CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208398Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: *Approval*

NDA 208398
Review # 1

Drug Name/Dosage Form	VERMOX™ Chewable (mebendazole chewable tablets)
Strength	500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Janssen Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	4/10/2016	All
Quality Amendment	6/10/2016	Drug Product
Quality Amendment	7/6/2016	Process
Quality Amendment	7/15/2016	Biopharmaceutics
Quality Amendment	7/22/2016	Drug Substance
Quality Amendment	8/31/2016	Process
Quality Amendment	9/15/2016	Labeling
Quality Amendment	9/19/2016	Process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Geatan Ladouceur	Branch I/DNAP I
Drug Product	George Lunn	Branch III/DNDP I
Process	Sateesh Sathigari	Branch III/DPA I
Microbiology	Sateesh Sathigari	Branch III/DPA I
Facility	Quallyna Porte	Branch II/DIA
Biopharmaceutics	Mei Ou/Elsbeth Chikhale	Branch II and I/ DBP
Regulatory Business Process Manager	Navi Bhandari	Branch I/DRBPM I
Environmental Analysis (EA)	George Lunn	Branch III/DNDP I
Application Technical Lead	Dorota Matecka	Branch III/DNDP I

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status*	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Mebendazole	Adequate	August 18, 2016	*Reviewed by G. Ladouceur for this NDA*
	IV		(b) (4)	Adequate	June 29, 2016	*Reviewed by G. Lunn for this NDA*
	III			N/A		
	III			N/A		
	III			N/A		

**Adequate, Adequate with Information Request, Deficient, or N/A (there is enough data in the application, therefore the DMF did not need to be reviewed)*

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115959	Vermox (mebendazole chewable tablets)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Acceptable (impurities)	*See review*	A. Ellis
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208398 is recommended for approval by the Office of Pharmaceutical Quality. The NDA, as amended, has provided sufficient chemistry, manufacturing and controls information to assure the identity, strength, purity, and quality of the drug product, mebendazole chewable tablets. All information requests and review issues have been addressed and there are no pending approvability issues. 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 September 27, 2016.

Based on the overall stability information submitted in the NDA, 24 months of expiration dating is granted for the proposed drug product, mebendazole chewable tablets, 500 mg, packaged in HDPE bottles and stored below 30°C.

II. Summary of Quality Assessments

A. Product Overview

Janssen Research & Development, LLC (JRD) is currently donating mebendazole tablets to the World Health Organization (WHO) for distribution to countries with moderate-to-high prevalence of soil-transmitted helminth (STH) infestations. This NDA provides for a new mebendazole chewable tablet, 500 mg, developed by JRD to improve ease of use in young children and to facilitate access to a therapy, which can help reduce morbidity and mortality associated with neglected tropical diseases not endemic in the US.

Proposed Indication(s) including Intended Patient Population	Treatment of single or mixed gastrointestinal (b) (4) caused by *Ascaris lumbricoides* (roundworm); *Trichuris trichiura* (whipworm); and (b) (4) in adult and pediatric patients (b) (4) year of age).
Duration of Treatment	One VERMOX™ Chewable, 500 mg tablet taken as a single dose (chewed completely before swallowing)
Maximum Daily Dose	500 mg
Alternative Methods of Administration	For patients who have difficulty chewing the tablet, VERMOX™ Chewable 500 mg tablet, can be placed in a spoon and approximately 2 to 3 mL of drinking water should be added. Within 2 minutes, the tablet absorbs the water and turns into a soft mass with semi-solid consistency, which then can be swallowed.

B. Quality Assessment Overview

Mebendazole is a synthetic broad-spectrum anthelmintic agent belonging to the class of benzimidazole derivatives. The chemical name of mebendazole is methyl-5-benzoyl-1H-benzimidazol-2-yl carbamate. Mebendazole (b) (4) its molecular weight is 295.30 and a molecular formula $C_{16}H_{13}N_3O_3$. The mebendazole drug substance is manufactured (b) (4) as a white to off-white powder freely soluble in formic acid, but practically insoluble in water and various organic solvents such as alcohol, ether and chloroform. (b) (4) (b) (4) (b) (4) In addition, the drug substance specification includes other relevant quality attributes such as appearance, identification, assay, impurities, (b) (4) (b) (4) The proposed acceptance criteria for impurities were revised during the NDA review and the drug substance specification was found adequate. The detailed chemistry, manufacture and control information for the mebendazole drug substance has been provided via a reference to DMF (b) (4) This DMF was reviewed was found to be adequate in support of the current NDA (DMF review dated August 18, 2016, in DARRTS).

The drug product, mebendazole chewable tablets, 500 mg, are round, flat radius-edged white to yellowish tablets, debossed for tablet identification ("M/500" on one side, and "J" on the other side). These tablets can be chewed directly or they can be allowed to disintegrate and turn into a soft mass (upon addition of 2-3 mL of water), which can be easily ingested. The inactive ingredients include crospovidone, magnesium stearate, microcrystalline cellulose (b) (4) povidone (b) (4), strawberry flavor, sucralose, and water. All the excipients are compendial except for the (b) (4). The information for the strawberry flavor is provided via a reference to (b) (4) which was reviewed in support of this NDA and found to be adequate (review dated June 29, 2016, in DARRTS).

The drug product specification includes tests and acceptance criteria for appearance, identity, assay, uniformity of dosage units, degradation products, dissolution, disintegration, (b) (4), and microbial limits (release and end of shelf-life). The proposed specification was found to be adequate following the revision of the acceptance criterion for dissolution, as discussed below. No impurities, other than those found in the drug substance, are observed. A reasonable justification of the specification has been provided. The analytical methods are described in reasonable detail and adequate validation data have been provided.

Batch analyses are provided for 14 batches (b) (4) tablets manufactured by Lusomedicamenta (the proposed commercial manufacturer) and one (b) (4) batch manufactured by (b) (4) Some early batches were manufactured using (b) (4), which had (b) (4) (b) (4) Therefore, microcrystalline cellulose (b) (4) will be used in the routine commercial manufacture of the mebendazole chewable tablets.

The commercial drug product packaging configuration includes white, high-density polyethylene (HDPE) bottle with (b) (4) closure, with induction seal liner, each containing 200 tablets each. The suitability of the container-closure system was demonstrated by adequate stability data and conformance to the relevant 21 CFR sections.

Stability information includes data for three batches in two different packaging configurations, including the commercial packaging configuration (b) (4), (b) (4) were supplied in the NDA. Additionally, tablets from each batch were tested (b) (4) There are no obvious trends and no out of specification results except for (b) (4). In-use studies were also carried out, in which tablets were mixed with 2-3 mL water forming a soft mass. This soft mass was tested and met the acceptance criteria with respect to assay, degradants, and (b) (4). It was also noted that at some stage, the induction seal will be removed and the bottle allowed standing with only the closure (b) (4) At the request of the Agency, the Applicant carried out an additional stability study on a bottle with no seal and only a loosely fitted cap. The stability data were provided to support a statement on the product label that opened bottles should be discarded after one month. The stability information, including the proposed expiration dating period of 24 months with the storage statement "Store below 30°C" was found acceptable.

Mebendazole chewable tablets are manufactured (b) (4) (b) (4) (b) (4) Overall, information regarding the drug product manufacturing process provided in the original NDA submission and subsequent amendments has been found acceptable.

The proposed in vitro dissolution method (USP Apparatus II paddle, (b) (4) 75 rpm) with adequate discriminating power for the proposed drug product was found acceptable. The dissolution method was validated in terms of accuracy, analysis repeatability, linearity, range, reproducibility, robustness, stability of solution, and filtration study. The dissolution data are confirmed to be within the linearity range of (b) (4) of mebendazole as established during the method validation. Therefore, the in vitro dissolution method validation is considered acceptable.

The dissolution data (individual, mean and profiles) of six registration stability/clinical/process validation batches were provided. The original proposed dissolution acceptance criterion of *Q* = (b) (4) *at* (b) (4) *minutes* was not supported by the provided dissolution data and a dissolution acceptance criterion of *Q*(b) (4)*% at 30 minutes* was recommended by the Agency. This acceptance criterion was accepted by the Applicant and the drug product specification table was revised accordingly.

The drug substance is manufactured by [redacted] (b) (4) and the drug product is manufactured by Lusomedicamenta Sociedade Tecnica Farmaceutica S.A., Barcarena, Portugal. A review of the application and inspectional documents of the facilities responsible for manufacturing mebendazole chewable tablets has determined that there are no significant outstanding risks. A pre-approval inspection was conducted at the drug product manufacturing facility with no significant findings. All facilities listed the current NDA were found acceptable to manufacture the proposed drug product and an overall "Approve" recommendation was issued by OPF on September 27, 2016.

C. Special Product Quality Labeling Recommendations

The following additional storage statement should be included on the bottle label and in the package insert:

"Discard after _/_/_. Discard unused portion 1 month after first opening."

D. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Labeling

CHAPTER IV: Process

CHAPTER V: Biopharmaceutics

CHAPTER VI: Facilities

ATTACHMENT I: Risk Assessment

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FACILITIES

Product Background: Treatment of Trichuris trichiura (whipworm); Ascaris lumbricoides (large roundworm); and (b) (4)

NDA: 208398

Drug Product Name / Strength: Vermox Chewable Tablets – Mebendazole / 500mg

Route of Administration: Oral

Applicant Name: Janssen Pharmaceuticals Inc.

Review Summary: ADEQUATE - A review of the application and inspectional documents of the facilities responsible for manufacturing Mebendazole chewable tablets has determined that there are no significant outstanding risks. A pre-approval inspection was conducted at the drug product manufacturing facility with no significant findings. All listed facilities are acceptable to manufacture product for NDA 208398.

List Submissions being reviewed (table):

Submission	Date
Original	4/19/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
[redacted] (b) (4)			Low – last inspection at time of initial facility risk assessment VAI. Since then, a more recent CGMP surveillance also initially classified VAI	**Approve** – based on manufacturing capability and inspectional history which included coverage of Mebendazole

Reviewer's Assessment: ACCEPTABLE

[redacted] (b) (4) is the drug substance manufacturer and tester of Mebendazole. (b) (4) [redacted]

Mebendazole drug substance is synthesized according to DMF [redacted] (b) (4), which is currently undergoing its initial review. In speaking with the drug substance reviewer, there is currently no risk information available for this DMF.

At the time of the initial facility risk assessment of [redacted] (b) (4) (see table immediately below), its last inspection was on 12/13/2013. The Quality, Facilities & Equipment, Materials, Production, Packaging & Labeling, and Laboratory Control systems were reviewed as well as a couple of other APIs [redacted] (b) (4) which the facility manufactures for use in drug products for the US market. Profile class CSN was covered. A 3-item FDA Form 483 was issued relating to inadequate re-qualification of suppliers, incomplete equipment qualification, and not following procedures. The inspection was classified VAI.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
[redacted]	[redacted]	(b) (4)	Manufacturing and testing of drug substance	Low	Low	Low	**Med**

The most recent inspection was a CGMP surveillance inspection, completed on 7/15/2016, which inspected Mebendazole (b) (4) APIs (not PAI coverage). Profile class CSN was covered as well as the Quality, Materials, Equipment & Facilities, Production, Laboratory, and Packaging & Labeling systems. Specifically related to Mebendazole, complaints, deviations, OOS, and change controls were reviewed in the APR. The investigator conducted a walkthrough of the facility grounds which included (b) (4) where Mebendazole is manufactured. The process validation protocol and report as well as executed and master manufacturing batch records, stability program, and method validation for Mebendazole were reviewed. The investigator reviewed the corrective actions to the 12/13/2013 inspection and deemed them adequate. At the conclusion of the inspection, a 4-item FDA Form 483 was issued for the following:

1. Laboratory control procedures not followed
2. Testing not completed contemporaneously
3. Document control inadequate
4. Clean hoses observed touching the floor

The inspection was classified VAI.

This review has determined that this firm has a history of manufacturing APIs of the profile class CSN. In fact, even though the most recent inspection of 7/15/2016 did not provide PAI coverage of Mebendazole, the inspector covered this product as it is one of the products manufactured for use in the US market. This coverage did not uncover any product specific deficiencies as evidenced by the observations noted above. (b) (4) is acceptable to manufacture and test drug substance Mebendazole for NDA 208398.

3.2.P.3 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Lusomedicamenta Sociedade Tecnica Farmaceutica S.A. Est Cons Pedroso 69 B Barcarena, Portugal	3005491771	Manufacturing, (b) (4)	• No previous FDA inspectional history	**Approve** – based on inspectional history and PAI coverage

(b) (4)	Stability testing of drug product - (b) (4)	• Low risk - history of NAIs	**Approve** - based on inspectional history and testing capability

Reviewer's Assessment: ACCEPTABLE

The following table contains the initial facility risk assessment for the facilities associated with drug product manufacturing of Mebendazole chewable tablets:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
Lusomedicamenta Sociedade Tecnica Farmaceutica S.A.	3005491771	TCM	Manufacturing, testing, and packaging of drug product	High	Low	Low	**High**
(b) (4)				Low	Low	Low	**Low**

Lusomedicamenta Sociedade Tecnica Farmaceutica S.A. (FEI 3005491771) located in Portugal, is the proposed manufacturer (b) (4) of the drug product, Mebendazole. Mebendazole chewable tablets are manufactured using a (b) (4)

At the time of the Initial Facility Risk Assessment, this facility had not been previously inspected which resulted in a high risk from a facility standpoint. A PAI was therefore recommended for the subject application. Prior to the PAI, an initial inspection of the firm was conducted on 4/15/2016, providing coverage for profile class (b) (4) (b) (4) No objectionable conditions were identified during the inspection. An FDA Form 483 was not issued and the inspection was classified NAI.

(b) (4)

(b) (4)

(b) (4)

The firm corrected most of the observations during the inspection or provided a written commitment to correct them prior to the closing meeting. The inspection was classified VAI and the inspector recommended approval of NDA 208398. Also see CMS WA # 137094.

Based on the 2 recent inspections of this facility, each of which provided in depth coverage of all 6 systems and with the most recent providing product-specific coverage for NDA 208398, Lusomedicamenta Sociedade Tecnica Farmaceutica S.A. is **acceptable** to manufacture and test Mebendazole chewable tablets for the subject application.

(b) (4), is responsible for the stability testing of the drug product. This site, Analytical and Pharmaceutical Development Center (APDC) conducts method development/transfer/validation, and performs stability testing on registration and commercial drug substances and drug products from other (b) (4) .

This facility has a history of NAI inspections. The most recent one was on 05/28/2014 which was a PAI providing coverage for another application as well as a CGMP surveillance inspection. The systems covered included Quality, Facilities & Equipment, Materials, and Laboratory Control systems and profile class CTL (control testing laboratory) was covered. (b) (4) (b) (4)

Based on (b) (4) proven capability in stability testing of several other products for the US market and its inspectional history, this facility is considered **acceptable** to perform stability testing of Mebendazole chewable tablets per NDA 208398.

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

QUALITY ASSESSMENT

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Facilities Reviewer Name and Date:

Quallyna Porte
Acting QAL / Biologist, OPQ/OPF/DIA/BII
8/16/2016

Secondary Reviewer Name and Date:

Derek Smith, PhD.

8/29/2016

Derek Smith

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Quallyna Porte

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ATTACHMENT I: Final Risk Assessment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability of mebendazole	(b) (4)	(b) (4)	Acceptable API incoming specification	Acceptable	
Content uniformity	(b) (4)		(b) (4)	Acceptable	
ysical stability	(b) (4)		(b) (4)	Acceptable	(b) (4)
Microbial limits	(b) (4)		(b) (4)	Acceptable	
Dissolution	(b) (4)		Acceptable dissolution method (b) (4)	Acceptable	
Disintegration	(b) (4)		Acceptable disintegration method and acceptance criterion for the drug	Acceptable	

	(b) (4)		(b) (4)		
Hardness		(b) (4)		Acceptable	
Palatability				Acceptable	*Formulation changes should be evaluated for potential impact on palatability*

OVERALL ASSESSMENT AND SIGNATURE:

Based on the OPQ Review Team conclusions, NDA 208398 is recommended for Approval from the Product Quality perspective.

Dorota M. Matecka -S

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Dorota Matecka, Ph.D., ATL for NDA 208398

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/s/

JONATHAN T DOW
10/28/2016

BIOPHARMACEUTICS

Product Background: The Applicant submitted this **NDA 208398** on 04/19/2016. The proposed drug product, VERMOX CHEWABLE (mebendazole chewable tablets), 500 mg, is an anthelmintic drug indicated for: Treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); and (b) (4)

NDA: 208398

Drug Product Name / Strength: VERMOX CHEWABLE (mebendazole chewable tablets), 500 mg

Route of Administration: Oral

Applicant Name: Janssen Pharmaceuticals Inc.

Review Summary:

List Submissions being reviewed (table):

04/19/2016	Original submission
07/15/2016	CMC/Biopharmaceutics Response to Information Requests
08/25/2016	CMC/Biopharmaceutics Response to Information Requests

The proposed in vitro dissolution method (USP Apparatus II paddle, (b) (4) 75 rpm) is considered acceptable with adequate discriminating power for the proposed drug product.

The dissolution method was validated in terms of accuracy, analysis repeatability, linearity, range, reproducibility, robustness, stability of solution, and filtration study. The dissolution data are confirmed to be within the linearity range of (b) (4) of mebendazole as established during the method validation. From a Biopharmaceutics perspective, the in vitro dissolution method validation is acceptable.

The dissolution data (individual, mean and profiles) of six registration stability/clinical/process validation batches were provided. The original proposed dissolution acceptance criterion of *Q* = (b) (4) *ai* (b) (4) *minutes* was not supported by the provided dissolution data. Based on the submitted data, FDA recommended a dissolution acceptance criterion of *Q* (b) (4) *% at 30 minutes*, which was accepted by the Applicant for drug product release and stability testing.

Overall Comment and Recommendation:

The proposed in vitro dissolution method and revised acceptance criterion for the proposed drug product have been assessed and found acceptable. From the Biopharmaceutics perspective, NDA 208398 for VERMOX™ Chewable (mebendazole) Tablets, 500 mg, is recommended for APPROVAL.

BCS Designation

Reviewer's Assessment: II or IV

Note: The drug substance, mebendazole, has very low solubility in water and multiple aqueous buffers. No permeability data are submitted. No BCS classification of the drug substance and drug product is claimed by the Applicant. Based on the solubility data, the proposed drug product could be classified as (b) (4) roduct.

Solubility: The drug substance has very low solubility in water and aqueous buffers, summarized in Table 1.

T

(b) (4)

Permeability: n/a

Dissolution: The dissolution method and acceptance criterion for drug product are reviewed in the following section.

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Therefore, the additional generated data will be reviewed in the CMC section. Based on the provided response, the proposed acceptance criterion of **Less than 120 seconds** for the disintegration time of the drug product is acceptable.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)
Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD
Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping
Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study
Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products
Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products
Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products
Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products
Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim
Reviewer's Assessment: n/a

Bridging of Formulations
Reviewer's Assessment:

Four formulations of the mebendazole tablets were used during the development. According to the Applicant "VERMOX® (mebendazole) 100 mg tablet (Formulation 1) was approved for oral use in the United States on 06/28/1974 (NDA 17481), and could be chewed, swallowed, crushed, or mixed with food. Marketing of this chewable tablet was discontinued in 2006. The mebendazole 500-mg non-chewable tablet (Formulation 2) was developed and is being donated to WHO for distribution to countries with moderate to high prevalence of soil-transmitted helminth (STH) infestations for use in preventive chemotherapy programs in school-age children (5 to 16 years). (b) (4)

The new mebendazole 500-mg chewable tablet (Formulation 4) was developed and used in clinical studies Mod5.3.1.1\GAI1002 and Mod5.3.5.1\GAI3003, and is the proposed formulation for the donation program in this submitted NDA. The tablets contain a strawberry flavor, are suitable for dosing children of all ages and are designed to disperse quickly when a minimal amount of water (eg, 2 to 5 mL) is added to the tablets. "

The four formulations of the drug product and the submitted clinical studies are listed in Table 22 and 23 below.

Table 22: Composition of the relevant tablet formulations (from M.2.7.2)

100-mg Chewable Tablet (approved; no longer marketed in the US)		500-mg Non-chewable Tablet (currently used in donation program and commercially available)		(b) (4)	New 500-mg Chewable Tablet (Studies Mod5.3.1.1\GAI1002 and Mod5.3.5.1\GAI3003)	
Formulation 1		Formulation 2		(b) (4)	Formulation 4	
Ingredient	mg/tablet	Ingredient	mg/tablet		Ingredient	mg/tablet
Mebendazole	100.0	(b) (4)	500.0		(b) (4)	500.0
Microcrystalline cellulose	(b) (4)	(b) (4)	(b) (4)		Povidone	(b) (4)
(b) (4)		Microcrystalline cellulose			Microcrystalline cellulose	
(b) (4) starch		(b) (4)			Crospovidone	
Magnesium stearate		Sodium starch glycolate			Sucralose	
(b) (4)		Magnesium stearate			Strawberry flavor	
Sodium saccharine		(b) (4)			Magnesium stearate	
(b) (4)		Methylcellulose			(b) (4)	
Sodium lauryl sulphate		(b) (4)				

* Does not appear in the final product

Table 23: Clinical studies related to tablet formulations (from M.5.2)

StudyID EudraCT Number First Patient First Visit Completion date Study Status	Country(ies) Number of Centers	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) duration of Treatment	Dose Regimen Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Bioavailability Study						
MEBENDAZOLGAI-1001 Synopsis N/A 03 April 2008 28 April 2008 Completed	India 1	Phase: 1 Open-label, single-dose, relative bioavailability, randomized, 2-way crossover design study Healthy men 18 to 60 years of age To determine the relative bioavailability of a new chewable tablet formulation of mebendazole with respect to the currently marketed tablet	Randomized=20 Treated=19	Vermox (mebendazole): Tablets and Mebendazole: Chewable tablets (Oral) Single-dose administration	Subjects were randomly assigned to receive the treatments in 1 of 2 possible sequences, AB or BA Treatment A - VERMOX (mebendazole) single 500-mg tablet Treatment B - Mebendazole (chewable) single 500-mg tablet Sequence AB: n=9; Sequence BA: n=10	Full Report 05 November 2008 EDMS-ERI-7703930 5.3.1.2
Food Effect Study						
MEBENDAZOLGAI1002 Synopsis 2013-004765-14 10 February 2014 23 April 2014 Completed	Belgium 1	Phase: 1 Open-label, randomized, single-center, single-dose, 2-way crossover study Healthy men and women between 18 and 55 years of age (inclusive), who had a BMI between 18 and 30 kg/m² (inclusive) and body weight of ≥50 kg To evaluate the effect of food on the bioavailability of mebendazole from a single 500-mg oral dose of a fast-disintegrating chewable tablet formulation of mebendazole	Randomized=16 Treated=16	Mebendazole (b) (4) (b) (4) chewable tablets (Oral) Single-dose administration	Subjects were randomly assigned to receive the treatments in 1 of 2 possible sequences, AB or BA Treatment A (Reference) – Single 500-mg dose of mebendazole in the fasted condition Treatment B (Test) – Single 500-mg dose of mebendazole just after ingestion of a high-fat breakfast Sequence AB: n=8; Sequence BA: n=8	Full Report 05 November 2014 EDMS-ERI-93480875 5.3.1.1

StudyID EudraCT Number First Patient First Visit Completion date Study Status	Country(ies) Number of Centers	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) duration of Treatment	Dose Regimen Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Safety Study						
MEBENDAZOLGAI3002 Synopsis 2015-001226-42 24 February 2010 12 March 2010 Completed	Tanzania 1	Phase: 3 Open-label, single-center, single-dose, single-arm, safety study Healthy boys and girls between 2 and 10 years of age, inclusive, living in a high prevalence area, where parasite infection was endemic To assess safety and tolerability of a chewable tablet formulation of mebendazole in a pediatric population	Treated=396	Mebendazole: Chewable tablet (Oral) Single-dose administration	Single mebendazole 500-mg chewable tablet n=396	Full Report 20 August 2010 EDMS-ERI-14160549 5.3.5.2
Efficacy and Safety Controlled Clinical Study						
MEBENDAZOLGAI3003 Synopsis 2016-000728-24 08 December 2014 03 September 2015 Completed	Ethiopia, Rwanda 3	Phase: 3 Double-blind, randomized, parallel-group, placebo-controlled multicenter, pediatric study Healthy boys or girls, of 1 to 16 years of age, inclusive, with positive egg count of *A. lumbricoides* and/or *T. trichiura* and who lived in a high STH-prevalence area To compare the efficacy and safety of a single dose of a 500-mg chewable mebendazole tablet with placebo in the treatment of *A. lumbricoides* and *T. trichiura* infestations	Randomized=295 Treated=284	Mebendazole: Chewable tablet; Placebo: Matching tablet (Oral) Single-dose administration at Visit 2 (double-blind phase) and Visit 3 (open-label phase)	Subjects were randomly assigned to receive either a single 500-mg chewable mebendazole tablet or matching placebo tablet at baseline (Visit 2) Subjects received a single open-label 500-mg chewable mebendazole tablet at Visit 3 Double-blind phase: n=284 (mebendazole: n=144; placebo: n=140); Open-label phase: n=278	Full Report 06 April 2016 EDMS-ERI-117445937 5.3.5.1

Key: *A. lumbricoides=Ascaris lumbricoides; T. trichiura=Trichuris trichiura*; BMI= basal metabolic index; NA=not applicable; STH= soil-transmitted helminth

Bridging studies between the formulations are not necessary because the proposed drug product is a locally acting drug with very low systemic availability.

Biowaiver Request

Reviewer's Assessment:

No biowaiver request is submitted nor required for review in this NDA.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies

Primary Biopharmaceutics Reviewer Name and Date:

8/30/2016
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

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

I concur with Dr. Ou's assessment and recommendation.
9/6/2016

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality