CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213004Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 18, 2019
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 213004
Product Name and Strength:	Talicia (omeprazole magnesium, amoxicillin, and rifabutin) Delayed-release Capsules, 10 mg*/250 mg/12.5 mg (*each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium))
Applicant/Sponsor Name:	RedHill Biopharma, Ltd. (RedHill)
OSE RCM #:	2019-957-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label and carton labeling that we received on October 17, 2019 for Talicia. The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Talicia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations from the Agency.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Rosenberger, J. FDA Communication: NDA 213004 Information Request. Silver Spring (MD): FDA, CDER, OSE, DAIP (US); 2019 October 8. NDA 213004.

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/s/

DEBORAH E MYERS
10/18/2019 12:17:16 PM

OTTO L TOWNSEND
10/18/2019 12:53:17 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 4, 2019

To: Mark Needles, M.D.
Division of Anti-Infective Products (DAIP)

Jacquelyn Rosenberger, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TALICIA (omeprazole magnesium, amoxicillin and rifabutin) delayed-release capsules, capsules, for oral use

NDA: 213004

In response to DAIP's consult request dated October 1, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Talicia.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on September 27, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 27, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 1, 2019
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 213004
Product Name and Strength:	Talicia (omeprazole magnesium, amoxicillin, and rifabutin) Delayed-release Capsules, 10 mg*/250 mg/12.5 mg (*each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium))
Applicant/Sponsor Name:	RedHill Biopharma, Ltd. (RedHill)
OSE RCM #:	2019-957-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted their revised container label and carton labeling that we received on September 27, 2019 for Talicia. The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Talicia (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Myers D. Label and Labeling Review for Talicia (NDA 213004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 29. RCM No.: 2019-957.

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/s/

DEBORAH E MYERS
10/01/2019 04:44:54 PM

IRENE Z CHAN on behalf of OTTO L TOWNSEND
10/02/2019 09:13:28 AM

Clinical Inspection Summary

Date	9/18/2019
From	Karen Bleich, M.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jacquelyn Rosenberger, Pharm.D, Regulatory Project Manager Mark Needles, M.D., Clinical Reviewer Yuliya Yasinskaya, M.D., Team Leader Division of Anti-Infective Products
NDA/BLA #	NDA 213004
Applicant	RedHill Biopharma Ltd.
Drug	Talicia (rifabutin, amoxicillin, omeprazole) fixed-dose combination [(b) (4)]
NME (Yes/No)	Yes
Therapeutic Classification	Priority review
Proposed Indication(s)	For treatment [(b) (4)] of *Helicobacter pylori* infection in adults
Consultation Request Date	7/10/2019
Summary Goal Date	10/4/2019
Action Goal Date	11/2/2019
PDUFA Date	11/2/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study RHB-105-01 and Study RHB-105-02 were submitted to the Agency in support of NDA 213004. A total of five clinical sites were selected for audit: Dr. Peter Winkle (Site 012) and Dr. Gilbert Martinez (Site 005) from Study RHB-105-01, and Dr. Yamil Canaan (Site 019), Dr. Felix Penate (Site 020), and Dr. Gregory Wiener (Site 034) from Study RHB-105-02. The sites selected were among the highest enrollers of study subjects, and thus contributed significantly to the overall efficacy determination. On-site inspections demonstrated no significant findings at any of the audited sites related to data integrity or human subject protection.

The data from Studies RHB-105-01 and RHB-105-02 appear reliable based on the available information and the conduct of the studies appears to have included appropriate protection of the rights and welfare of the human research subjects.

II. BACKGROUND

RedHill Pharma seeks approval to market Talicia for the treatment (b) (4) of *Helicobacter pylori* (*H. pylori*) infection in adults. Talicia is a novel triple drug combination of two antibiotics (rifabutin and amoxicillin) and a proton pump inhibitor (omeprazole). The components of Talicia have been marketed in the U.S. and in other countries for many years.

The clinical data to support the use of Talicia includes two Phase 3 studies. The studies were similar in design: adult subjects with dyspepsia and *H. pylori* infection were treated with the study drug for 14 days and then reassessed for resolution of the *H. pylori* infection. Study RHB-105-01 included a placebo arm. Study RHB-105-02 included an active comparator arm. The studies are summarized below.

Study RHB-105-01

Title of Study: "A randomized, placebo-controlled phase 3 study to assess the safety and efficacy of RHB-105 in the treatment of confirmed *Helicobacter pylori* (*H. pylori*) infection in dyspepsia patients"
Number of Subjects: 119
Study Sites: 13 sites in the United States
Study Period: November 25th, 2013 – August 24th, 2015
Primary Objective:
To assess the effectiveness of RHB-105 to eradicate *H. pylori* as indicated by ^{13}C urea breath test (UBT) for *H. pylori.*
Primary Efficacy Endpoint:
The occurrence of *H. pylori* eradication, confirmed via ^{13}C UBT testing 28-35 days after completion of treatment (EOT)

Study RHB-105-02

Title of Study: "A randomized, double-blind active comparator controlled phase 3 study to assess the safety and efficacy of RHB-105 in the treatment of confirmed *Helicobacter pylori* (*H. pylori*) infection"
Number of subjects: 455
Number of sites: 55 sites in the U.S.
Study Period: July 18th, 2017 – November 12th, 2018
Primary Objective:
To assess the effectiveness of RHB-105 to eradicate *H. pylori* as indicated by ^{13}C UBT for *H. pylori.*
Primary Efficacy Endpoint:
The occurrence of *H. pylori* eradication confirmed via 13C UBT testing at Visit 5 (Day 43-71) after completion of treatment.

III. RESULTS (by site):

Study RHB-105-01

1. Dr. Peter Winkle, Anaheim, California (Site 012)

The site screened 38 subjects and enrolled 12 subjects. The inspection was conducted from 8/19/2019 – 8/22/2019. At the time of the inspection, the study was closed.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, and financial disclosures.

A comprehensive review of the source document records for all 12 enrolled subjects was performed, including protocol deviations, primary efficacy endpoint test results, study drug administration, and adverse events. The source data was compared to the data listings submitted to the application.

No significant inconsistencies or deficiencies were identified at the site.

2. Dr. Gilbert Martinez, Chino, California (Site 005)

The site screened 85 subjects and enrolled 43 subjects. The inspection was conducted from 8/12/2019 – 8/15/2019. At the time of the inspection, the study was closed.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all 43 enrolled subjects was performed for informed consent documentation, primary efficacy endpoint test results, randomization, subject discontinuations, and adverse events. Additionally, six subjects were audited for protocol deviations, concomitant medications, and test article accountability. The source data was compared to the data listings submitted to the application.

The inspection revealed that protocol deviations occurred for two subjects (Subject (b) (6) and Subject (b) (6)) at the study site that were not listed as protocol deviations in the data listings. Subjects (b) (6) and (b) (6) had been in the treatment arm of the study and they tested positive for *H. pylori* at the end of the study. Per protocol, they should have subsequently undergone upper endoscopy with culture and sensitivity testing. Instead, they were treated with standard of care medical therapy (without endoscopy). The site reported the events to the sponsor and to the site's IRB. The events were reported by the sponsor in the Clinical Study Report as "missed endoscopy" as follows:

- (b) (6) – The patient had Visit 5, but endoscopy was not performed due to unblinding results workflow showing all as placebo even for those not placebo.
- (b) (6) – The patient had Visit 5, but endoscopy was not performed due to unblinding results workflow showing all as placebo even for those not placebo.

From: RHB-105-01 Clinical Study Report: Section 12.5.4.3 Endoscopy

The cause of the error was that Subjects (b) (6) and (b) (6) were temporarily mis-classified as having been in the placebo arm of the study at the scheduled unblinding at Visit 4A. Per protocol, subjects in the placebo arm of the study who remained positive for *H. pylori* at the end of the study were offered standard medical therapy.

The mis-classification of subjects in the treatment arm as placebo arm occurred because of a study-wide problem caused by the software system responsible for the scheduled unblinding at Visit 4A. An information request was subsequently sent by OSI to the sponsor in order to identify the scope of the problem, the root cause, and the resolution of the problem.

According to the sponsor, the problem was identified on March 28th, 2014 and resolved on April 29th, 2014. The incorrect classification of subjects at the unblinding visit was caused by an error in the clinical trial platform software used by the sponsor. There were no protocol deviations related to the error at any sites other than the two cases described above that occurred at Site 005.

The protocol deviations described above were not adequately reported in the NDA data listings. The sponsor did, however, describe the events as missed endoscopies in the Clinical Study Report. The inconsistency between the submitted data listings and the events at the site have been reviewed and determined to be insignificant to the overall integrity of the study data. There were no other inconsistencies identified between the data submitted with the application and the site records.

Study RHB-105-02

3. Dr. Yamil Canaan, Miami, Florida (Site 019)

The site screened 56 subjects and enrolled 29 subjects. The inspection was conducted from 8/19/2019 – 8/22/2019. At the time of the inspection, the study was closed.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, blinding and randomization procedures, and financial disclosures. Exclusion and inclusion criteria were reviewed for all enrolled subjects.

A comprehensive review of the source document records for 15 enrolled subjects was performed, including adverse events, protocol deviations, and concomitant medications. The primary efficacy endpoint test result was reviewed for all 29 enrolled subjects. The source data was compared to the data listings submitted to the application.

No significant inconsistencies or deficiencies were identified at the site.

4. Dr. Felix Penate/Dr. Carlos Vaca, Miami, Florida (Site 020)

Dr. Penate was the Principal Investigator for the study at Site 020 but he no longer works at the inspected location. Dr. Penate transferred his Principal Investigator's responsibilities for this protocol to Dr. Vaca on March 20th, 2018.

The site screened 55 subjects and enrolled 27 subjects. The inspection was conducted from 8/19/2019 – 8/22/2019. At the time of the inspection, the study was closed.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all 27 enrolled subjects was performed, including primary efficacy endpoint test results, adverse events, protocol deviations, and concomitant medications. The source data was compared to the data listings submitted to the application.

No significant inconsistencies or deficiencies were identified at the site.

5. Dr. Gregory Wiener, Chula Vista, California (Site 034)
The site screened 60 subjects and enrolled 26 subjects. The inspection was conducted from 7/15/2019 – 7/18/2019. At the time of the inspection, the study was closed.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all 26 enrolled subjects was performed, including the primary efficacy endpoint test result, adverse events, protocol deviations, eligibility criteria, and concomitant medications. The source data was compared to the data listings submitted to the application.

No significant inconsistencies or deficiencies were identified at the site.

{See appended electronic signature page}

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Central Doc. Rm. NDA #213004
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OSI/Office Director/David Burrows
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OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Karen Bleich
OSI/ GCP Program Analysts/Yolanda Patague/Joseph Peacock
OSI/Database PM/Dana Walters

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KAREN B BLEICH
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09/24/2019 05:16:56 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2019
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 213004
Product Name and Strength:	Talicia (omeprazole magnesium, amoxicillin, and rifabutin) Capsules, 10 mg*/250 mg/12.5 mg (*each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)[a]
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	RedHill Biopharma, Ltd. (RedHill)
FDA Received Date:	May 2, 2019
OSE RCM #:	2019-957
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

[a] The established name and strength have not yet been determined for this product.

Reference ID: 4469497

1 REASON FOR REVIEW

As part of the approval process for Talicia (omeprazole magnesium, amoxicillin, and rifabutin) Capsules, the Division of Anti-Infective Products (DAIP) requested that we review the proposed Talicia prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2, *Dosage and Administration*			
1.	As currently presented, the text reads, “Each dose of TALICIA includes rifabutin 50 mg,	Prescribers may become confused about the dose . Lack of information regarding the specific dose	To provide clarity regarding the dose, add “(4 capsules)” following the text “Each dose…”

Reference ID: 4516497

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	amoxicillin 1000 mg and omeprazole 40 mg [redacted (b) (4)]."	(4 capsules) may lead to wrong dose or strength medication errors.	For example, "Each dose (4 capsules) of TALICIA includes.."
2.	As currently presented, the text reads, "Each dose of TALICIA includes rifabutin 50 mg, amoxicillin 1000 mg and omeprazole 40 mg [redacted (b) (4)]."	Numbers (i.e., doses) larger than 1,000 without properly placed commas (e.g., 1000), have been misinterpreted as hundreds "100" or ten-thousands "10000."	To decrease the potential for wrong strength/dose medication errors and improve the legibility of this large number we recommend insertion of a comma in the number "1000." For example, "Each dose of TALICIA includes rifabutin 50 mg, amoxicillin 1,000 mg and omeprazole 40 mg [redacted (b) (4)]."
Full Prescribing Information – Section 3, *Dosage Forms and Strengths*			
1.	As currently presented the individual strengths precede each of the individual active ingredients (i.e., "…12.5 mg of rifabutin, 250 mg of amoxicillin and 10 mg of omeprazole…").	For consistency and readability, each individual strength should follow each individual active ingredient. Customarily, the product strength follows the product name. As currently presented for this multiple ingredient product, the user could misinterpret the strength. For example, 250 mg follows rifabutin, but the product contains 12.5 mg of rifabutin and 250 mg represents the amount of amoxicillin.	Change each individual strength to follow each individual active ingredient. For example, "…rifabutin 12.5 mg, amoxicillin 250 mg and omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)."

Reference ID: 4516497

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16, *How Supplied/Storage and Handling*			
1.	As currently presented that storage statement reads, "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]."	The units of measurement following the first numbers in the temperature ranges (e.g., Centigrade symbol (C) following the 20° and Fahrenheit symbol (F) following the 68°) are missing.	To provide clarity and consistency with the storage statement, add the Centigrade symbol (C) following 20° and Fahrenheit symbol (F) following 68° within the storage statement. For example, "Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]."
2.	As currently presented the individual strengths precede each of the individual active ingredients (i.e., "…12.5 mg of rifabutin, 250 mg of amoxicillin and 10 mg of omeprazole…").	For consistency and readability, each individual strength should follow each individual active ingredient. Customarily, the product strength follows the product name. As currently presented for this multiple ingredient product, the user could misinterpret the strength. For example, 250 mg follows rifabutin, but the product contains 12.5 mg of rifabutin and 250 mg represents the amount of amoxicillin.	Change each individual strength to follow each individual active ingredient. For example, "…rifabutin 12.5 mg, amoxicillin 250 mg and omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)."
3.	As currently presented, both the container label and carton labeling have the same National Drug Code (NDC) number (57841-115-02).	Cartons containing more than one unit should have a different NDC number than that of the containers within the carton.	To provide differentiation between the carton and two bottles within the carton, we have provided a recommendation to the Applicant to revise the NDC package code numbers (last 2

Reference ID: 4516497

Table 2. Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			digits) so that the container (bottle) label and carton labeling NDC numbers are different. Additionally, we have recommended that if the Applicant changes the carton labeling NDC, that they update the NDC number in Section 16, *How Supplied/Storage and Handling* of the Full Prescribing Information as appropriate.

Table 3. Identified Issues and Recommendations for RedHill Biopharma, Ltd. (RedHill) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the format for expiration date is not defined.	The use of abbreviations within the expiration date can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month,

Reference ID: 4516497

Table 3. Identified Issues and Recommendations for RedHill Biopharma, Ltd. (RedHill) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As currently presented, the strength statement includes a forward slash (i.e., "/") between each of the active ingredients and their corresponding strengths (i.e., "rifabutin/12.5 mg amoxicillin/250 mg omeprazole/10 mg").	The product strength is considered to be "critical information" that should stand out on the principal display panel.[b] The inclusion of a forward slash between each of the active ingredients and their corresponding strengths is not customary and not aligned with the strength presentation on the side panel (i.e., "Each capsule contains rifabutin 12.5 mg, amoxicillin 250 mg, and omeprazole 10 mg…"). Inconsistent labeling may contribute to confusion that can result in medication error.	To improve readability remove the forward slashes between each of the active ingredient and their corresponding strengths. For example, "rifabutin 12.5 mg amoxicillin 250 mg omeprazole 10 mg"
3.	As currently presented, both the container label and carton labeling have the same National Drug	Cartons containing more than one unit should have a different NDC number than	To provide differentiation between the carton and two bottles within the carton, revise the NDC package code

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 134-151). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Reference ID: 4516497

Table 3. Identified Issues and Recommendations for RedHill Biopharma, Ltd. (RedHill) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Code (NDC) number (57841-115-02).	that of the containers included in the carton.	numbers (last 2 digits) so that the container (bottle) label and carton labeling NDC numbers are different. Additionally, if you opt to change the carton labeling NDC, update the NDC number in Section 16, *How Supplied/Storage and Handling* of the Full Prescribing Information as appropriate.
4.	As currently presented, (b) (4) However, the proposed prescribing information, Section 2, *Dosage and Administration* includes the full word "ounces" (i.e., "(8 ounces)."	Abbreviations can be misinterpreted and result in confusion, as well as medication errors.	To provide clarity and minimize the potential for misinterpretation, we recommend (b) (4)
5.	As currently presented the storage statement reads, "Store between 68° to 77°F (20° to 25°C)."	Per USP[c], the Centigrade temperatures precede the Fahrenheit temperatures in storage statements. Additionally, the units of measurement following the first numbers in the temperature ranges (e.g., Fahrenheit symbol (F) following the 68° and	To provide clarity and consistency with the storage statement, change the current text such that the Centigrade temperatures precede the Fahrenheit temperatures and add the Centigrade symbol (C) following 20° and Fahrenheit symbol (F) following 68° within the storage statement.

[c] USP General Chapter <659> Packaging and Storage Requirements.

Reference ID: 4516497

Table 3. Identified Issues and Recommendations for RedHill Biopharma, Ltd. (RedHill) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Centigrade symbol (C) following the 20°) are missing.	Additionally, to provide further clarity and to inform patients how the product is to be stored, we recommend adding "Controlled Room Temperature" to the storage statement. For example, "Store between 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]."
Container Label(s)			
1.	As currently presented, there is no linear barcode included on the container labels.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual container label as required per 21CFR 201.25(c)(2). We recommend that the container label linear barcode be oriented in a vertical position to improve scannability of the barcode, as barcodes placed in a horizontal position may not scan due to the curvature of the container. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

4 CONCLUSION

Our evaluation of the proposed Talicia prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask

Reference ID: 4516497

that the Division convey Table 3 in its entirety to RedHill Biopharma, Ltd. (RedHill) so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Talicia that RedHill Biopharma, Ltd. (RedHill) submitted on May 2, 2019.

Table 4. Relevant Product Information for Talicia	
Initial Approval Date	N/A
Active Ingredient	Omeprazole, amoxicillin, and rifabutin
Indication	treatment (b) (4) of *H. pylori* infections in adults
Route of Administration	oral
Dosage Form	capsule
Strength	10 mg*/250 mg/12.5 mg *Each capsule contains omeprazole 10 mg (equivalent to 10.3 mg omeprazole magnesium)
Dose and Frequency	Administer four (4) capsules every 8 hours with food for 14 days.
How Supplied	carton containing 2 bottles of 84 capsules
Storage	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Container Closure	(b) (4) child-resistant (b) (4) screw cap (b) (4)

Reference ID: 4519497

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Talicia labels and labeling submitted by RedHill Biopharma, Ltd. (RedHill).

- Container label(s) received on May 2, 2019
- Carton labeling received on May 2, 2019
- Prescribing Information \\cdsesub1\evsprod\nda213004\0001\m1\us\114-labeling\114a-draft-label\uspi-version-apr-2019.docx

F.2 Label and Labeling Images

Container label

(b) (4)

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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