 mg,** Clarithromycin Tablets USP, **500 mg,** Amoxicillin Capsules USP, **500 mg**

c) Chem. Type/Submission Priority (ONDC only):
   i. Chem. Type: 5 (new combination)
   ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antiulcer and Antibiotic

11. DOSAGE FORM: Capsules and Tablets

12. STRENGTH/POTENCY: Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, **500 mg**

13. ROUTE OF ADMINISTRATION: Oral

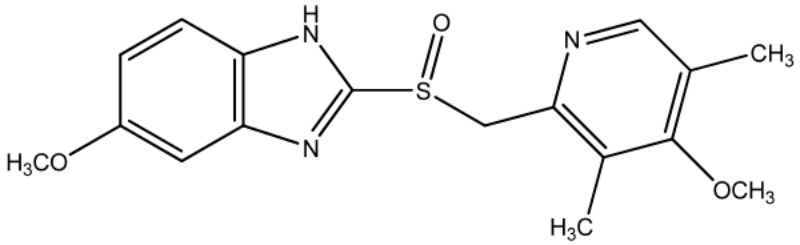
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

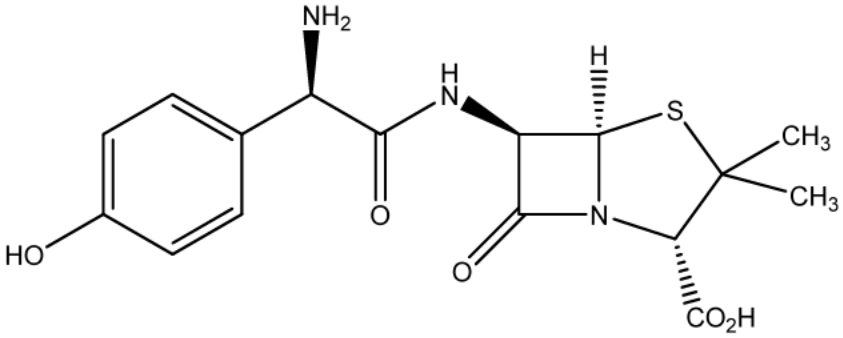
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omeprazole:



Molecular formula: $C_{17}H_{19}N_3O_3S$, Molecular weight of 345.42

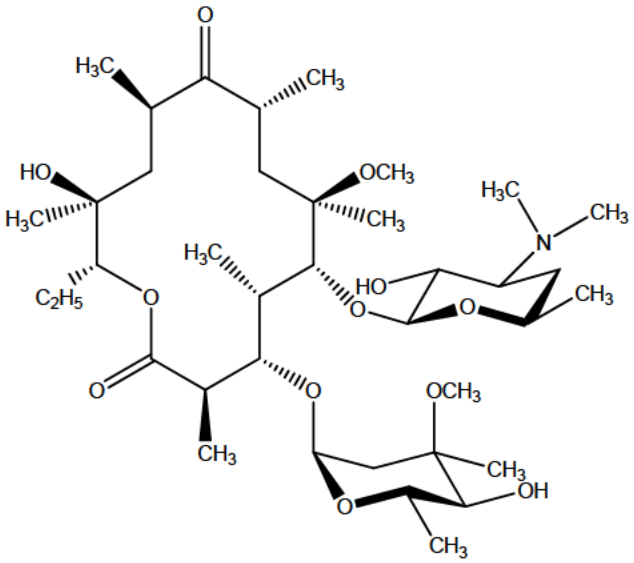
Amoxicillin:



3 H_20

Molecular formula: $C_{16}H_{19}N_3O_5S$ •3H2O, Molecular weight: 419.45

Clarithromycin:



Molecular formula: $C_{38}H_{69}NO_{13}$, Molecular weight is 747.96.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	Omeprazole API	3	Adequate	03/06/2008	See DMF
			Amoxicillin API	3	Adequate	1/08/2010	See DMF
			Amoxicillin API	3	Adequate	2/11/2007	See DMF
			(b) (4)	4	Adequate	Module 3 3.2.P.7.1 7/16/10	NDA 50,824
				4	Adequate	Module 3 3.2.P.7.1 7/16/10	NDA 50,824

[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
Omeprazole Tablet Manufacture and Testing	ANDA 75-576	Dr. Reddy
Amoxicillin Capsules Manufacture and Testing	ANDA 62-881	STADA Production Ireland, Ltd
Clarithromycin Tablet manufacture and Testing	ANDA 65-178	Roxanne labs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	See attached report		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	See DMEPA Review		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion	7/16/10	J. Medwid
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. _ _ Yes ____ No If no, explain reason(s) below: Not Applicable

The Chemistry Review for NDA 50-824

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for the copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. All labeling issues have been addressed as of the date of this review. Therefore, from the CMC perspective, this NDA is recommended for approval.

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)

See review #2

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

The copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** are packaged in blister cards for 1 full day of treatment and then put in cartons containing 10 one-day blisters. A ten-day supply is intended for the treatment of patients with H. Pylori infection and duodenal ulcer disease (active or up to 1-year history) to eradicate H. pylori in adults.

A professional sample is also described in this NDA, which contains a 1-day supply (one blister card).

C. Basis for Approvability or Not-Approval Recommendation

Sufficient information is available on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug substances and drug product. The NDA also has provided sufficient stability information on the three dosage forms blister-packed together to assure strength, purity, and quality of the drug product during the expiration dating period.

Acceptable resolution of labeling of both the insert and carton labeling have been completed at the time of this review.

A Pre-Approval Inspection of (b) (4) (b) (4), the site for stability testing of the co-packaged product) was conducted by (b) (4) in (b) (4) and a 483 was issued (see Attachment 4). Follow-up responses from (b) (4) dated (b) (4) satisfied all of the concerns for the 483 and the laboratory was deemed acceptable.

The Office of Compliance has provided a final recommendation of acceptable for all sites as of July 12, 2010. An updated summary dated Feb 7, 2011 was attached to this review.

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III. Administrative

A. Reviewer's Signature

Jeffrey Medwid, Chemist

B. Endorsement Block

Stephen Miller, Acting Branch Chief

C. CC Block

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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.

/s/

JEFFREY B MEDWID
02/07/2011

STEPHEN P MILLER
02/07/2011
I concur - this NDA is recommended for approval from the CMC perspective.

NDA 50-824

Copackage consisting of:
Omeprazole Delayed-Release Capsules USP **20 mg,**
Clarithromycin Tablets USP, **500 mg,**
Amoxicillin Capsules USP, **500 mg**

DAVA Pharmaceuticals', Inc.

Jeffrey B. Medwid, PhD
ONDQA
Division of Pre-Marketing Assessment II
Branch IV

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III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

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DRUG SUBSTANCE 11

P DRUG PRODUCT [Name, Dosage form] 13

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 27

A. Labeling & Package Insert 27

B. Environmental Assessment Or Claim Of Categorical Exclusion 28

III. List Of Deficiencies To Be Communicated 28

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1. Attachment 1 EER Report July 12, 2010
2. Attachment 2 Recommended changes to the carton labels.

Chemistry Review Data Sheet

1. NDA 50-824

2. REVIEW: #2

3. REVIEW DATE: July 16, 2010

4. REVIEWER: Jeffrey B. Medwid, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Quality Review #1	08-Jul-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 50-824, (Original assigned as NDA (b) (4))	Sept 22, 2009
NDA 50-824 (withdrawn due to Patent issues)	
NDA 50-824 (Resubmitted)	Nov 20, 2009

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Name: **DAVA Pharmaceuticals, Inc.**

Chemistry Review Data Sheet

Address: Parker Plaza, 400 Kelby Street. loth FI.
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Representative: Susan F. Hamet
Vice President Regulatory Affairs

Telephone: Phone (Direct): (201) 592-4476
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be Determined

b) Non-Proprietary Name (USAN): Omeprazole Delayed-Release Capsules USP **20 mg,** Clarithromycin Tablets USP, **500 mg,** Amoxicillin Capsules USP, **500 mg**

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9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

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13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

Chemistry Review Data Sheet

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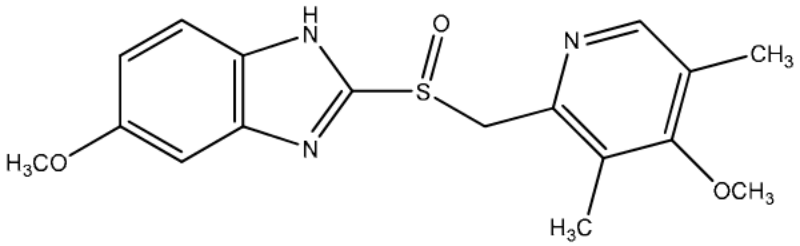

Molecular formula: $C_{17}H_{19}N_3O_3S$, Molecular weight of 345.42

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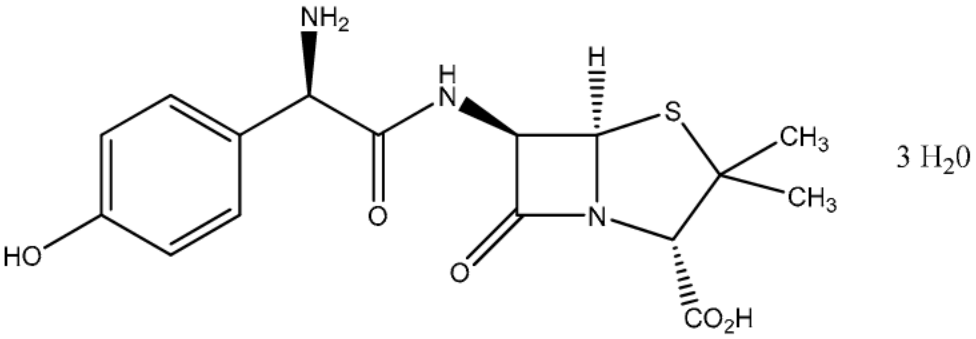

Molecular formula: $C_{16}H_{19}N_3O_5S$ •3H2O, Molecular weight: 419.45

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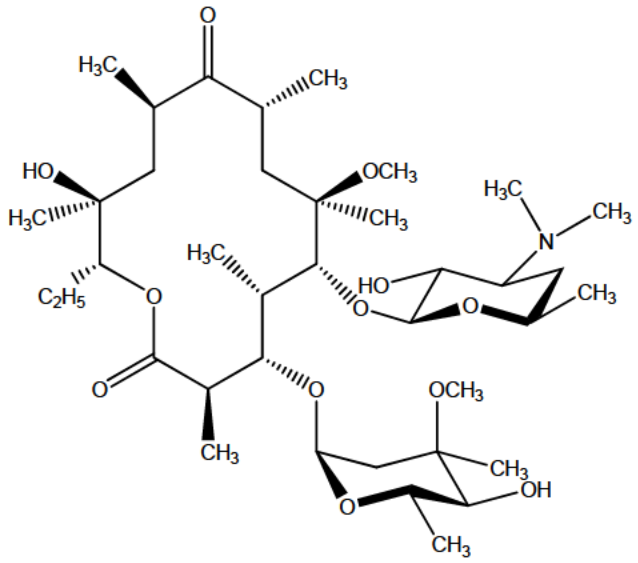

Molecular formula: $C_{38}H_{69}NO_{13}$, Molecular weight is 747.96.

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			Amoxicillin API	3	Adequate	2/11/2007	See DMF
			(b) (4)	4	Adequate	Module 3 3.2.P.7.1 7/16/10	NDA 50,824
				4	Adequate	Module 3 3.2.P.7.1 7/16/10	NDA 50,824

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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
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Amoxicillin Capsules Manufacture and Testing	ANDA 62-881	STADA Production Ireland, Ltd
Clarithromycin Tablet manufacture and Testing	ANDA 65-178	Roxanne labs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	See attached report		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	See DMEPA Review		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion	7/16/10	J. Medwid
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. _ _ Yes ____ No If no, explain reason(s) below: Not Applicable

The Chemistry Review for NDA 50-824

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for the copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

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)

The NDA is submitted for approval of a copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg.** All three Active Pharmaceutical Ingredients (APIs) are prepared and released according to either an approved ANDA (Clarithromycin) or acceptable DMFs (Amoxicillin and Omeprazole). All API's are USP grade material. The specification for all three API's are at least as tight as the approved USP specifications listed in the current USP and are the subject of currently active ANDAs. Consequently no recommendations will be made to the API manufacturers to tighten specifications.

The three drug products are then manufactured and released under approved ANDAs as listed in section 17 of the Chemistry Review Data Sheet. The specification for all three drug products are at least as tight as the approved USP specifications listed in the current USP and are the subject of approved ANDA's. Consequently no recommendations will be made to the drug product manufacturers to tighten specifications.

The three drug products are then shipped to (b) (4) (b) (4)

The stability testing of the blister-packed product is conducted by (b) (4) (b) (4)

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

The copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** are packaged in blister cards for 1 full day of treatment and then put in cartons containing 10 one day blisters. A ten-day supply is intended for the treatment of patients with H. Pylori infection and duodenal ulcer disease (active or up to 1-year history) to eradicate H. pylori in adults.

A professional sample is also described in this NDA, which contains a 1-day supply (one blister card).

C. Basis for Approvability or Not-Approval Recommendation

Sufficient information is available on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug substances and drug product. The NDA also has provided sufficient stability information on the three dosage forms blister-packed together to assure strength, purity, and quality of the drug product during the expiration dating period.

Acceptable resolution of labeling of both the insert and carton labeling still needs to be completed. Recommendations regarding the blister and carton labels and the package insert were sent to DAVA on July 6, 2010, and CMC recommendations for the package insert will be included in the annotated package insert which will be sent with the Complete Response letter.

A Pre-Approval Inspection of (b) (4), the site for stability testing of the co-packaged product) was conducted by (b) (4) in (b) (4), and a 483 was issued (see Attachment 4). Follow-up responses from (b) (4) dated (b) (4), satisfied all of the concerns for the 483 and the laboratory was deemed acceptable.

The Office of Compliance has provided a final recommendation of acceptable for all sites as of July 12, 2010.

.

III. Administrative

A. Reviewer's Signature

Jeffrey Medwid, Chemist

B. Endorsement Block

Stephen Miller, Acting Branch Chief

C. CC Block

26 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50824	ORIG-1	DAVA PHARMACEUTICALS INC	OMEPRAZOLE 25MG/AMOXOCILLIN 500MG/CLARITHROMYCIN 500MG

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

/s/

JEFFREY B MEDWID
07/16/2010

STEPHEN P MILLER
07/16/2010
I concur - from the CMC perspective this NDA is not recommended for approval until issues related to labeling are resolved

NDA 50-824

Copackage consisting of:
Omeprazole Delayed-Release Capsules USP **20 mg,**
Clarithromycin Tablets USP, **500 mg,**
Amoxicillin Capsules USP, **500 mg**

DAVA Pharmaceuticals', Inc.

Jeffrey B. Medwid, PhD
ONDQA
Division of Pre-Marketing Assessment II
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C. Basis for Approvability or Not-Approval Recommendation 11

III. Administrative 12

A. Reviewer's Signature 12

B. Endorsement Block 12

C. CC Block 12

Chemistry Assessment 13

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 13

DRUG SUBSTANCE 13

P DRUG PRODUCT [Name, Dosage form] 15

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 29

A. Labeling & Package Insert 29

B. Environmental Assessment Or Claim Of Categorical Exclusion 30

III. List Of Deficiencies To Be Communicated 30

Attachment 1 Latest Chemistry Review of Omeprazole DMF (b) (4)

Attachment 2 Latest Chemistry Review of Amoxicillin DMF (b) (4)

Attachment 3 Latest Chemistry Review of Amoxicillin DMF (b) (4)

Attachment 4 483 Issued to (b) (4)

Attachment 5 EIR (b) (4) issued

Attachment 6 Response from (b) (4)
Attachment 7 Response from (b) (4)
Attachment 8 EER Report June 8, 2010
Attachment 9 DAVA Carton Labels and recommended changes

Chemistry Review Data Sheet

1. NDA 50-824

2. REVIEW: #1

3. REVIEW DATE: July 8, 2010

4. REVIEWER: Jeffrey B. Medwid, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 50-824, (Original assigned as NDA (b) (4))	Sept 22, 2009
NDA 50-824 (withdrawn due to Patent issues)	
NDA 50-824 (Resubmitted)	Nov 20, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: **DAVA Pharmaceuticals, Inc.**

Address: Parker Plaza, 400 Kelby Street. loth FI.
Fort Lee, New Jersey 07024

Representative: Susan F. Hamet
Vice President Regulatory Affairs

Telephone: Phone (Direct): (201) 592-4476
Phone (Main): (201) 947-7442
Fax: (201) 592-4640
Email: shamt@dava~hm.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be Determined

b) Non-Proprietary Name (USAN): Omeprazole Delayed-Release Capsules USP **20 mg,** Clarithromycin Tablets USP, **500 mg,** Amoxicillin Capsules USP, **500 mg**

c) Chem. Type/Submission Priority (ONDC only):
   i. Chem. Type:
   ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antiulcer and Antibiotic

11. DOSAGE FORM: Capsules and Tablets

12. STRENGTH/POTENCY: Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, **500 mg**

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

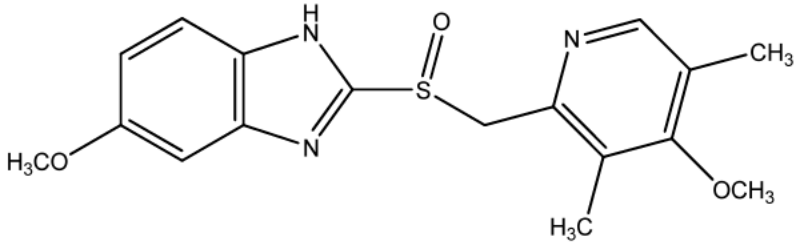
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Omeprazole Delayed-release Capsules, USP:

The active ingredient in omeprazole (omeprazole) Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



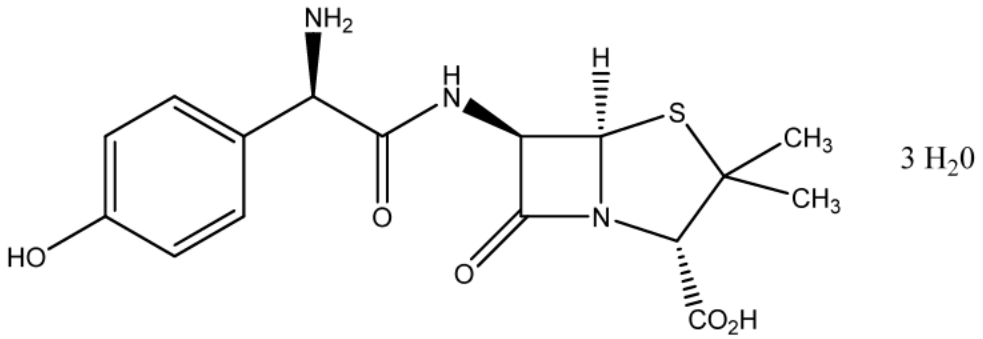
Omeprazole is a white to off-white crystalline powder that melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Omeprazole delayed-release capsules meet USP *Drug release test 2*.

Each omeprazole delayed-release capsule contains 20 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: crospovidone, hypromellose, lactose, magnesium stearate, mannitol, meglumine, methacrylic acid copolymer, poloxamer, povidone and triethyl acetate. The capsule shells contain: D&C Red #28, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, yellow iron oxide, gelatin, silicon dioxide, silicon dioxide, sodium lauryl sulfate and titanium dioxide. Imprinting ink contains: D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Red No. 40 aluminum lake, n-butyl alcohol, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black iron oxide.

Amoxicillin Capsules, USP:

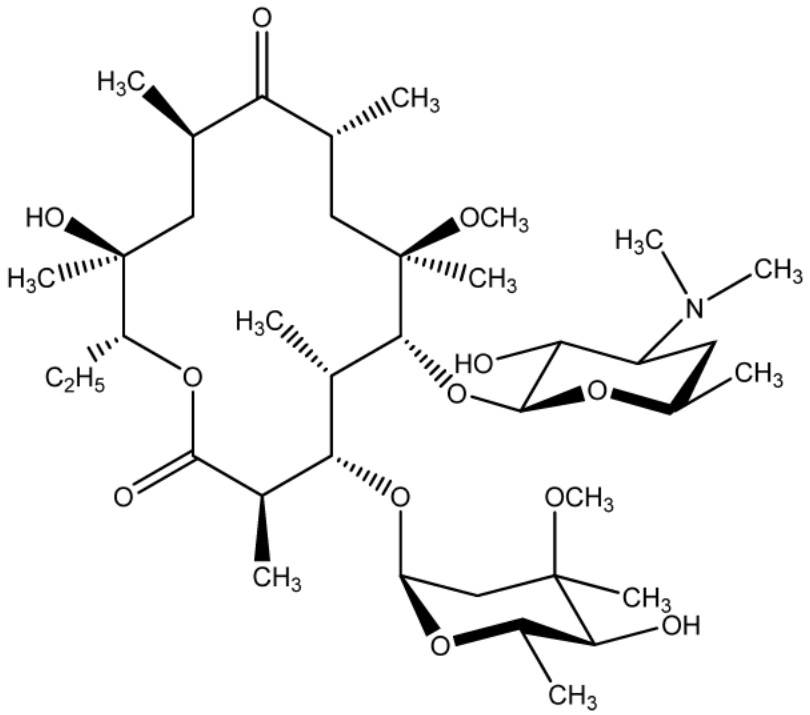
Amoxicillin, is a semisynthetic antibiotic, an analogue of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically it is (2S, 5R, 6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid trihydrate. Its empirical formula is C16H19N3O5S •3H2O with a molecular weight of 419.45. Amoxicillin has the following structure:



Amoxicillin capsules are intended for oral administration. Amoxicillin capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. Amoxicillin capsules USP also contain Magnesium stearate, NF, Sodium Lauryl Sulfate NF. The capsule shell contains D&C Red No. 33, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, Gelatin NF, Sodium Lauryl Sulfate NF, Titanium Dioxide USP. Each 500 mg capsule contains up to 0.0052 mEq (0.119 mg) of sodium.

Clarithromycin tablets, USP:

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*0*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. Clarithromycin has the following structure:



Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. Each tablet for oral administration contains 500 mg of clarithromycin and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose. Opadry

II (White), povidone, stearic acid, and talc. Opadry II (White) contains hypromellose, polyethylene glycol, polydextrose, titanium dioxide and triacetin.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)	Omeprazole API	3	Adequate	03/06/2008	See DMF attachment #1
			Amoxicillin API	3	Adequate	1/08/2010	See DMF Attachment #2
			Amoxicillin API	3	Adequate	2/11/2007	See DMF Attachment #3
			(b) (4)	4	Adequate	Module 3 3.2.P.7.1	NDA 50,824
				4	Adequate	Module 3 3.2.P.7.1	NDA 50,824

[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
Omeprazole Tablet Manufacture and Testing	ANDA 75-576	Dr. Reddy
Amoxicillin Capsules Manufacture and Testing	ANDA 62-881	STADA Production Ireland, Ltd
Clarithromycin Tablet manufacture and Testing	ANDA 65-178	Roxanne labs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	See attached report		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	See DMEPA Review		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. _ _ Yes ____ No If no, explain reason(s) below: Not Applicable

The Chemistry Review for NDA 50-824

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** is not recommended for approval at this time.

From the chemistry, manufacturing and controls perspective the following issues will need to be resolved:

1. Acceptable Inspections of all sites added into EES. At the time of this review, July 8, 2010, all sites have been found acceptable and reported in EES as such except Strada Production Ireland. The inspection has been completed. Documentation and final recommendation into EES has not been completed.

2. Acceptable resolution of labeling of both the insert and carton labeling still need to be completed. Recommendations regarding the blister and carton labels and the package insert were sent to DAVA on July 6, 2010.

These pending issues are expected to be resolved prior to the PDUFA goal date.

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)

The NDA is submitted for approval of a copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg.** All three Active Pharmaceutical Ingredients (APIs) are prepared and released according to either an approved ANDA (Clarithromycin) or acceptable DMFs (Amoxicillin and Omeprazole, see attachments 1, 2 and 3) as listed in section 17 of the Chemistry Review Data Sheet. All API's are USP grade material. The specification for all three API's are at least as tight as the approved USP specifications listed in the current

USP and are the subject of currently active ANDAs. Consequently no recommendations will be made to the API manufacturers to tighten specifications.

The three APIs are then manufactured and released under approved ANDAs as listed in section 17 of the Chemistry Review Data Sheet. The specification for all three drug products including Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** are at least as tight as the approved USP specifications listed in the current USP and are the subject of approved ANDA's. Consequently no recommendations will be made to the drug product manufacturers to tighten specifications.

The three drug products Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** are then shipped to (b) (4)

The stability testing of the blister-packed product is conducted by (b) (4) (b) (4)

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

The copackage consisting of Omeprazole Delayed-Release Capsules USP, **20 mg,** Clarithromycin Tablets USP, **500 mg,** and Amoxicillin Capsules USP, 500 **mg** are packaged in blister cards for 1 full day of treatment and then put in cartons containing 10 one day blisters. A ten day supply is intended for the treatment of patients with H. Pylori infection and duodenal ulcer disease (active or up to 1-year history) to eradicate H. pylori in adults.

C. Basis for Approvability or Not-Approval Recommendation

Sufficient information is available on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug substances and drug product. The NDA also has provided sufficient stability information on the three dosage forms blister-packed together to assure strength, purity, and quality of the drug product during the expiration dating period.

Acceptable resolution of labeling of both the insert and carton labeling still need to be completed. Recommendations regarding the blister and carton labels and the package insert were sent to DAVA on July 6, 2010.

A Pre-Approval Inspection of (b) (4), the site for stability testing of the co-packaged product) was conducted by (b) (4) in (b) (4), and a 483 was issued (see Attachment 4). Follow-up responses from (b) (4)

dated [redacted] (b) (4), satisfied all of the concerns for the 483 and the laboratory was deemed acceptable.

However, the Office of Compliance has not provided a final recommendation as of July 8, 2010.

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III. Administrative

A. Reviewer's Signature

Jeffrey Medwid, Chemist

B. Endorsement Block

Stephen Miller, Acting Branch Chief

C. CC Block

44 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50824	ORIG-1	DAVA PHARMACEUTICALS INC	OMEPRAZOLE 25MG/AMOXOCILLIN 500MG/CLARITHROMYCIN 500MG

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

/s/

JEFFREY B MEDWID
07/08/2010

STEPHEN P MILLER
07/08/2010
I concur - CMC can not recommend approval until labeling and inspectional issues are resolved.

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 50-824 **Applicant: DAVA** **Stamp Date: 19 June 2009**

Drug Name: Patient Compliance Pack, OME 20 mg, Clarith 500 mg and Amox 500 mg.

NDA/BLA Type:

505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		(b) (4)
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?		X	IR Letter to be sent 8/19/2009 requesting status of sites for inspection.
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		Approved ANDA's
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		Approved ANDA's
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?	N/A		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified? a. ANDA75-576 Omeprazole, Dr. Reddy b. ANDA 65-178 Clarithromycin, Roxane Labs c. ANDA 62-881 Amoxacillin, DAVA	X		3 LOA for 3 ANDA's And 2 DMF's (b) (4)
10	Is information on the investigational formulations included?	N/A		
11	Is information on the methods validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	N/A		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jeffrey Medwid, Ph.D. 18 August 2009
Reviewing Chemist Date

Norman Schmuff, Ph.D. See DARRTS
Team Leader/Supervisor Date

Dec 2008 version of Filing Template
from:http://inside.fda.gov/ProgramsInitiatives/Drugs/21stCenturyReview/UCM034686.html

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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.

/s/

JEFFREY B MEDWID
08/18/2009

NORMAN R SCHMUFF
08/19/2009