CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213004Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213004
Assessment # 2

Drug Product Name	Talicia (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules
Dosage Form	Capsule
Strength	10 mg*/250 mg/12.5 mg *Each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	RedHill Biopharma Ltd.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0022	October 23, 2019	Drug Product

Refer to NDA 213004 Assessment #1 for the description of the QUALITY ASSESSMENT TEAM, RELATED/SUPPORTING DOCUMENTS, and CONSULTS

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on October 4, 2019.

II. SUMMARY OF QUALITY ASSESSMENTS

Refer to OPQ IQA Assessment #1

A. Quality Assessment Overview

Drug Substance: Adequate

Refer to OPQ IQA Assessment #1

Drug Product: Adequate

The applicant had requested a (b) (4)-month shelf life, but this request was not granted per the review. Five registration batches are included with the stability data in the submission. The amount of stability data submitted is 30 months on one batch, 12 months each on 2 batches and 3 and 6 months on the 4th and 5th batches. Supporting data was submitted for 2 clinical batches. Based on the stability data, a shelf life of 24-month is assigned for the capsules stored at 25°C.

The following comment was sent to the applicant on 10/22/2019:

We acknowledge your request for a (b) (4)-month shelf life. One registration batch had 30 months of stability data, and the other 2 registration batches had 12 months of stability data. Since the shelf life is based on the evaluation of three batches per ICH Q1E, we can extrapolate the 12 months of stability data and can grant a 24-month shelf life. The shelf life can be extended post-approval based on satisfactory data via an Annual Report to the NDA. Please acknowledge this comment and the 24-month shelf life.

The applicant responded on 10/23/2019 that they acknowledge and accept the 24-month shelf life. This is acceptable.

cp

Labeling: Adequate

Refer to OPQ IQA Assessment #1

Manufacturing: Adequate

Refer to OPQ IQA Assessment #1

Biopharmaceutics: Adequate

Refer to OPQ IQA Assessment #1

Microbiology (if applicable): Adequate

Refer to OPQ IQA Assessment #1

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
10/25/2019 07:48:22 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213004
Assessment # 1

Drug Product Name	Talicia (omeprazole magnesium, amoxicillin, and rifabutin) delayed-release capsules
Dosage Form	Capsule
Strength	10 mg*/250 mg/12.5 mg *Each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	RedHill Biopharma Ltd.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	May 2, 2019	All
Amendment (eCTD 004)	May 28, 2019	Drug Product
Amendment (eCTD 007)	July 3, 2019	Drug Product, EA
Amendment (eCTD 010)	July 23, 2019	Process
Amendment (eCTD 011)	August 7, 2019	Biopharmaceutics, Drug Product
Amendment (eCTD 012)	August 13, 2019	Biopharmaceutics
Amendment (eCTD 014)	August 28, 2019	Process
Amendment (eCTD 016)	September 24, 2019	Biopharmaceutics
Amendment (eCTD 018)	September 30, 2019	Drug Product/Pharm.Tox

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Haripada Sarker
Drug Product	Shrikant Pagay	Balajee Shanmugam
Manufacturing	Jiao Yang	Steve Frisbee
Microbiology	Jiao Yang	Steve Frisbee
Biopharmaceutics	Yang Zhao	Elsbeth Chikhale

Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika E. Englund	
Laboratory (OTR)	N/A	
Environmental	Raanan Bloom	Per 7/26/2019 e-mail correspondence, the EA team informed the DP reviewer to accept the updated EA exclusion claim

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	7/21/2017	Reviewed by David Skanchy
	II			Adequate	7/03/2019	Reviewed by Ying Lin
	II			Adequate	10/04/2019	Reviewed by Sharon Kelly
	IV			Refer to DP review for evaluation		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	114552	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	Adequate			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on October 4, 2019.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Helicobacter pylori (H. pylori) infection affects over 50% of the adult population worldwide and 30-40% of the population in United States. This NDA provides for a novel triple drug combination of two antibiotics, rifabutin and amoxicillin, and a proton pump inhibitor (PPI), omeprazole (as omeprazole magnesium), for the treatment (b) (4) of H. pylori infection in adults.

Proposed Indication(s) including Intended Patient Population	Treatment of Helicobacter pylori infection in adults.
Duration of Treatment	Four capsules taken orally once every eight hours for fourteen days with food.
Maximum Daily Dose	150 mg/3000 mg/120 mg *daily dose (12.5mg/250mg/10mg per capsule)*
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

This NDA describes a fixed dose combination product which contains three drug substances: Amoxicillin trihydrate (DMF (b) (4)), Rifabutin (DMF (b) (4)) and Omeprazole magnesium (DMF (b) (4)). The re-test periods for these three drug substances are (b) (4) months respectively. All three drug substances have corresponding USP monographs and the referenced DMFs for all three were found adequate to support this NDA.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the review by Sharon Kelly.

Drug Product: Adequate

The proposed product, Talicia capsule, is a delayed release capsule. Each capsule contains 10 mg of omeprazole as omeprazole magnesium, 250 mg of amoxicillin as amoxicillin trihydrate and 12 mg of rifabutin. The capsule is orange, opaque and size '00'. The capsules are filled into a HDPE bottle with a (b) (4) child-resistant closure. The product is supplied as a carton which contains 2 bottles of Talicia (84 capsules) for a total of 168 capsules.

The excipients in the drug product are found in the Inactive Ingredient database (IID), however, meglumine was found to exceed the daily limits approved in other applications. Based on the daily intake of 12 capsules, the total quantity of meglumine is (b) (4) mg of meglumine, which exceeds levels in the IID. The levels of this excipient were discussed with the pharm/tox team and found to be adequate. Refer to the pharm/tox review for complete details.

The evaluation of the elemental impurities risk assessment and data found that the elemental impurity content of the Class 1 and 2A impurities were below (b) (4) the PDE limits. No additional elemental impurity testing is included in the final drug product specification. The control of the specified impurities was also found acceptable in the drug product specification.

The applicant had requested a (b) (4)-month shelf life, but this request was not granted per the review. Five registration batches are included with the stability data in the submission. The amount of stability data submitted is up to 30 months on one batch, 12 months each on 2 batches and 3 and 6 months on the 4th and 5th batches. Also, supporting data is submitted for the 2 clinical batches. Based on the stability data, a shelf life of 24-month is assigned for the capsules stored at 25°C.

A comment will be sent to the applicant to inform them that the (b) (4)-month shelf life is not granted.

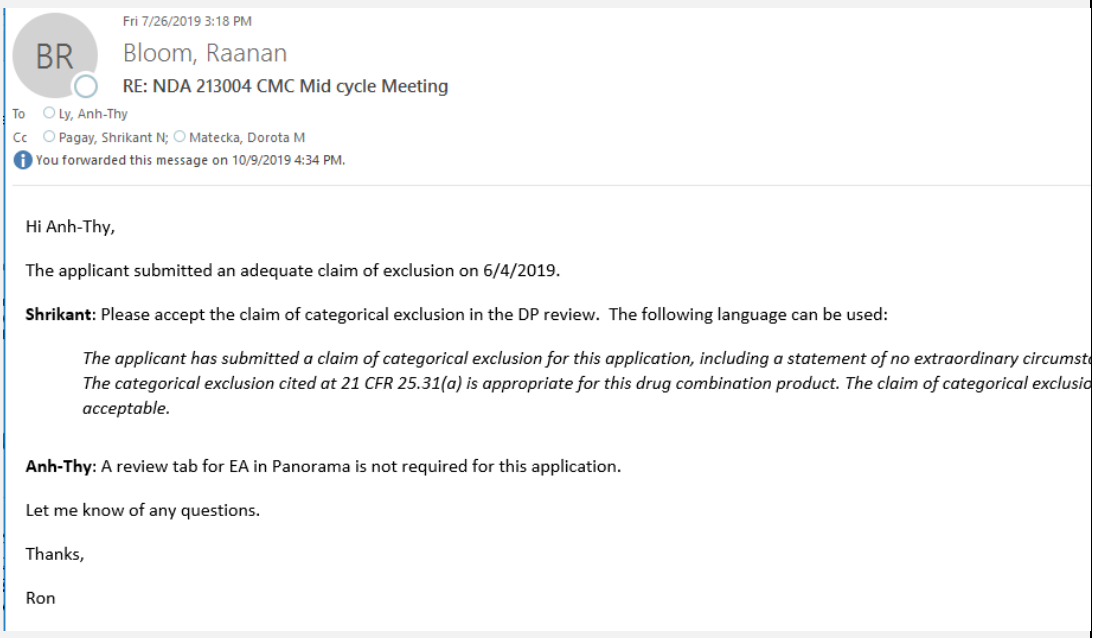
Environmental Assessment:

The Drug product review referenced the separate Environmental Assessment (EA) review. Per the e mail from Raanan Bloom on 7/26/2019, the EA team requested that the DP reviewer accept the updated EA exclusion claim via an insert in the DP review. There is no separate EA

review, but per the 7/26/2019 e mail, the EA exclusion is acceptable. On 7/3/2019, the applicant had submitted the following statement:

Talicia is a combination of 3 generic drugs: amoxicillin, rifabutin, omeprazole. The use of this product would not be expected to significantly increase environmental exposure levels.

Redhill Bipharma Ltd. thereby claims that approval of this NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(a) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.



Fri 7/26/2019 3:18 PM

BR Bloom, Raanan

RE: NDA 213004 CMC Mid cycle Meeting

To Ly, Anh-Thy

Cc Pagay, Shrikant N; Matecka, Dorota M

You forwarded this message on 10/9/2019 4:34 PM.

Hi Anh-Thy,

The applicant submitted an adequate claim of exclusion on 6/4/2019.

Shrikant: Please accept the claim of categorical exclusion in the DP review. The following language can be used:

The applicant has submitted a claim of categorical exclusion for this application, including a statement of no extraordinary circumst
The categorical exclusion cited at 21 CFR 25.31(a) is appropriate for this drug combination product. The claim of categorical exclusio
acceptable.

Anh-Thy: A review tab for EA in Panorama is not required for this application.

Let me know of any questions.

Thanks,

Ron

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Shrikant Pagay.

cp

Labeling: Adequate

The labeling comments were communicated to the OND Project Manager.

Manufacturing: Adequate

(b) (4)

(b) (4)

PAI inspections were conducted for (b) (4) and (b) (4) facilities. The inspections revealed the firm has the expertise and experience to perform the proposed functions with acceptable quality control. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on October 4, 2019.

Biopharmaceutics: Adequate

The Biopharmaceutics Review evaluated the adequacy of (1) the proposed dissolution methods and acceptance criteria for QC testing of the proposed drug product, (2) delayed release claim of omeprazole, and (3) bridging of different manufacturing sites/API sources/formulation composition for clinical formulations and commercial formulations.

Since amoxicillin trihydrate and rifabutin are high solubility compounds in the immediate release component of the drug product, the reviewer considered the dissolution risk with regards to these 2 APIs to be low risk. Based on the in vitro dissolution data, minimal omeprazole release in acidic medium, the formulation design, and PK characteristics measured in the clinic, the proposed product was found to meet the delayed-release claim. The acceptance criteria for the dissolution of omeprazole was also found acceptable (***USP 1 at 100 rpm, in 900 mL of 0.1N HCl medium for 2 hours followed by 900 mL of 50 mM phosphate pH 6.8 medium***).

An alcohol dose dumping study was requested, and it was observed that with the increase in alcohol, dissolution of omeprazole increased. About 100% of omeprazole dissolved in the medium of 0.1N HCl containing 40%

alcohol at the 2 hour time point. Per discussion with the Office of Clinical Pharmacology, a statement was included in the labeling that the product should not be given to patients together with alcohol.

There are differences in drug product manufacturing sites, amoxicillin/rifabutin API sources, and composition, between the formulations used in the pivotal Phase 3 clinical trials (Studies RHB-105-01 and RHB-105-02) and the commercial formulation. The applicant provided data to establish bridging for these differences. The biopharmaceutics review considers that the bridging among different drug product manufacturing sites, API suppliers and minor formulation changes is adequately established.

This NDA is recommended for approval from a biopharmaceutics perspective. For additional details, refer to the review by Yang Zhao.

Microbiology (if applicable): Adequate

The microbiology assessment was included in the Manufacturing review since this is a solid oral product. No separate microbiology review was conducted.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Formulation, manufacture	18	(b) (4)	Acceptable	
Physical stability (solid state)		36		Acceptable	
Content Uniformity (amoxicillin)	Formulation, manufacture	16		Acceptable	
Content Uniformity (omeprazole and rifabutin)	Formulation, manufacture	36		Acceptable	
Microbial Testing	Formulation, Manufacture	6		Acceptable	
Dissolution	Formulation, manufacture	48		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date:

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

BIOPHARMACEUTICS

Drug Product Name: Talicia (Omeprazole magnesium, Amoxicillin, and Rifabutin) Delayed-Release Capsules

Strengths: 10 mg (omeprazole as 10.3 mg omeprazole magnesium)/250 mg (amoxicillin)/12.5 mg (rifabutin)

Route of Administration: Oral

Applicant Name: RedHill Biopharma Ltd.

Indication: Treatment (b) (4) of *Helicobacter pylori* infection in adults

List of Reviewed Submissions:

Original submission dated 5/2/2019
Response dated 7/23/2019 to the Information Request dated 7/3/2019
Response dated 8/7/2019 to the Information Request dated 7/26/2019
Response dated 8/13/2019 to the Information Request dated 7/26/2019
Response dated 9/24/2019 to the Information Request dated 9/20/2019

Biopharmaceutics Review Team:

Primary Reviewer: Yang Zhao, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

REVIEW SUMMARY:

Submission: RedHill Biopharma Ltd. submitted NDA 213004 seeking approval for Talicia (Omeprazole magnesium, Amoxicillin, and Rifabutin) Delayed-Release Capsules, 10 mg (omeprazole)/250 mg (amoxicillin)/12.5 mg (rifabutin), under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for the treatment (b) (4) of *Helicobacter pylori* infection in adults.

Review Objective: The Biopharmaceutics Review evaluated the adequacy of **(1)** the proposed dissolution methods and acceptance criteria for QC testing of the proposed drug product, **(2)** delayed release claim of omeprazole, and **(3)** bridging of different manufacturing sites/API sources/formulation composition for clinical formulations and commercial formulations.

Reviewer's Assessment:

(1) Dissolution Methods and Acceptance Criteria: Considering the nature of formulation design for delayed release (b) (4) of omeprazole, this Reviewer considered that the proposed dissolution method (***USP 1 at 100 rpm, in 900 mL of 0.1N HCl medium for 2 hours followed by 900 mL of 50 mM phosphate pH 6.8 medium***) is acceptable for the routine QC testing of the proposed omeprazole from the proposed drug product. The revised dissolution acceptance criterion of "***Acid stage: NMT*** (b) (4) ***% omeprazole dissolved at 120 minutes; Buffer stage: NLT*** (b) (4) ***% (Q) omeprazole dissolved at 20 minutes***" is acceptable for omeprazole. In addition, omeprazole dissolution in acid increased with the increase in the level of alcohol. This was discussed with the Office of Clinical Pharmacology. A statement "The

Omeprazole/Amoxicillin/Rifabutin Delayed Release Capsules should not be given to patients together with alcohol" will be included in the labeling.

Considering that the drug substances, amoxicillin trihydrate and rifabutin are high solubility compounds and the proposed drug product show immediate release characteristics with regards to amoxicillin and rifabutin, this Reviewer considers that the dissolution risk with regards to amoxicillin and rifabutin is deemed low from a Biopharmaceutics standpoint and the proposed dissolution method for amoxicillin and rifabutin (***USP 1 at 100 rpm, in 900 mL of 0.01N HCl medium***) is acceptable as the quality control test for the proposed drug product. The revised dissolution acceptance criterion of "***NLT (b)(4)% (Q) dissolved in 20 minutes***" is acceptable for both amoxicillin and rifabutin.

Final Dissolution Methods and Acceptance Criteria for Talicia Delayed-Release Capsules

Compound	USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Proposed dissolution acceptance criteria
omeprazole	USP 1 (basket)	100	0–2 hours: 0.1N HCl; Followed by: 50 mM phosphate pH 6.8/37 °C	900 900	Acid stage: NMT (b)(4)% omeprazole dissolved at 120 minutes; Buffer stage: NLT (b)(4)% (Q) omeprazole dissolved at 20 minutes
amoxicillin	USP 1 (basket)	100	0.01N HCl/37 °C	900	NLT (b)(4)% (Q) at 20 minutes
rifabutin	USP 1 (basket)	100	0.01N HCl/37 °C	900	NLT (b)(4)% (Q) at 20 minutes

(2) Delayed Release Claim of Omeprazole: Based on the in vitro dissolution data (minimal omeprazole release in acidic medium), the design of the formulation and the in vivo pharmacokinetic characteristics measured in clinical study RHB-P2-418 [Time to reach omeprazole peak plasma concentration (T_{max}) of the proposed product is 2 hours, which is similar to the T_{max} of the approved Delayed-Release Omeprazole Listed Drug (LD) product (Prilosec capsules, NDA-22056)], the proposed fixed dose combination (FDC) product meets the "delayed release" claim.

(3) Bridging Different Formulations: The Applicant established the bridging between different drug product manufacturing sites using clinical study PK data for omeprazole. The Applicant established the bridging between different drug product manufacturing sites and different API suppliers using in vitro comparative dissolution data for amoxicillin and rifabutin. The Applicant established the bridging between clinical batches and commercial batches (with a minor formulation change) using in vitro dissolution data. This Reviewer considers that the bridging among different drug product manufacturing sites, different amoxicillin and rifabutin API suppliers, and minor formulation changes is adequately established.

OVERALL RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 213004 for Talicia (Omeprazole magnesium, Amoxicillin, and Rifabutin) Delayed-Release Capsules, 10 mg (omeprazole, as 10.3 mg omeprazole magnesium)/250 mg (amoxicillin)/12.5 mg (rifabutin) is **ADEQUATE** and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

1. DRUG PRODUCT:

The proposed drug product is a size 00, orange, hard gelatin shell fixed dose combination (FDC) capsule containing 10 mg of omeprazole in delayed-release (b) (4) and 250 mg of amoxicillin and 12.5 mg of rifabutin in (b) (4). Delayed-release omeprazole (b) (4) of amoxicillin and rifabutin. The formulation is designed (b) (4). The proposed drug product is submitted as a 505(b)(2) and Listed Drugs (LDs) are Prilosec® Delayed Release Capsules (omeprazole, NDA-22056), Amoxil® Capsules (amoxicillin, NDA-50459), Mycobutin® Capsules (rifabutin, NDA-50689). Study RHB-P2-418 is the relative bioavailability study comparing the proposed product vs. LDs.

The composition of the proposed Omeprazole/Amoxicillin/Rifabutin Delayed Release Capsules FDC is shown in Table 1.

Table 1. Composition of commercial Omeprazole/Amoxicillin/Rifabutin Capsules FDC

Component	Quality Standard	Function	mg per capsule
(b) (4)			(b) (4)
Amoxicillin	USP	Active drug substance	
Rifabutin	USP	Active drug substance	
Pregelatinized starch	NF	(b) (4	
(b) (4)			
Omeprazole magnesium	USP	Active drug substance	10.3[5) 6)]
Mannitol-starch	In-house	(b) (4)	(b) (4)
Crospovidone	NF		
Sodium lauryl sulfate	NF		
Meglumine	USP		
Magnesium stearate	NF		
(b) (4)	In-house		
	In-house		
	USP		
Total			
Capsule			
Hard gelatin capsule, Size 00	In-house	Encapsulate contents	
Total			

1) Equivalent to 250 mg of amoxicillin (b) (4)

(b) (4)

5) Equivalent to 10 mg of omeprazole, (b) (4).
(b) (4)

2. PROPOSED DISSOLUTION METHOD:

2.1 Dissolution Testing:

The proposed dissolution methods and acceptance criteria for Omeprazole/Amoxicillin/Rifabutin Capsules FDC are as follows:

Compound	USP Apparatus	Speed (rpm)	Medium/Temp	Volume (mL)	Proposed dissolution acceptance criteria
omeprazole	USP 1 (basket)	100	0–2 hours: 0.1N HCl; Followed by: 50 mM phosphate pH 6.8/37 °C	900 900	Acid stage: NMT (b) (4)% omeprazole dissolved at 120 minutes; Buffer stage: NLT (b) (4)% (Q) omeprazole dissolved at (b) (4) minutes
amoxicillin	USP 1 (basket)	100	0.01N HCl/37 °C	900	NLT (b) (4)% (Q) in (b) (4) minutes
rifabutin	USP 1 (basket)	100	0.01N HCl/37 °C	900	NLT (b) (4)% (Q) in (b) (4) minutes

Per the Applicant, the solubility for omeprazole magnesium, amoxicillin trihydrate, and rifabutin are reported in Table 2. Per BCS criteria, amoxicillin trihydrate (3*250 mg/900 mL=0.83 mg/mL<solubility of 1.18 mg/mL at pH 1.2) and rifabutin (3*12.5 mg/900 mL=0.042 mg/mL< solubility of 0.5 mg/mL at pH 6.8) are high solubility compounds.

Table 2. Applicant's reported solubility for omeprazole magnesium, amoxicillin trihydrate, and rifabutin

Different pH media	Omeprazole magnesium	Amoxicillin trihydrate	Rifabutin
	Solubility, mg/mL		
1.2	instable	1.18	3.4
4.5	instable	3.14	8.27
6.8	0.20	4.25	0.50

It is noted that the Applicant did not provide a dissolution method development report, nor investigate the discriminating ability of the dissolution methods. Though the Applicant did not demonstrate the discriminating ability of the dissolution method, considering the selection of the dissolution conditions (e.g., apparatus, rotation speed, dissolution media and the volume) and the nature of the formulation design for delayed release (b) (4) of omeprazole and immediate release of amoxicillin/rifabutin, this Reviewer considered that the proposed dissolution methods is acceptable for the routine QC testing of the proposed

Omeprazole/Amoxicillin/Rifabutin Delayed Release Capsules at batch release and during stability studies.

2.2 Dissolution Data:

The Batches L143-01051/L143-01052 (C00323, from (b) (4), referred to as "(b) (4)") and 501570 (from (b) (4), referred to as "(b) (4)") were used in clinical studies RHB-P2-418 (phase 1 study evaluating relative bioavailability, study objectives: to determine the relative bioavailability of omeprazole, amoxicillin, and rifabutin following the administration of the proposed product vs. LDs under fasting conditions and to assess the safety on healthy volunteers) and RHB-105-12 (phase 1 study evaluating food effect) (Table 3)[1]. Studies RHB-105-01 and RHB-105-02 are phase 3 efficacy and safety studies.

Table 3. Batch description of Omeprazole/Amoxicillin/Rifabutin Capsules FDC product used in clinical studies for marketing purpose

Trial	Lot/Batch	Manufacturer	Population
Study RHB-P2-418	L143-01051/L143-01052	(b) (4)	Healthy Subject
Study RHB-105-12	RHB-105: 501570 Active comparator: 501571		Healthy Subject
Study RHB-105-01	RHB-105 –Lot number L143-01051/52 Placebo- Lot Number L143-01047		Patients with *H. pylori* infection
Study RHB-105-02	RHB-105: 501570, 502032 Active comparator: 501571, 502033		Patients with *H. pylori* infection

Abbreviations: *H. pylori* = *Helicobacter pylori*

[1] \\cdsesub1\evsprod\nda213004\0001\m2\27-clin-sum\summary-biopharm.pdf

Registration batches included Batches 502032, 501337, 502095, and 502637 (Table 4).

Table 4. Batch description of Omeprazole/Amoxicillin/Rifabutin Capsules FDC product

Batch	Condition	Table number	Batch Purpose	Stability time points completed
501337	Accelerated	Table 2	Registration/stability	0,1,3,6
	Long Term	Table 3		0,3,6,9,12,18,24,30
502032	Accelerated	Table 4	Registration/stability	0,1,3,6
	Long Term	Table 5		0,3,6,9,12
502095	Accelerated	Table 6	Registration/stability	0,1,3,6
	Intermediate	Table 7		0,3,6,9,12
	Long Term	Table 8		0,3,6,9,12
502509	Accelerated	Table 9	Registration/stability	0,1,3,6
	Long Term	Table 10		0,3,6
502637	Accelerated	Table 11	Registration/stability	0,1,3
	Long Term	Table 12		0,3
C00323	Accelerated	Table 13	Clinical phase III, supporting stability	0,1,2,3
	Intermediate	Table 14		0,3,6,9
	Long Term	Table 15		0,3,6,9,12,18,24
501570	Long Term	Table 16	Clinical phase III, supporting stability	0,12,18,24[1)]

1) Study on material from 501570 was placed on stability after being returned from the warehouse. Samples were retested, and stability study started in Oct 2017, 12 months after manufacture (retest data was used for 12 month timepoint)

The provided dissolution profile data for omeprazole, amoxicillin, and rifabutin were shown in Figure 1 and Tables 5, 8–14. It was observed that the omeprazole dissolution for Batches C00323 and 501570 decreased by about 4–6% from the times points of 20 minutes to 60 minutes during the buffer stage dissolution test (Figure 1). In the Information Request (IR) dated 7/26/2019, the Applicant was asked to provide an explanation for the decrease in omeprazole dissolution. In the Response dated 8/7/2019, the Applicant reported that omeprazole dissolution profiles for all batches showed a similar trend with a maximum dissolution observed at the time points of 20 to 30 minutes and a gradual degradation afterwards (Table 5). The Applicant explained that this omeprazole degradation in the buffer stage may be due to an interaction between the dissolved (b) (4) in basic solution and the dissolved omeprazole, resulting in the production of omeprazole related substances (Table 6). The Applicant stated that this omeprazole degradation seems to be significant when stored at room temperature or refrigerated after 24 hours. The Applicant reported that HPLC sample analysis was completed within 8 hours of sampling to minimize degradation. In an IR dated 9/20/2019, the Applicant was asked to provide individual dissolution data for omeprazole from all available batches. In the Response dated 9/24/2019, the Applicant provided individual dissolution data for omeprazole from all available batches (Table 7). Based on the individual dissolution data, there were a gradual decrease in omeprazole dissolution data from 30 minutes to 60 minutes. This Reviewer considers that the proposed dissolution method for omeprazole is reasonable and an appropriate dissolution acceptance

criterion should be set prior to the time point of 30 minutes in order to avoid the gradual decrease phase in omeprazole dissolution.

Figure 1. Omeprazole dissolution results from Batch (b) (4) L143-01051/L143-01052 B0T100 (also named C00323, used in clinical studies RHB-P2-418 and RHB-105-01) and Batch (b) (4) 501570 using the buffer stage of the proposed method

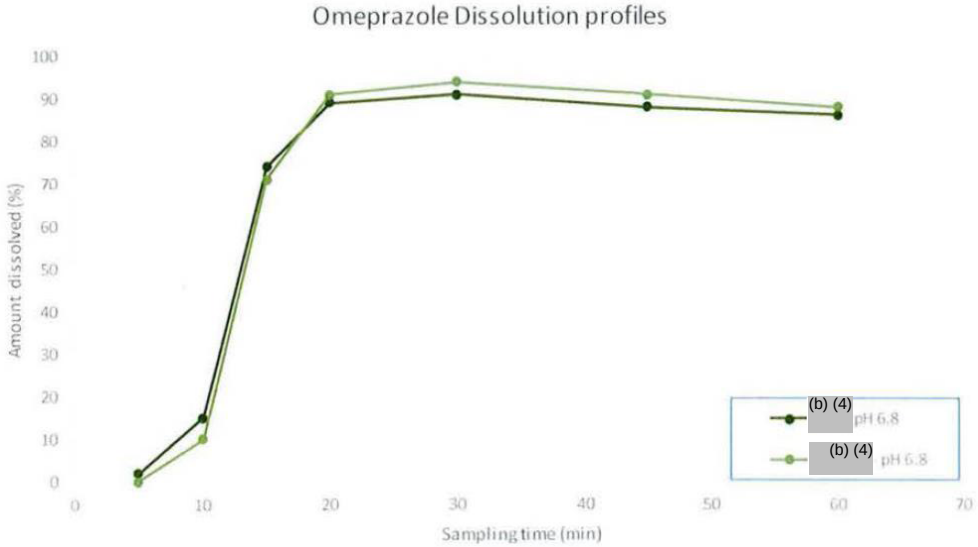


Table 5. Omeprazole dissolution results from all available batches using the buffer stage of the proposed method (provided in the response dated 8/7/2019)

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Lot #	C00323	501337	501570	502032	502095	502509	502637
				15 min 85.5%	15 min 84.9%	15 min 85.4%	15 min 83.2%
	20 min 90%	20 min 89%	20 min 90%	20 min 90.4%	20 min 89.0%	20 min 86.8%	20 min 87.5%
	30 min 90%	30 min 93%	30 min 89%	30 min 90.2%	30 min 88.4%	30 min 87.2%	30 min 87.4%
	45 min 88%	45 min 91%	45 min 87%	45 min 87.8%	45 min 86.0%	45 min 85.8%	45 min 85.6%
	60 min 86%	60 min 89%	60 min 84%	60 min 85.1%	60 min 83.5%	60 min 83.6%	60 min 83.3%
Maximum % (time)	90% (30 mins)	93% (30 mins)	90% (20 mins)	90.4% (20 mins)	89.0% (20 mins)	87.19% (30 mins)	87.5% (20 mins)

Table 6. Production of omeprazole related substances during the buffer stage dissolution (provided in the response dated 8/7/2019)

	Related substances/assay method	
Time (min.)	% LC	Total Related Substances (%LC)
Acid – 120	Not tested	N/A
Buffer - 30	86 (82-86)	3
Buffer - 45	87 (86-88)	4
Buffer - 60	87 (85-88)	4

Table 7. Individual omeprazole dissolution data (provided in the response dated 9/24/2019) using the buffer stage of the proposed dissolution method

Batch C00323 (used in clinical trial RHB-105-01 and RHB-P2-418)

Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	Not tested	(b) (4)			
2					
3					
4					
5					
6					

Batch 501570 (used in clinical trial RHB-105-02 and RHB-105-12)

Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	Not tested	(b) (4)			
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Batch 501337

Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	Not tested	(b) (4)			
2					
3					
4					
5					
6					

Batch 502032

Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	(b) (4)				
2					
3					
4					
5					
6					

Batch 502095

Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	(b) (4)				
2					
3					
4					
5					
6					

Batch 502637

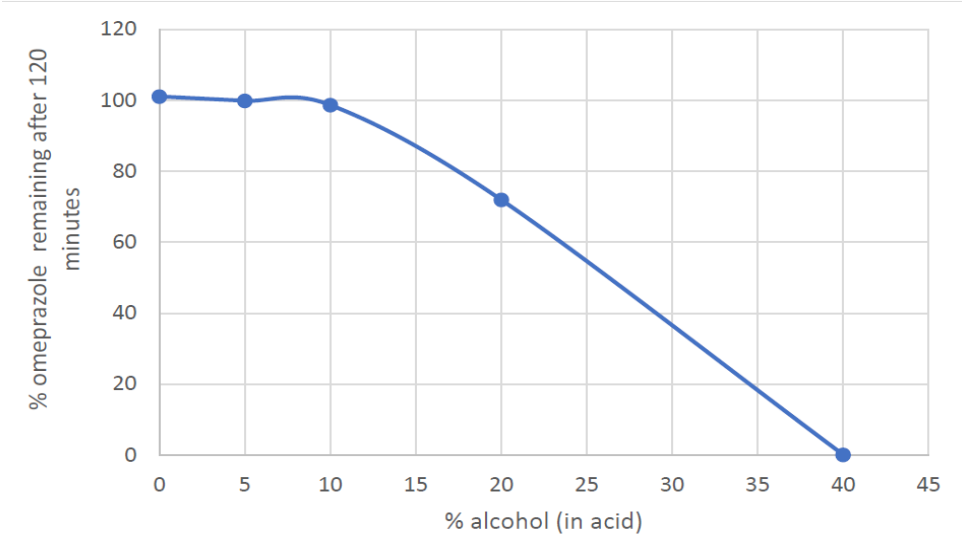
Vessel #	15 mins	20 mins	30 mins	45 mins	60 mins
1	(b) (4)				
2					
3					
4					
5					
6					

Reviewer's Assessment: *Though the Applicant didn't investigate the discriminating ability of the dissolution methods, considering the selection of the dissolution conditions, the nature of formulation design for delayed release* (b) (4) *of omeprazole and immediate release of amoxicillin/rifabutin, and the dissolution profile data obtained, this Reviewer considered that the proposed dissolution methods (**USP 1 at 100 rpm in 900 mL of 0.1N HCl followed by 900 mL of 50 mM phosphate pH 6.8 for omeprazole, USP 1 at 100 rpm in 900 mL of 0.01N HCl for amoxicillin and rifabutin**) are **acceptable** for the routine QC testing of the proposed Omeprazole/Amoxicillin/Rifabutin Delayed Release Capsules at batch release and during stability studies.*

2.3 Alcohol Dose Dumping Study for Omeprazole:

In the IR dated 7/26/2019, the Applicant was requested to provide omeprazole dissolution profile data for the proposed Omeprazole/Amoxicillin/Rifabutin Capsules FDC product upon exposure to alcohol at the acid stage. In the Response dated 8/13/2019, the Applicant provided in vitro alcohol dose dumping study data for Batch 502032. Because omeprazole is an acid-labile drug with a half-life of 10 minutes in acid (pH < 4), dissolved omeprazole rapidly degrades in acid. Therefore, the remaining omeprazole within the (b) (4) capsule was measured to determine the amount of un-dissolved drug (Figure 2). It was observed that, with the increase in the level of alcohol, dissolution of omeprazole increased, with about 100% omeprazole dissolved in the medium of 0.1N HCl containing 40% of alcohol at the time point of 2 hours.

Figure 2. % Remaining omeprazole in the proposed FDC capsule after exposure to the medium of 0.1N HCl containing different concentrations of alcohol for 120 minutes (provided in the response dated 8/13/2019)



Reviewer's Assessment: *Per in vitro alcohol dose dumping study, omeprazole dissolution increased with the increase in the level of alcohol. These results were discussed with the Office of Clinical Pharmacology. The drug product label will include a statement "The*

Omeprazole/Amoxicillin/Rifabutin Delayed Release Capsules should not be given to patients together with alcohol".

2.4 Dissolution Stability Data:

The Applicant provided dissolution data for clinical batches (C00323 and 501570) and registration batches stored under long-term stability conditions (Tables 8–14).

It was noted that, for the clinical batch C00323 stored under long-term conditions, the dissolution data for omeprazole and amoxicillin at the 24-month stability time point decreased by about 10% (Table 8). In the IR dated 7/26/2019, the Applicant was asked to provide a root cause analysis for this decrease. In the Response dated 8/7/2019, the Applicant stated that, in terms of omeprazole dissolution stability data, the 24-months dissolution stability data analysis appeared to be an outlier, considering the additional provided 36-months dissolution stability data (Table 8). However, in terms of amoxicillin dissolution stability data, the Applicant stated that an increase in amoxicillin related substances was observed from 0.7% to 1.1% over the 24 months storage period, and reported that the decreasing trend of amoxicillin dissolution over the storage duration was not observed in other registration batches manufactured at (b) (4) site. This Reviewer considered that the provided explanation for the amoxicillin dissolution decrease upon storage at long term conditions observed for the clinical batch C00323 does not fully explain the observed dissolution decrease. The Drug Product Reviewer will determine the shelf life of the proposed product. In addition, in the IR dated 9/20/2019, individual omeprazole dissolution data for the clinical batch C00323 stability samples were requested. In the Response dated 9/24/2019, individual omeprazole dissolution data for the clinical batch C00323 stability samples were provided (Table 9).

Table 8. Mean dissolution results for batch C00323 long-term stability samples (encapsulation date of 5/30/2013)[2] using the proposed dissolution method (data provided in the response dated 8/7/2019)

			Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Amoxicillin Dissolution	20 min	(b) (4)	90	90	85	89	86	82	80	83
	30 min		96	93	90	95	91	90	85	87
	45 min		97	93	92	97	92	91	87	88
	60 min		97	92	93	97	91	91	88	88
Omeprazole Dissolution	Acid 120 min	NMT (b) (4)%	0	2	0	2	0	2	3	2
	Buffer 20 min	(b) (4)	90	96	100	94	95	99	84	94
	30 min		90	95	98	93	93	96	86	93
	45 min		88	92	95	90	91	93	83	91
	60 min		86	90	92	87	88	92	80	89

Test Parameter		Limit	Initial	3 months	6 months	9 months	12 months	18 months	24 months
Rifabutin Dissolution	20 min	(b) (4)	95	98	95	95	99	91	97
	30 min		97	97	94	94	99	91	93
	45 min		98	96	94	93	99	91	93
	60 min		97	96	94	93	98	90	93

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[2] \\cdsesub1\evsprod\nda213004\0007\m3\32-body-data\32p-drug-prod\rhb105-oralcapsule\32p8-stab\stability-data.pdf

Table 9. Individual dissolution results for batch C00323 long-term stability samples (encapsulation date of 5/30/2013)[3] using the proposed dissolution method

Amoxicillin Dissolution

		Initial	3 months	6 months	9 months	12 months	18 months[1]		24 months	36 months
							Stage 1	Stage 2		
20 min	(b) (4)									(b) (4)
30 min										
45 min										
60 min										

[1] Stage 2 testing was required. Results conform with stage 2, average of 12 units (S_1+S_2) is ≥Q, and no unit is <Q – (b) (4)%.

Omeprazole Dissolution in the buffer stage of the proposed dissolution method

		Initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Acid Stage	(b) (4)								(b) (4)
20 min									
30 min									
45 min									
60 min									

[3] \\cdsesub1\evsprod\nda213004\0007\m3\32-body-data\32p-drug-prod\rhb105-oralcapsule\32p8-stab\stability-data.pdf

Table 10. Dissolution results for batch 501570 long-term stability samples (encapsulation date of 10/20/2016)[4] using the proposed dissolution method

Test Parameter		Limit	Release	12 month *initial	18 months	24 months
Omeprazole Dissolution	Acid – 120 mins	NMT (b) (4)%	3.3	4.9	6.1	Not tested
	Buffer - 15 mins	(b) (4)	N/A	87	87	Not tested
	20 min		90	90	89	Not tested
	30 min		89	90	88	Not tested
	45 min		87	87	86	Not tested
	60 min		84	85	83	Not tested
Amoxicillin Dissolution	15 min		Not tested	95	90	93
	20 min		72	97	93	94
	30 min		91	96	92	94
	45 min		94	94	91	93
	60 min		94	93	90	91
Rifabutin Dissolution	15 min		Not tested	89	91	95
	20 min		83	93	94	97
	30 min		93	93	94	98
	45 min		94	92	94	97
	60 min		94	92	94	97

Table 11. Dissolution results for Batch 502032 stored under long term conditions, using the proposed dissolution method

Test Parameter		Limit	Initial	3 month	6 month	9 month	12 month
Amoxicillin Dissolution	15 min	(b) (4)	85	94	98	92	94
	20 min		94	96	101	94	95
	30 min		95	96	100	94	95
	45 min		95	95	98	93	94
	60 min		94	93	97	93	93
	15 mins		85	90	95	90	96
Rifabutin Dissolution	20 mins		94	93	98	93	98
	30 min		95	93	98	94	99
	45 min		95	93	98	94	99
	60 min		94	93	97	93	98
Omeprazole Dissolution	Acid 120 min	NMT (b) (4)%	< 1	4.0	3.9	3.2	4.0
	Buffer 15 min	(b) (4)	86	85	90	88	89[1]
	20 min		90	90	90	90	90[1]
	30 min		90	90	87	91	89[1]
	45 min		88	87	85	89	87[1]
	60 min		85	84	81	86	84[1]

Table 12. Dissolution results for Batch 501337 stored under long term conditions, using the proposed dissolution method

Test Parameter		Limit	Initial	3 months	6 months	9 months	12 months	18 months	24 months	30 months
Amoxicillin Dissolution	20 min	(b) (4)	85	96	92	90	89	95	92	96
	30 min		96	96	95	95	94	96	92	97
	45 min		96	94	95	94	93	95	91	95
	60 min		95	93	93	93	91	93	90	94
Rifabutin Dissolution	20 min		86	93	92	94	92	97	94	100
	30 min		99	96	95	96	98	98	95	101
	45 min		100	96	96	96	98	98	95	101
	60 min		99	96	95	96	98	98	94	100
Omeprazole Dissolution	Acid 120 min	NMT (b) (4)%	1.6	0.4	2.0	0.6	1.7	2.9	1.5	0.0
	Buffer 20 min	(b) (4)	89	93	89	88	93	92	94	88
	30 min		93	92	92	92	96	91	93	88
	45 min		91	90	90	90	93	89	91	85
	60 min		89	87	87	87	91	86	89	82

[4] \\cdsesub1\evsprod\nda213004\0007\m3\32-body-data\32p-drug-prod\rhb105-oralcapsule\32p8-stab\stability-data.pdf

Table 13. Dissolution results for Batch 502095 stored under long term conditions, using the proposed dissolution method

Test Parameter		Limit	Initial	3 month	6 month	9 month	12 month
Amoxicillin Dissolution	15 min	(b) (4)	93	90	91	95	92
	20 min		96	95	94	97	95
	30 min		96	95	94	97	95
	45 min		96	94	93	100	94
	60 min		94	93	92	95	93
Rifabutin Dissolution	15 mins		94	89	88	97	93
	20 mins		98	95	94	100	96
	30 min		98	95	95	100	97
	45 min		98	95	94	99	97
	60 min		97	95	94	98	97
Omeprazole Dissolution	Acid 120 min	NMT (b) (4)%	6.1	7.4	5.4	5.2	3.1
	Buffer 15 min	(b) (4)	85	84	84	86	74
	20 min		89	86	86	89	75
	30 min		88	85	86	89	74
	45 min		86	83	86	87	76
	60 min		83	80	81	84	73

Table 14. Dissolution results for Batch 502637 stored under long term conditions, using the proposed dissolution method

Test Parameter			Limit	Initial	3 months
Amoxicillin Dissolution		15 min	(b) (4)	93	93
		20 min		96	97
		30 min		96	97
		45 min		95	96
		60 min		94	95
Rifabutin Dissolution		15 mins		96	95
		20 mins		100	99
		30 min		101	100
		45 min		100	99
		60 min		100	99
Omeprazole Dissolution	Acid	120 min	NMT (b) (4)%	4.6	3.7
	Buffer	15 min	(b) (4)	83	89
		20 min		87	88
		30 min		87	86
		45 min		86	84
		60 min		83	80

It was noted that the Batch 502509 demonstrated slower dissolution than other batches, in particular for amoxicillin (49% drug release compared with 85%–93% from other batches at 15 minutes) and rifabutin (65% drug release compared with 94% from other batches at 15 minutes) (Table 15). In the IR dated 7/26/2019, the Applicant was asked to provide an explanation for the slower dissolution of Batch 502509. In the Response dated 8/7/2019, the Applicant stated that (b) (4) was added (b) (4) for Batch 502509 in order to improve homogeneity and meet (b) (4). The Applicant explained that the (b) (4) added (b) (4) was the cause for the slower dissolution for this batch (b) (4)

(b) (4). The Applicant also stated that the standard amount of (b) (4) batch of amoxicillin/rifabutin/ (b) (4) is (b) (4) Per the assigned Process Reviewer, (b) (4) demonstrated by higher (b) (4) time and higher (b) (4) might be the possible reason for the slower dissolution for the Batch 502509 (Table 16). This Reviewer considers that setting the dissolution acceptance criterion for the proposed product should be able to reject this developmental batch. The final agreed upon dissolution acceptance criterion of NLT (b) (4)% (Q) at 20 minutes for amoxicillin and rifabutin is able to reject this Batch 502509.

Table 15. Dissolution results for Batch 502509 (considered as a developmental batch by this Reviewer) stored under long term conditions, using the proposed dissolution method

Test Parameter		Limit	Initial	3 months	6 months
Amoxicillin Dissolution	15 min	(b) (4)	49	80	67
	20 min		67	97	81
	30 min		90	104	92
	45 min		99	104	98
	60 min		100	103	100
Rifabutin Dissolution	15 mins		65	83	75
	20 mins		80	94	85
	30 min		94	98	94
	45 min		99	98	99
	60 min		99	98	101
Omeprazole Dissolution	Acid - 120 min	NMT (b) (4)%	6.6	8.8	7.3
	Buffer - 15 min	(b) (4)	85	81	86
	20 min		87	85	86
	30 min		87	85	87
	45 min		86	84	85
	60 min		84	81	82

Table 16. (b) (4) for the registration batches

(b) (4)

Reviewer's Assessment: *Dissolution data for omeprazole and amoxicillin, not rifabutin, for a clinical batch (C00323, used in the clinical studies RHB-P2-418 and RHB-105-01) at the 24-month stability time point decreased by about 10%. The dissolution data for omeprazole (94% at 20 minutes) for the same batch at the 36-month stability time point meet the dissolution acceptance criterion of NLT (b) (4)% (Q) at 20 minutes, while, dissolution data for amoxicillin (83% at 20 minutes) at the 36-month stability time point (b) (4) meet the dissolution acceptance criterion of NLT (b) (4)% (Q) at 20 minutes. These results were discussed with the Drug Product Reviewer. The Drug Product Reviewer will determine the shelf life of the proposed product.*

2.5 Dissolution Acceptance Criteria:

The Applicant's proposed dissolution acceptance criteria of "acid stage: NMT (b) (4)% dissolved at 120 minutes and buffer stage: NLT (b) (4)% (Q) dissolved at (b) (4) minutes for omeprazole, NLT (b) (4)% (Q) in (b) (4) minutes for amoxicillin and rifabutin" are permissive and not acceptable. Therefore, in the IR dated 9/20/2019, the Applicant was recommended to revise the dissolution acceptance criteria.

In the Response dated 9/24/2019, the Applicant revised the dissolution acceptance criteria per recommendation as follows:

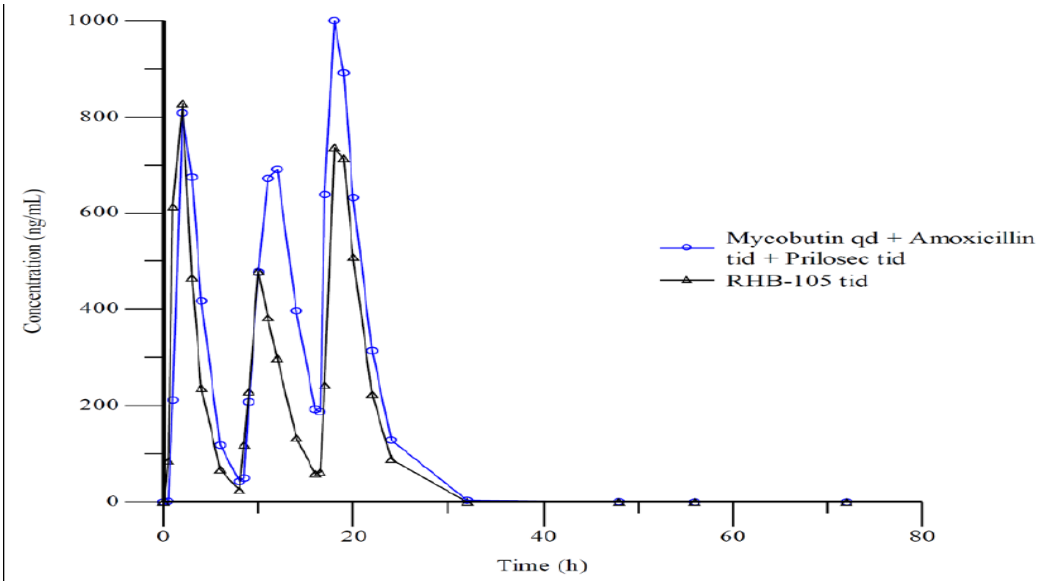
For omeprazole: acid stage: NMT (b) (4)% omeprazole dissolved at 120 minutes;
buffer stage: NLT (b) (4)% (Q) omeprazole dissolved at 20 minutes;
For amoxicillin: NLT (b) (4)% (Q) in 20 minutes;
For rifabutin: NLT (b) (4)% (Q) in 20 minutes.

Reviewer's Assessment: *Based on the provided dissolution data, the agreed upon dissolution acceptance criteria of "for omeprazole: acid stage: NMT (b) (4)% at 120 minutes; buffer stage: NLT (b) (4)% (Q) at 20 minutes; for amoxicillin: NLT (b) (4)% (Q) in 20 minutes; for rifabutin: NLT (b) (4)% (Q) in 20 minutes" are acceptable.*

3. DELAYED RELEASE CLAIM OF OMEPRAZOLE:

Based on the in vitro dissolution data (minimal drug release in acidic medium), the nature of formulation design, and in vivo clinical study RHB-P2-418 [Time to reach peak plasma concentration (T_{max}, 2 hours) of the proposed product is similar to the T_{max} of the Delayed-Release Omeprazole LD product (Prilosec), Figure 3], omeprazole meets the "delayed release" claim.

Figure 3. Omeprazole concentration-time profiles following 4× the proposed Omeprazole/Amoxicillin/Rifabutin Capsules FDC product vs. 40 mg Delayed-Release Omeprazole (Prilosec, LD) administered tid in study RHB-P2-418



Reviewer's Assessment: *The proposed Omeprazole/Amoxicillin/Rifabutin Capsules FDC product meets the "delayed release" (DR) claim based on the DR characteristics of omeprazole.*

4. BRIDGING DIFFERENT CLINICAL AND COMMERCIAL FORMULATIONS:

It is noted that there are differences in drug product manufacturing sites, amoxicillin/rifabutin API sources, and composition, between the formulations used in the pivotal Phase 3 clinical trials (Studies RHB-105-01 and RHB-105-02) and the commercial formulation (Table 17).

Table 17. Composition of the pivotal phase 3 clinical batches manufactured at differed drug product manufacturing sites[1,2] and containing amoxicillin/rifabutin from different API sources[1,2] vs. commercial formulation

Component	Study RHB-105-01 mg per capsule[1]	Study RHB-105-02 mg per capsule[2]	Commercial mg per capsule[2]
	(b) (4)		
Amoxicillin	(b) (4)	(b) (4)	(b) (4)
Rifabutin			
Pregelatinized starch			
	(b) (4)		
Omeprazole magnesium		10.3[7,8]	10.3[7, 8]
Mannitol-starch			(b) (4)
Crospovidone			
Sodium lauryl sulfate			
Meglumine			
Magnesium stearate			
	(b) (4)		
Total			
Capsule			
Hard gelatin capsule, Size 00			
Total			
			(b) (4)
3 Equivalent to 250 mg of amoxicillin		(b) (4)	
			(b) (4)
7 Equivalent to 10 mg of omeprazole,		(b) (4)	
			(b) (4)

4.1 Bridging to support the manufacturing site change, API source change, and minor formulation compositional change between the drug product used in the first pivotal clinical study (RHB-105-01) and those used in the second pivotal clinical study (RHB-105-02):

The differences between the drug product used in the first pivotal clinical study (RHB-105-01) and those used in the second pivotal clinical study (RHB-105-02) shown in Table 17 include: (1) different drug product manufacturing site; The first pivotal clinical study used drug product batches manufactured at (b) (4) (batch C00323), while, the second pivotal clinical study

used drug product from (b) (4) (batches 501570 and 502032), which is the proposed commercial drug product manufacturer. The Applicant stated that all major equipment used at the (b) (4) and (b) (4) drug product manufacturing sites were similar, except for (b) (4) (2) different API sources to manufacture the drug product batches for the first and the second pivotal clinical studies. Batch C00323 used in the first pivotal clinical study vs. Batch 501570 used in the second pivotal clinical study contain amoxicillin and rifabutin with different drug substance particle sizes from different API suppliers (Table 18); and (3) (b) (4) between the drug product used in the first pivotal clinical study and the second pivotal clinical study are different, resulting in minor changes in the amounts of certain excipients.

Table 18. API used for manufacture of Batch C00323 (also named as L143-01051/52, used in Study RHB-P2-418) and Batch 501570 (used in Study RHB-105-12)

	Rifabutin Supplier and PSD	Amoxicillin supplier and PSD	Omeprazole supplier and PSD
L143-01051/52	(b) (4)		
501570			

1 (b) (4)
2

The bridging to support the product manufacturing site change, the amoxicillin/rifabutin API source change, and minor formulation compositional change will be established based on (1) PK data for omeprazole, (2) in vitro dissolution profile data for amoxicillin and rifabutin.

(1) Based on the results from the clinical studies RHB-P2-418 (Batch C00323 used, tid dosing, fast) and RHB-105-12 (Batch 501570 used, single dose, fast), omeprazole demonstrated similar exposure levels of mean C_{max} (830 ng/mL vs. 740 ng/mL) and mean AUC (2111 ng·h/mL vs. 1693 ng·h/mL) after the first dose administration (see \\cdsesub1\evsprod\nda213004\0001\m2\27-clin-sum\summary-biopharm.pdf).

(2) Based on the comparative dissolution profiles for Batch C00323 (the first pivotal clinical study batch) vs. Batch 501570 (the second pivotal clinical study batch) in dissolution media of pH 2.0, 4.5, and 6.8 (see in Response dated 7/23/2019), both batches demonstrated the similar dissolution profiles for amoxicillin and rifabutin (Figures 4 and 5).

Figure 4. Amoxicillin dissolution profiles of Batch C00323 (the first pivotal clinical study batch) vs. Batch 501570 (the second pivotal clinical study batch)

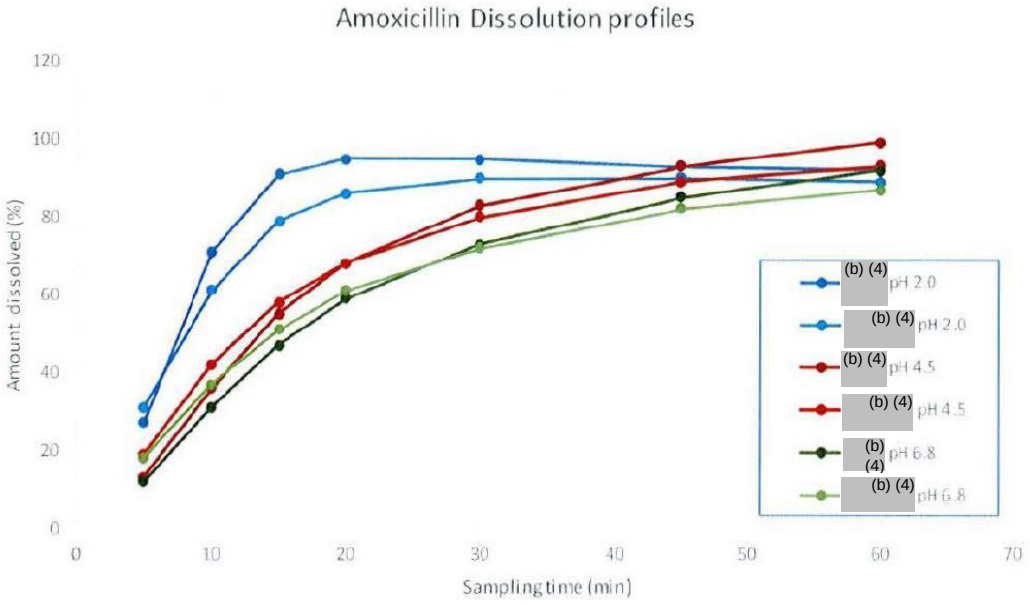
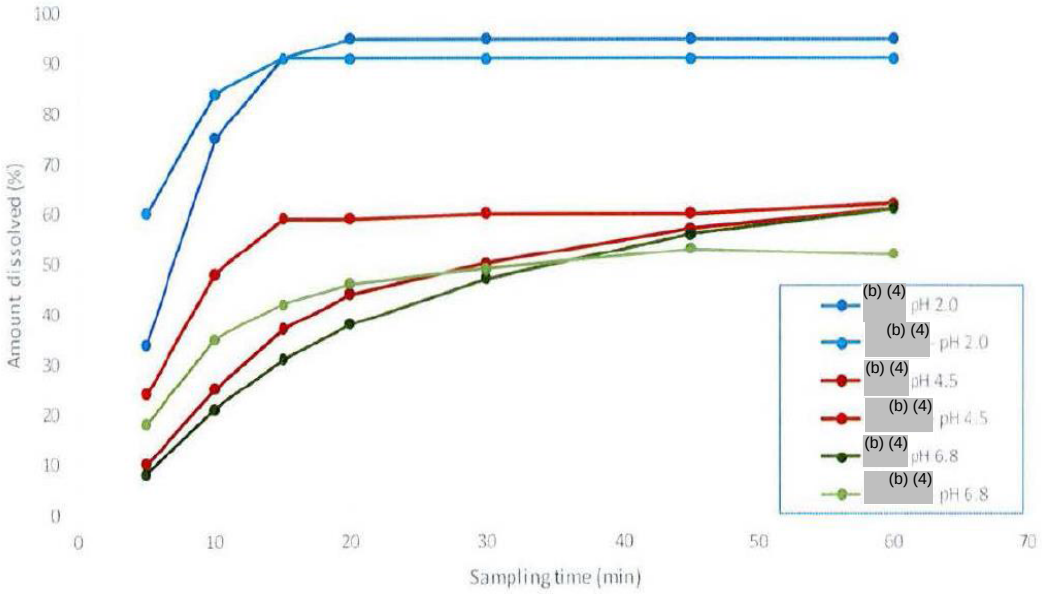


Figure 5. Rifabutin dissolution profiles of Batch C00323 (the first pivotal clinical study batch) vs. Batch 501570 (the second pivotal clinical study batch)



Reviewer's Assessment: *Due to the delayed release characteristics of omeprazole, a drug product manufacturing site change will normally require a BE study. Although drug product manufactured at both manufacturing sites was used in the pivotal phase 3 clinical studies, no PK plasma samples were analyzed during the pivotal clinical studies. Instead, the PK of the proposed FDC drug product was determined in study RHB-P2-418, using drug product manufactured at* (b) (4) *. Based on the provided omeprazole PK data in the studies RHB-P2-418 (using* (b) (4)

drug product) and RHB-105-12 (using (b) (4) *drug product), the bridging between the two drug product manufacturing sites is established for omeprazole.*

In addition, the Applicant established the bridging between the two drug product manufacturing sites and different API suppliers using in vitro comparative dissolution data for amoxicillin and rifabutin.

In conclusion, the similar PK profile data for omeprazole and similar in vitro dissolution profile data for amoxicillin and rifabutin, support the drug product manufacturing site change and the amoxicillin and rifabutin API source change, and minor formulation change between the two manufacturing sites. In addition, the use of drug product manufactured at different sites, containing API from different sources, with slightly different compositions as described above, in both pivotal clinical studies demonstrating the safety and efficacy of the proposed drug product, supports the similarity between the drug product batches used in the first and second pivotal clinical studies.

4.2 Bridging to support the minor formulation compositional change between the drug product used in the second pivotal clinical trial (RHB-105-02) and the commercial formulation:

The difference between the drug products used in the second pivotal clinical study and the commercial formulation shown in Table 19 only includes (b) (4) a minor change in the amount of excipient. The Applicant reported that, for commercial production, (b) (4) was proposed for both amoxicillin and rifabutin (b) (4), while the clinical batches manufactured at the same site of (b) (4) contained (b) (4) for amoxicillin and (b) (4) for rifabutin.

Therefore, the bridging to support the similarity of the minor compositional change between the drug products used in the second pivotal clinical study and the commercial drug products will be established by in vitro dissolution profile data for omeprazole, amoxicillin, and rifabutin.

Based on the dissolution profiles obtained using the proposed dissolution methods for the batches 501570 and 502032 (used in the second pivotal clinical study) vs. the registration batches 501337, 502095, and 502637 (commercial formulation) (Table 12–16), all batches demonstrated similar dissolution profiles for omeprazole, amoxicillin, and rifabutin, because all batches demonstrated >85% drug release within 15 or 20 minutes, which eliminates the need to calculate the dissolution similarity f_2 factors.

Reviewer's Assessment: *The Applicant established the bridging between drug product used in the second clinical trial and commercial drug product (with a minor formulation change) using in vitro dissolution data.*

Overall, this Reviewer considers that the bridging among different drug product manufacturers, drug substance manufacturers, and minor formulation changes is adequately established.

APPENDIX Communication history with the Applicant

IR dated 7/3/2019:
\\cdsesub1\evsprod\nda213004\0010\m1\us\111-info-amend\nda-213004-information-request-002.pdf
Response dated 7/23/2019:
\\cdsesub1\evsprod\nda213004\0010\m1\us\111-info-amend\1-11-1-response-to-cmc-ir2-final-7-23-2019.pdf

IR dated 7/26/2019:
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Response dated 8/7/2019:
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Response dated 9/24/2019:
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Yang Zhao

Digitally signed by Yang Zhao
Date: 10/05/2019 12:26:56AM
GUID: 56f958740001a1f9707b4476d760e12f

Elsbeth Chikhale

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Date: 10/05/2019 12:28:30AM
GUID: 50743ccc000031928b54eba1769a5df9

CHAPTER IV: LABELING
NDA 213-004

1.0 PRESCRIBING INFORMATION

TALICIA (omeprazole magnesium, amoxicillin and rifabutin) delayed-release capsules

---------- **DOSAGE AND ADMINISTRATION** ----------
Administer four (4) TALICIA capsules every 8 hours with food for 14 days. (2)
Swallow
Do not take TALICIA with alcohol

Assessment of Product Quality Related Aspects of the Prescribing Information: The product name is finalized after consulting OPPQ.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	yes	
Established name(s)	Yes	
Route(s) of administration	yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	yes	Designated as delayed release capsule per the labeling guideline
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

1.2 FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

Administer four (4) TALICIA capsules every 8 hours for 14 days with food. Instruct patients to swallow the TALICIA capsules whole, with a full glass of water (8 ounces). Each dose (4 capsules) of TALICIA includes omeprazole 40 mg, amoxicillin 1,000 mg and rifabutin 50 mg. Do not crush or chew TALICIA capsules. Do not take TALICIA with alcohol.

If a dose is missed, patients should continue the normal dosing schedule until the medication is completed. Do not take two doses at one time to make up for a missed dose.

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	yes	Special instructions provided Are satisfactory

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Each TALICIA delayed-release capsule contains omeprazole 10 mg (equivalent to 10.3 mg of omeprazole magnesium) amoxicillin 250 mg (b) (4) and rifabutin 12.5 mg. The capsules are orange, opaque, with "RHB" imprinted in black on the capsule cap and "105" imprinted in black on the capsule base.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	yes	
Strength(s) in metric system	yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	yes	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	

11 DESCRIPTION

TALICIA delayed-release capsules contain omeprazole, amoxicillin and rifabutin for oral administration. Each delayed-release capsule contains:

- omeprazole, 10 mg (equivalent to 10.3 mg of omeprazole magnesium)
- amoxicillin250 mg (equivalent to (b) (4) mg of amoxicillin trihydrate)
- rifabutin 12.5 mg

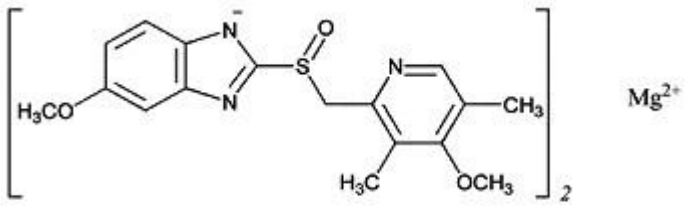
Omeprazole magnesium, a proton pump inhibitor, amoxicillin and rifabutin are antibacterial drugs. (b) (4)

Each TALICIA delayed-release capsule contains the following inactive ingredients: crospovidone, FD&C Red 3, FD&C Yellow 6, gelatin, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol-starch, methacrylic acid copolymer, meglumine, pregelatinized starch, silica, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide and triethyl citrate.

Omeprazole magnesium is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl] (b) (4) -benzimidazole, magnesium salt (2:1).

Omeprazole magnesium is a white to off white powder with a melting point with degradation at 200°C. The salt is slightly soluble (0.25 mg/mL) in water at 25°C, and it is soluble in methanol.

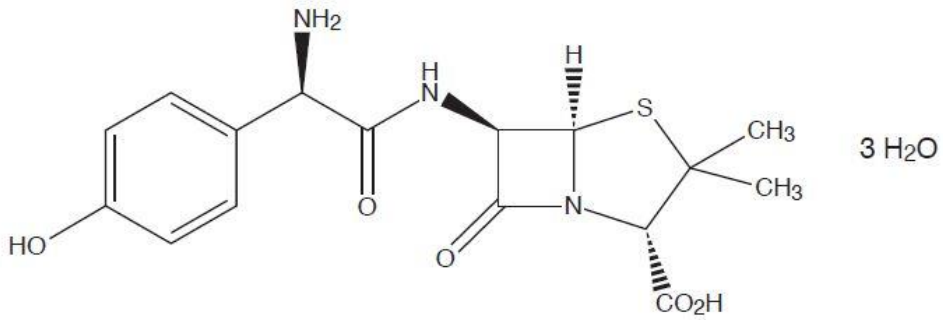
Omeprazole magnesium has a molecular formula of $(C_{17}H_{19}N_3O_3S)_2$ Mg, with a molecular weight of 713.12. The structural formula is:



Amoxicillin is a semisynthetic antibiotic, an analog of ampicillin, (b) (4)

Chemically it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2- amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid trihydrate.

Amoxicillin has a molecular formula of $C_{16}H_{19}N_3O_5S \cdot 3\ H_2O$, with a molecular weight of 419.45. (b) (4) The structural formula is:

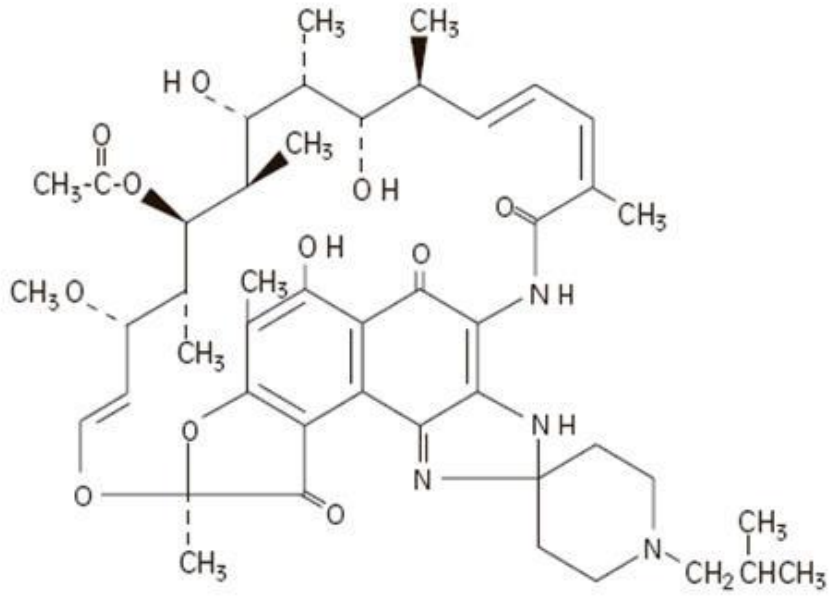


Rifabutin is (b) (4)

(9S,12E,14S,15R,16S,17R,18R,19R,20S,21S,22E,24Z)-6,16,18,20-tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-spiro [9,4-

(epoxypentadeca[1,11,13]trienimino)-2H-furo[2',3':7,8]naphth[1,2-d] imidazole-2,4'-piperidine]-5,10,26-(3H,9H)-trione-16-acetate.

Rifabutin has a molecular formula of $C_{46}H_{62}N_4O_{11}$, with a molecular weight of 847.02. The structural formula is:



Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/mL). The n-octanol/water partition coefficient is 3.2.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	yes	
Dosage form(s) and route(s) of administration	yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	yes	
Chemical name, structural formula, molecular weight	yes	
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	NA	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No promotional statements included	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	yes	
Strength(s) in metric system	yes	
Available units (e.g., bottles of 100 tablets)	yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

16 HOW SUPPLIED/STORAGE AND HANDLING

TALICIA is supplied as an orange, opaque capsule containing omeprazole 10 mg (equivalent to 10.3 mg of omeprazole magnesium), amoxicillin 250 mg (b) (4) and rifabutin 12.5 mg with "RHB" imprinted in black on the capsule cap and "105" imprinted in black on the capsule body TALICIA capsules are supplied in a carton containing two bottles of 84 capsules each.

NDC 57841-115-02 Carton containing 2 Bottles of 84 capsules

Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Store and Dispense in original container with a child-resistant closure (b) (4). Keep bottle tightly closed

(b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	yes	Dispense in original container is supported by In use stability. It is also supported by the dosage requirement for one treatment (2 bottles of 84 capsules/bottle).
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	
Storage conditions. Where applicable, use USP storage range rather than	yes	

storage at a single temperature.		
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	NA	
Include information about child-resistant packaging	yes	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

1).). Change the order in which drug substances are placed in the Package Insert Sections 1,2,3 and 11. The proposed sequence is Omeprazole magnesium, Amoxicillin and Rifabutin

2). Editorial changes made on the proposed PI will be submitted by the Team PM.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT." NA

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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

Item	Container Label	Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Acceptable	Acceptable
Dosage strength	yes	yes
Route of administration	yes	yes
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	See comment for amoxicillin	See comment for amoxicillin
Net contents (e.g. tablet count)	yes	yes
“Rx only” displayed on the principal display	yes	yes
NDC number	yes	yes
Lot number and expiration date	yes	yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	yes	yes
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Yes (listed as CODE)	yes

Item	Container label	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	yes	yes
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	-	-

Assessment of Carton and Container Labeling: *Adequate after the proposed changes by the sponsor.*
1). Change the container and carton labels as per Sections 1,2,3, and 11 in the package insert

2). (b) (4)

3). Store and Dispense in original container with a child-resistant closure (b) (4) *. Keep bottle tightly closed*

4). Dispense in the original carton containing a total of 148 Talicia Capsules

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."NA

ITEMS FOR ADDITIONAL ASSESSMENT

NA

Overall Assessment and Recommendation: Adequate after the proposed change

1). Change the order in which drug substances are placed in the Package Insert Sections 1,2,3 and 11 and on the container and the carton label. The proposed sequence is Omeprazole magnesium, Amoxicillin and Rifabutin

2). Editorial changes made on the proposed PI will be submitted by the Team PM.

3). (b) (4)

4). Store and Dispense in original container with a child-resistant closure (b) (4) *. Keep bottle tightly closed*

5). Dispense in the original carton containing a total of 148 Talicia Capsules

Primary Labeling Assessor Name and Date: Shrikant Pagay, Ph.D., R.Ph. 9/23/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Shrikant Pagay

Digitally signed by Shrikant Pagay
Date: 9/23/2019 06:06:04PM
GUID: 508da72000029ff475f33bf61de241b2

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 10/01/2019 09:55:13AM
GUID: 50758d5000003c1b1962e036ea11002c

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
10/09/2019 06:25:45 PM