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APPLICATION NUMBER:

208398Orig1s000

MEDICAL REVIEW(S)

Clinical Review
 Sheral S. Patel, M.D.
 NDA 208398 – 505(b)(2)
 VERMOX™ CHEWABLE (mebendazole 500 mg chewable tablets)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	208398
Priority or Standard	Priority
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Division/Office	Division of Anti-Infective Products Office of Antimicrobial Products
Reviewer Name(s)	Sheral S. Patel, M.D.
Review Completion Date	30 September 2016
Established Name	Mebendazole 500 mg chewable tablets
(Proposed) Trade Name	VERMOX™ CHEWABLE
Applicant	Janssen Pharmaceuticals, Inc.
Formulation(s)	Tablet, oral
Dosing Regimen	Single oral dose
Applicant Proposed Indication(s)/Population(s)	Anthelmintic indicated for the treatment of single or mixed gastrointestinal infestations by <i>Trichuris trichiura</i> (whipworm); <i>Ascaris lumbricoides</i> (large roundworm); and <i>Ancylostoma duodenale</i> (b) (4) Adults and pediatrics (greater than 1 year of age)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Anthelmintic indicated for the treatment of gastrointestinal infections by <i>Trichuris trichiura</i> (whipworm); <i>Ascaris lumbricoides</i> (large roundworm); and <i>Ancylostoma duodenale</i> (b) (4) Adults and pediatrics (greater than 1 year of age)

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DPMH	Division of Pediatrics and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

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NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STH	soil-transmitted helminth
TEAE	treatment emergent adverse event
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Mebendazole is a synthetic broad-spectrum anthelmintic agent for oral administration belonging to the class of benzimidazole derivatives. Mebendazole has low systemic bioavailability, with 90% of the drug remaining in the gastrointestinal tract, where it exerts activity against soil-transmitted helminths (STH).

The Applicant submits data to support the approval of mebendazole rapidly disintegrating 500 mg oral chewable tablets (IND 115959, conditional proprietary name, VERMOX CHEWABLE (mebendazole) 500 mg Chewable Tablets).

The proposed indication is:

*VERMOX™ Chewable (mebendazole) 500 mg chewable tablet is an anthelmintic indicated for the treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); (b) (4)*

VERMOX™ Chewable (mebendazole) 500 mg chewable tablets are intended for adults and pediatrics (b) (4) 1 year of age) to be administered as a single dose.

An alternative method of administration for (b) (4) who have difficulty swallowing the tablet is proposed. The VERMOX™ Chewable (mebendazole) 500 mg chewable tablets can be placed in a spoon and approximately 2 to 3 mL of drinking water should be added. The tablet absorbs the water within two minutes and turns the tablet into a soft mass with semi-solid consistency.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provides substantial evidence that the new mebendazole 500 mg chewable tablet is effective for the treatment of single- and mixed- species soil transmitted helminth infections caused by roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) (b) (4) (b) (4) in populations (b) (4) than 1 year of age.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

This clinical reviewer recommends APPROVAL of the Applicant's new mebendazole 500 mg chewable tablet for the treatment of single- and mixed- species soil transmitted helminth infections caused by roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) (b) (4) in populations 1 year of age and older.

Soil transmitted helminth (STH) infections are considered a neglected tropical disease and are caused by four main species of parasitic worms: roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*). More than 1.5 billion people, or 24% of the world's population, have STH infections.¹ Morbidity from STH infections is related to worm burden and can include nutritional impairment, cognitive impairment, intestinal obstruction and rectal prolapse.^{2,3}

The approved therapy for the treatment of STH in the United States is mebendazole 100 mg chewable tablet, which is administered twice daily for 3 days. The label states that 100 mg tablets have not been studied in children less than 2 years of age.

A 500 mg solid oral mebendazole tablet, used for single dose administration to treat STH, is not available in the United States. Although the solid oral tablet can be crushed and administered with a small amount of potable water, if available, for children less than 5 years old, this is not a preferred method for several reasons: 1.) additional work required for crushing the tablet, 2.) unpleasant taste of the medication, 3.) possible choking hazard if the medication is not completely crushed, and 4.) chance of insufficient dosing if part of the medication is lost. Given these reasons, the WHO recommends that only chewable deworming tablets should be given to children under 5 years old, and that chewable tablets be crushed and mixed with water in children under 3 years old. The WHO recommends a 500-mg chewable dose for all ages ≥1 year, with no adjustment in dosage needed based on age, weight or surface area.⁴

The Applicant's proposed new mebendazole 500 mg chewable tablet would be administered as a single dose. It is a rapidly disintegrating formulation which turns into a soft semi-solid mass when mixed with a small amount of water. In addition, the 500 mg chewable tablet has been studied in children as young as 1 year old.

The new mebendazole 500 mg chewable tablet is effective for treatment of STH infections. A single Phase 3 study (GAI3003) showed that one dose of mebendazole 500 mg chewable tablet is more effective than placebo in the treatment of *A. lumbricoides* (83% vs. 11%, respectively) and *T. trichiura* (34% vs. 7%, respectively) in pediatric subjects as young as one year. Cure rates for subjects with single and double infections of

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A. lumbricoides and *T. trichiura* in the mebendazole group were similar. In addition, overall cure rates abstracted from the literature indicate that a single 500 mg mebendazole dose is superior to placebo for *A. lumbricoides*, *T. trichiura*, (b) (4) in adults and children.

The new mebendazole 500 mg chewable tablet is safe for treatment of STH infections. Safety results from 712 subjects enrolled in four Applicant-conducted clinical studies, showed that subjects exposed to the mebendazole 500 mg chewable tablet had few non-serious treatment emergent adverse events which were consistent with what has been reported through the Applicant's internal study reports and more than 40 years of post-marketing surveillance. There was no discernible relationship of TEAEs and feeding status, age or sex in the clinical studies.

The Applicant's new mebendazole 500 mg chewable tablets offers several improvements over existing therapy including:

1. Better patient compliance with single dose administration, which may contribute to improved efficacy
2. Ability to administer drugs to individuals who may have difficulty chewing a tablet, such as young children, and potentially minimize adverse events such as choking
3. Potential to treat children as young as 1 year of age, a special population

The new mebendazole 500 mg chewable tablet would be an option for young children, a vulnerable population, who may have difficulty swallowing or chewing tablets, are at high risk for acquiring STH infections, and are a target population for WHO STH mass drug administration public health programs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Soil transmitted helminth (STH) infections are considered a neglected tropical disease. • STH infections are caused by four main species of parasitic worms: roundworm (<i>Ascaris lumbricoides</i>), whipworm (<i>Trichuris trichiura</i>) and hookworms (<i>Necator americanus</i> and <i>Ancylostoma duodenale</i>).	• STH infections are a serious condition.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- More than 1.5 billion people, or 24% of the world's population, have STH infections.¹ - Morbidity from STH infections is related to worm burden and can include nutritional impairment, cognitive impairment, intestinal obstruction and rectal prolapse.^{2,3}	
Current Treatment Options	- There are four drugs on the World Health Organization (WHO) Model List of Essential Medicines for the treatment and control of STH infections: mebendazole, albendazole, levamisole, and pyrantel pamoate.^{5,6} In addition, ivermectin can be used for the treatment of Ascaris and Trichuris infections.^{5,7} - Only the mebendazole 100 mg chewable tablet form is FDA approved for STH infection and is administered as a multi-dose treatment.^{7,8} - A mebendazole 500 mg solid oral tablet formulation is available outside the U.S. which can be crushed and administered with a small amount of potable water, if available, for children less than 5 years old. The WHO recommends a 500-mg chewable dose for all ages ≥1 year, with no adjustment in dosage needed based on age, weight or surface area.⁴	- Mebendazole and albendazole, both benzimidazole antihelmintics, are frequently used for WHO single-dose mass drug administration STH public health programs.^{2,9} Albendazole, pyrantel pamoate and ivermectin are FDA-approved for other indications. Levamisole is FDA approved for veterinary use. - The FDA approved mebendazole 100 mg chewable tablet is not practical for STH mass drug administration programs and may pose dosing challenges in children less than 3 years of age who may not be able to chew the tablet. - The mebendazole 500 mg solid oral tablet is not a preferred method of administration for several reasons: 1.) additional work required for crushing the tablet, 2.) unpleasant taste of the medication, 3.) possible choking hazard if the medication is not completely crushed, and 4.) chance of insufficient dosing if part of the medication is lost.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- In the single Phase 3, randomized, double-blind, placebo-controlled, study (GAI3003), cure rates for subjects (age 1 to 16 years) in the new mebendazole 500 mg chewable tablet treatment arm were superior to placebo for <i>A. lumbricoides</i> (mebendazole, 72/86 [83.7%]; placebo, 9/81 [11.1%]) and <i>T. trichiura</i> (mebendazole, 42/124 [33.9%]; placebo, 9/119 [7.6%]) at the end of the double-blind period (Day 19). In addition, cure rates for subjects with single and double infections of <i>A. lumbricoides</i> and <i>T. trichiura</i> in the mebendazole group were similar. - Overall cure rates abstracted from the literature indicate that a single 500 mg mebendazole dose is superior to placebo for <i>A. lumbricoides</i>, <i>T. trichiura</i>, (b) (4) in adults and children. - In both Study GAI3003 and the literature review, cure rates and egg reduction rates were not as high for <i>T. trichiura</i> (b) (4) in comparison to <i>A. lumbricoides</i> with single dose mebendazole 500 mg treatment (any formulation).	- The new mebendazole 500 mg chewable tablet is effective for the treatment of single- and mixed- species soil transmitted helminth infections caused by roundworm (<i>Ascaris lumbricoides</i>), whipworm (<i>Trichuris trichiura</i>) and (b) (4) <i>duodenale</i>) in populations 1 year of age and older. - Cure rates and egg reduction rates were superior to placebo for all STH infections studied in Study GAI3003 and the literature.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk</u>	- Safety results from 712 subjects enrolled in four Applicant-conducted clinical studies (GAI1001, GAI1002, GAI3002, and GAI3003), showed that subjects exposed to the mebendazole 500mg chewable tablet had few non-serious TEAEs which were consistent with what has been reported through the Applicant's internal study reports and more than 40 years of post-marketing surveillance. - There was no discernible relationship of TEAEs and feeding status, age or sex in the clinical studies. - There was no association of TEAEs in circumstances where higher mebendazole systemic exposures have been described, such as high fat meals and administration to children less than 3 years old.	- The new mebendazole 500 mg chewable tablet is safe for the treatment of single- and mixed- species soil transmitted helminth infections caused by roundworm (<i>Ascaris lumbricoides</i>), whipworm (<i>Trichuris trichiura</i>) (b) (4) (duodenale) in populations greater than 1 year of age. - The safety profile of the new mebendazole 500 mg chewable tablet is consistent with postmarketing surveillance reports where different formulations, doses and duration of treatments have been used for over 845 million estimated treatment courses since 1988.
<u>Risk Management</u>	Safety issues requiring risk management can be communicated through labeling.	No risk evaluation and mitigation strategies, post-marketing requirements or commitments are recommended.

2 Therapeutic Context

2.1. Analysis of Condition

Soil transmitted helminth (STH) infections are considered a neglected tropical disease. STH infections are caused by four main species of parasitic worms: roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*).

The World Health Organization (WHO) estimates that more than 1.5 billion people, or 24% of the world's population, have soil-transmitted helminth (STH) infections.¹ Furthermore, there are over 270 million preschool children and over 600 million school-age children living in areas of intense transmission, and are in need of treatment and prevention interventions.¹

Morbidity from STH infections is related to worm burden and can include nutritional impairment (i.e., intestinal bleeding, impaired iron status, anemia, nutrient malabsorption, competition for micronutrients, impaired growth, loss of appetite, reduction of food intake, diarrhea, dysentery), cognitive impairment, intestinal obstruction and rectal prolapse.^{2,3}

WHO recommends control of STH infections to decrease morbidity by periodic treatment of at-risk populations living in endemic areas.⁹ At-risk individuals include preschool children, school-age children, women of childbearing age (including pregnant women in the second and third trimesters and breastfeeding women) as well as adults in certain high-risk occupations, such as tea pickers and miners. Periodic treatment decreases worm burden, which can decrease morbidity.

WHO recommends single dose mebendazole (500 mg) or albendazole (400 mg) for treatment of STH infections.

2.2. Analysis of Current Treatment Options

There are four drugs on the WHO Model List of Essential Medicines for the treatment and control of STH infections: mebendazole, albendazole, levamisole, and pyrantel pamoate (**Table 20**).^{5,6} In addition, ivermectin can be used for the treatment of STH.^{5,7} Only the mebendazole 100 mg chewable tablet form is FDA approved for multi-dose treatment of STH.^{7,8} Albendazole, pyrantel pamoate and ivermectin are FDA-approved for other indications. Levamisole is FDA approved for veterinary use.

Mebendazole and albendazole, both benzimidazole antihelminthics, are frequently used for

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WHO single-dose mass drug administration STH public health programs.^{2,9} The dosing regimen for the currently approved mebendazole 100 mg chewable tablet (twice daily for 3 days) is not practical for STH mass drug administration programs. In addition, the 100 mg chewable tablet may pose dosing challenges in children less than 3 years of age who may not be able to chew the tablet.

There is a mebendazole 500 mg solid oral tablet formulation available outside the U.S. which can be crushed and administered with a small amount of potable water, if available, for children less than 5 years old. This is not a preferred method of administration for several reasons: 1.) additional work required for crushing the tablet, 2.) unpleasant taste of the medication, 3.) possible choking hazard if the medication is not completely crushed, and 4.) chance of insufficient dosing if part of the medication is lost. WHO recommends that only chewable deworming tablets should be given to children under 5 years old, and that chewable tablets be crushed and mixed with water in children under 3 years old. The WHO recommends a 500-mg chewable dose for all ages ≥ 1 year, with no adjustment in dosage needed based on age, weight or surface area.⁴

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

The approved reference product is VERMOX (mebendazole) 100 mg chewable tablets (NDA 017481, approved 28 June 1974). Marketing for VERMOX (mebendazole) 100 mg chewable tablets was discontinued in 2006 due to commercial reasons; however safety reporting continues.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of key regulatory interactions is summarized in **Table 1**. Please refer to the Clinical Review for the pre-NDA meeting filed under IND 115959 SD25 for additional details.

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Table 1: Summary of Key Regulatory Interactions

Correspondence Date [FDA Meeting or Written Response]	Correspondence Description
26 Oct 2012	Pre-IND Meeting to discuss the development plan for a WHO donation program for a new formulation of mebendazole 500-mg chewable tablets
27 Aug 2013	Pre-IND CMC Meeting with continued discussion of nonclinical and clinical questions to discuss product development
14 Jan 2014	FDA Non-Clinical Hold Comments on Initial IND 115959 Submission
14 Feb 2014	CMC Pre-NDA Written Response on the draft registration stability protocol
03 Sep 2014	Orphan Drug Designation Letter granting mebendazole 500-mg chewable tablets orphan drug status (Designation No. 13-3970).
25 Nov 2014	FDA Comments on Phase 3 GAI3003 Protocol
04 Jun 2015	Pre-NDA Biostatistics Response
11 Aug 2015	CMC and Nonclinical Written Response to discuss chemistry/manufacturing and pre-clinical aspects of the NDA filing
08 Mar 2016	Pre-NDA Meeting to discuss and obtain Agency agreement on the content and format of the NDA for mebendazole 500-mg chewable tablets.

Source: NDA 208398, Module 1.2, Reviewer's Guide, Regulatory History.

3.3. Foreign Regulatory Actions and Marketing History

Mebendazole is licensed in 123 countries around the world. The registered formulations of mebendazole are 100-mg, 200-mg, and 500-mg oral tablets, 500-mg chewable tablets, and oral suspensions of 20 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, and 100 mg/5 mL. The 500-mg solid oral tablet of VERMOX (mebendazole) was first registered in Belgium in March 1971 and is used in approximately 60 countries for the mass treatment of single or mixed gastrointestinal infections by *E. vermicularis*, *T. trichiura*, *A. lumbricoides*, *A. duodenale*, and *N. americanus*. Both the 100-mg and 500-mg chewable tablets are listed in the World Health Organization (WHO) Model List of Essential Medicines for Children for the treatment of STH infections. Currently, the Applicant is donating the commercial 500-mg VERMOX solid oral tablets to the WHO for distribution to countries with moderate-to-high prevalence of STH infections for single-dose preventive chemotherapy programs in school-age children.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Good Clinical Practices within the Office of Scientific Investigations was consulted on 23 May 2016. Only foreign data are used to support the application and only one Phase 3 study (GAI3003) was conducted. Study GAI3003 was conducted at 3 clinical sites, 2 in Ethiopia (Gondar and Jimma) and 1 in Rwanda (Kigali). Because the majority (255/ 295) of subjects was enrolled at the Ethiopian sites, DAIP requested that these sites be inspected. The inspection summary goal date was 15 September 2016; however there were challenges due to the local security situation, particularly at the Gondar, Ethiopia site. The inspection was completed at the Jimma, Ethiopia site on 21 September 2016 and the preliminary field classification was No Action Indicated (NAI). Please see the OSI review by John Lee, M.D. for additional information. Please refer to **Section 6.2.1** for details regarding the Applicant's pre-FDA site inspection findings.

4.2. Product Quality

Please refer to the relevant Product Quality Reviews for this NDA.

Note that two different mebendazole 500 mg formulations were used during the clinical development program (**Table 4**). The Applicant initially developed a mebendazole 500 mg chewable tablet. Subsequently, the Applicant developed a rapidly disintegrating mebendazole 500mg chewable tablet which turns into a soft semi-solid mass with the addition of 2 to 3 mL of water. This new rapidly disintegrating chewable tablet was used in the Phase 3 study and is referred to as the new mebendazole 500 mg chewable tablet throughout the review.

According to FDA June 2016 Draft Guidance for Industry entitled, 'Quality Attribute Considerations for Chewable Tablets', the nomenclature, "[DRUG] Chewable Tablets" will be used for tablets that MUST be chewed and for which there is no alternative route of administration.¹⁰ In addition, the Guidance states that 'The labels and labeling for these products will also include a labeling statement indicating that the tablets MUST be chewed'.

Application of this Guidance to the proposed product was a conundrum for the review team. The product is a chewable tablet too large to be swallowed whole; however in patients who have difficulty chewing, 2 to 3 mL of water turns the tablet into a soft mass with semi-solid consistency (see video submitted to IND 115959, July 2013). Multiple discussions were held with the Office of Product Quality (OPQ) regarding the appropriate nomenclature and labeling of the mebendazole 500 mg chewable tablet. This involved OPQ representatives from the

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Office of New Drug Products (including Dorota Matecka, PhD and George Lunn, PhD) and Office of Policy for Pharmaceutical Quality (including Yana Mille, RPh and Richard Lostritto, PhD).

Ultimately, the team agreed upon the name of ‘VERMOX™ CHEWABLE (mebendazole chewable tablet)’. In Section 2 Dosage and Administration of the label, directions on how to turn the tablet into a semi-solid mass are provided *without* a separate heading of ‘Alternate Methods of Administration’.

4.3. Clinical Microbiology

Please refer to the Clinical Microbiology Review by Shukal Bala, PhD. Dr. Bala notes that, in rodents and dogs experimentally infected with different helminth species, as well as naturally infected dogs, multiple doses of mebendazole were effective in reducing parasite burden. *In vitro* and *in vivo* studies suggest a potential for development of STH resistance to mebendazole due to a (b) (4) in the parasite β -tubulin gene. However, an association between mutations in the STH β -tubulin gene and clinical response in human subjects with STH has not been evaluated. Furthermore, the Phase 3 study (GAI3003) and published studies suggest that a single 500 mg dose of mebendazole is effective in curing and reducing egg count in patients infected with *A. lumbricoides*, *T. trichiura*, *A. duodenale*, and *N. americanus*. Dr. Bala also notes that *A. lumbricoides* appears to be more sensitive compared to *T. trichiura* and hookworms (*A. duodenale* and *N. americanus*). The major effect is on decreasing the egg count. Dr. Bala concludes that treatment with a single dose of mebendazole should be effective in decreasing the intensity and reducing transmission of STH infections. Please refer to Dr. Bala’s review for details.

Note that on 6 September 2016 the Applicant notified the Division of a protocol deviation in the recording of consensus Kato-Katz egg count values from the Quality Control readings to the Case Report Forms. Several follow-up information requests were sent to the Applicant for clarification. Ultimately, it was determined that the protocol deviations affected the final clinical outcome in 3 subjects and did not substantially impact efficacy conclusions.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology Toxicology Review by Amy Nostrandt, DVM, PhD.

In carcinogenicity tests of mebendazole in mice and rats, no carcinogenic effects were seen at doses as high as 40 mg/kg (0.4 to 0.8-fold the MRHD, based on mg/m²) given daily over two years. No mutagenic activity was observed with mebendazole in a bacterial reverse gene mutation test. Mebendazole was mutagenic in the absence of S-9 when tested using a continuous (24 hour) treatment incubation period in the mouse lymphoma thymidine kinase

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assay. Mebendazole was aneugenic *in vitro* in mammalian somatic cells. In the *in vivo* mouse micronucleus assay, orally administered mebendazole induced an increased frequency of micronucleated polychromatic erythrocytes with evidence suggestive of aneugeniciy. Doses up to 40 mg/kg in rats (0.8-fold the MRHD, based on mg/m²), given to males for 60 days and to females for 14 days prior to gestation, had no effect upon fetuses and offspring.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology Review by Abhay Joshi, PhD.

4.5.1. Mechanism of Action

Mebendazole acts locally in the intestinal lumen of humans to interfere with cellular tubulin formation within the intestines of STH resulting in disrupted glucose uptake and digestive functions which ultimately lead to autolysis and parasite death.

4.5.2. Pharmacodynamics

Similar to other formulations, the new mebendazole 500 mg chewable tablet is poorly absorbed after oral administration.

4.5.3. Pharmacokinetics

A summary of mean mebendazole pharmacokinetic (PK) parameters in Studies GAI3003 and GAI1002 is shown in **Table 2**. In both studies, subjects received the new mebendazole 500 mg chewable tablet. Please refer to the Analysis of Submission Specific Safety Issues in **Sections 8.5.1 Feeding Status** and **8.5.2 Age** for detailed discussion regarding PK and safety from a clinical perspective.

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Table 2 Mean (SD) Mebendazole Pharmacokinetic Parameters for Pediatric Subjects and Healthy Adult Subjects.

Parameter	GAI3003(Pediatric)*			GAI1002 (Adult)*	
	1 to <3 yrs	3 to <7 yrs	7 to 16 yrs	Fed	Fasted
N	22	12	10	16	16
Dose (mg/kg)	45.7	28.2	17.3	7.04	7.04
(Range)	(29.4 - 56.2)	(23.6 - 34.5)	(10.5 - 25.6)	(5.66 - 9.82)	(5.66 - 9.82)
C _{max} (ng/mL)	210 (212)	49.9 (26.8)	34.2 (13.8)	56.2 (35.8)	14.0 (9.17)
t _{max} (h) ^a	2.5	2.0	3.0	4.0	1.5
	(1.0 – 8.0)	(0.98 – 3.0)	(1.0 – 8.0)	(2.0 – 6.0)	(0.50 – 3.0)
AUC ₀₋₈ (ng.h/mL)	697 (367) ^b	242 (139) ^c	182 (66.3)	ND	ND
AUC _{last} (ng.h/mL)	1,320 (844)	416 (215)	387 (190)	400 (194) ^{d,e}	111 (60.0) ^{d,e}

^a Median (Range);

^b n=21; ^c n=9; ^d n=15;

^e AUC₂₄, for comparison to AUC_{last} in pediatric subjects; the last sample was taken approximately 24 hours postdose in the PK substudy. Thus, for this study AUC₂₄ = AUC_{last}

*In pediatric subjects, parameters were determined based on concentrations in whole blood fingerstick samples; in adults, parameters were determined based on concentrations in venous plasma samples.

ND – Not determined

Source: Mod5.3.1.1\GAI1002\Tab3 and : Mod5.3.5.1\GAI3003\Tab7

Source: NDA 20398, Module 2.7.2, Summary of Clinical Pharmacology, Table 20.

Note that on 6 September 2016 the Applicant notified the Division of a protocol deviation in the PK sub-study, where two children were administered study drug and spit out the medication. See Section 6.2.1 for additional details regarding Data Integrity for Study GAI3003. Although the overall conclusions are unchanged by excluding the two children, PK parameters do change and indicate decreased systemic exposures, which is reassuring (Table 3).

Table 3 Mean Capillary Whole Blood Mebendazole Pharmacokinetic Parameters by Age Group and Comparison with the Plasma Pharmacokinetic Parameter Estimates in Adults

	Reported Estimates				Compared to Adult Estimates (Fold increase)		
	1 to <3 years [#] (N = 20)	≥3 to <7 years [#] (N = 12)	≥7 to 16 years [#] (N = 10)	Adults ^{\$} (N = 16)	1 to <3 years	≥3 to <7 years	≥7 to 16 years
Mean C _{max} (ng/mL)	(b) (4) ~~174~~	49.9	34.2	56.2	(b) (4) ~~3.1~~	0.9	0.6
Maximum C _{max} (ng/mL)	~~739~~	101	52.1	156	~~4.7~~	0.6	0.3
Mean AUC _{Last} (ng*h/mL)	~~1196~~	416	387	456	~~2.6~~	0.9	0.8
Maximum AUC _{Last} (ng*h/mL)	~~2373~~	874	747	986	~~2.4~~	0.9	0.8

^{\$}Adult PK parameter estimates are calculated from plasma samples in fed condition

[#]Pediatric PK parameter estimates are calculated from whole blood capillary fingerstick samples and most administrations were with food

Source: NDA 208398 Clinical Pharmacology Review by Abhay Joshi, PhD, Table 5.

Note that originally submitted values are indicated by strikethrough, with the revised calculations, where the two children who spit out study drug were excluded, next to it.

4.5.4 Review Issues Identified by Clinical Pharmacology

The Clinical Pharmacology reviewer, Abhay Joshi, PhD identified three main review issues with the application. Please refer to Dr. Joshi's review for details.

1. *Higher systemic exposure to mebendazole in young children (age 1 to less than 3 years):* The mean mebendazole systemic exposure from a single dose of 500 mg mebendazole chewable tablet was approximately 4-fold higher in the youngest pediatric patients (1 to < 3 years) than the older pediatric patients (3 to < 7 years and 7 to 16 years) and adults. The higher exposure was partially attributed to the fixed ("non-weight normalized") dosing strategy of one 500 mg chewable tablet as a one-time dose. However, the observed higher exposure in pediatrics (>1 years) was deemed clinically insignificant based on the safety data from the same study. Thus, the proposed single one-time 500 mg dose of Vermox Chewable in pediatric patients is acceptable from a Clinical Pharmacology perspective.

2. *Food effect:* In healthy volunteers, administration of the newer to-be-marketed mebendazole chewable tablet formulation with a high fat breakfast resulted in approximately 3- to 4-fold higher systemic exposure compared to when administered under fasted conditions. However, there was no apparent association between higher systemic exposure and safety findings, based on review of safety data from the same study. Thus, Vermox Chewable tablets will be recommended to be given without regard to meals/food.

3. *Capillary sampling method:* The Applicant's proposal to use whole blood mebendazole concentrations from fingerstick capillary samples as a surrogate for venous PK plasma sampling was not acceptable because of the observed sporadic higher concentrations in some capillary samples, in both pediatrics and adults. For the majority of inconsistencies, mebendazole concentrations in capillary fingerstick samples were higher than concentrations in respective venous plasma samples; therefore, it can be approximated that the mebendazole plasma levels will be equal or lower than the levels that are detected in the fingerstick samples. Therefore, the Reviewer agrees with the Applicant's proposed approach of using mebendazole concentrations in whole blood capillary fingerstick samples as "worst case" or "maximum" estimates for the systemic PK exposure to mebendazole.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable.

4.7. Consumer Study Reviews

This section is not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant submits information from 4 clinical studies (**Table 4**), internal study reports and the literature.

Table 4 Clinical Studies for Mebendazole Chewable 500 mg Tablet

Study / Formulation	Dosing / Treatment Model	Planned / Actual Number of Subjects	Study Design	Primary Objective
MEBENDAZOLGAI1001 ³ Previous Chewable	A single 500-mg oral dose of VERMOX tablet vs single 500-mg oral dose of mebendazole chewable tablet	20/19	An open-label, single-dose, relative bioavailability, randomized, 2-way crossover design study	To determine the relative bioavailability of a new chewable tablet formulation of mebendazole with respect to the currently marketed tablet in healthy adult subjects
MEBENDAZOLGAI1002 ⁴ New Chewable	Treatment A (Reference): A single 500-mg dose of mebendazole, fast disintegrating chewable tablet formulation, in the fasted condition. Treatment B (Test): A single 500-mg dose of mebendazole, fast disintegrating chewable tablet formulation, just after ingestion of a high-fat breakfast	16/16	A Phase 1, open-label, randomized, single-center, single-dose, 2-way crossover study	To evaluate the effect of food on the bioavailability of mebendazole from a single 500-mg oral dose of a rapidly disintegrating chewable tablet formulation of mebendazole in healthy adult subjects
MEBENDAZOLGAI3002 ⁵ Previous Chewable	A single mebendazole 500-mg chewable tablet on Day 1 followed by 30 min of observation. Subjects returned to the study center 3 days (±1 day) postdose for safety assessments	375/396	An open-label, single-center, single-dose, single-arm safety study	To assess the safety and tolerability of a mebendazole 500-mg chewable tablet formulation in a pediatric population (children 2 to 10 years of age, inclusive)
MEBENDAZOLGAI3003 ⁶ New Chewable	A single mebendazole 500-mg rapidly disintegrating chewable tablet or a matching placebo was given after screening and baseline assessments. All subjects were given a single mebendazole 500-mg fast disintegrating chewable tablet at Day 19 followed by PK assessments in a subpopulation of subjects	250/295	A randomized, multicenter, double-blind, parallel-group, placebo-controlled study	To compare the efficacy and safety of a single dose of a new 500-mg rapidly disintegrating chewable tablet of mebendazole and placebo in the treatment of <i>A. lumbricoides</i> and <i>T. trichiura</i> in pediatric subjects aged between 1 and 16 yrs followed by PK assessments in a subpopulation of subjects

Source: NDA 208398, Module 2.5, Clinical Overview, Table 1.

5.2. Review Strategy

The Applicant submits data from clinical studies, internal study reports and the literature to support the use of the new mebendazole 500 mg chewable tablet for single dose treatment of

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single- or mixed- species infections. This clinical reviewer considered all sources of data in review of this application. Efficacy analyses were conducted by the Statistical Reviewer, Janelle Charles, PhD. Supportive analyses were conducted by the Clinical Microbiology Reviewer, Shukal Bala, PhD. All safety analyses were conducted by this Clinical Reviewer. Please refer to **Section 8.1** for the Safety Review Approach.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1.MEBENDAZOLGAI3002

6.1.1. Study Design

MEBENDAZOLGAI3002 was an open-label, single-dose study to assess the safety of the ‘previous’ 500 mg mebendazole chewable tablet in children 2 to 10 years of age, inclusive. MEBENDAZOLGAI3002 is referred to as GAI3002 throughout the review. GAI3002 was not used to support efficacy; however is briefly described here for reference purposes.

GAI3002 was conducted at one site, Pemba Island in Zanzibar, Tanzania.

According to the Applicant, the “study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements”.

Study visits included the following:

1. Day 1: Screening visit. Eligible children entered into the study and administered a single mebendazole 500-mg chewable tablet. The children remained at the study center and AEs were recorded at approximately 30 minutes postdose.
2. Day 3 (± 1 day): Subjects returned to the study center for safety assessments, including AEs, changes in vital sign measurements, and physical examinations.

6.1.2. Study Results

Please refer to **Section 8**.

6.2. MEBENDAZOLGAI3003

6.2.1. Study Design

Overview and Objective

MEBENDAZOLGAI3003 is entitled “A Double-Blind, Randomized, Multi-Center, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of a 500-mg

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Chewable Tablet of Mebendazole in the Treatment of Soil-Transmitted Helminth Infestations (*Ascaris lumbricoides* and *Trichuris trichiura*) in Pediatric Subjects”. MEBENDAZOLGAI3003 will be referred to as GAI3003 throughout the review.

Objectives:

1. *Primary:* Compare the efficacy and safety of a single dose of a new 500-mg chewable mebendazole tablet with placebo in the treatment of *Ascaris lumbricoides* and *Trichuris trichiura* infestations in pediatric subjects.
2. *Secondary:* Assess systemic exposure to mebendazole following oral dosing of a 500-mg chewable tablet in pediatric subjects.
3. *Exploratory:* Compare efficacy and safety of the 500-mg chewable mebendazole tablet to placebo in treatment of (b) (4) in pediatric subjects.

Hypotheses:

Null hypothesis 1: In children infected with *A. lumbricoides*, cure rate (CR) is comparable following treatment with a single dose of a 500 mg chewable mebendazole tablet compared with placebo. Cure was defined as average posttreatment zero egg count.

Null hypothesis 2: In children infected with *T. trichiura*, CR is comparable following treatment with a single dose of a 500-mg chewable mebendazole tablet compared with placebo.

Trial Design

GAI3003 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of a single dose of a 500-mg chewable mebendazole tablet for the treatment of *A. lumbricoides* and *T. trichiura* infections in children between the ages of 1 and 16 years.

GAI3003 was conducted at three sites, 2 in Ethiopia (Gondar and Jimma) and 1 in Rwanda (Kigali). In order to ensure the safety of study subjects, an Independent Data Monitoring Committee (IDMC) was established to review unblinded study data. A pharmacokinetic (PK) substudy was also conducted. According to the Applicant, the “study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements”.

The overall study design for GAI3003 is summarized in **Figure 1** and **Table 21**. The study included 5 site visits:

1. Day -3 to -1: Screening
2. Day 1: Baseline and randomization, and initiation of double-blind treatment

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3. Day 19±2: End of double-blind phase; collection of stool sample for efficacy evaluation in the double-blind phase, mebendazole dosing to all subjects, starting in the open label phase, and collection of the first blood samples for PK analysis (for PK sub-study subject)
4. Day 20±2: Collection of the last blood samples for PK analysis
5. Day 26±3: Complete the open label follow-up phase

Key Inclusion Criteria:

1. Male or female subjects of age 1 to 16 years, inclusive, living in a high STH-prevalence area.
2. Female subjects ≥9 years old who had negative urine pregnancy test at screening or at the time of randomization.
3. Subjects, who were otherwise healthy, based on medical history, physical examination, vital signs, hemoglobin, and concomitant medications.
5. Subjects were available to return to the study site for all visits, including follow-up.
6. Parent(s)/guardians of subjects (or legally-accepted representatives) provided signed informed consent document and were willing to have the child participate in the study.
7. Children ≥6 years of age were asked to assent to their participation using age-appropriate language to agree to participate

Study Drugs

The 'new' mebendazole chewable 500 mg chewable tablet and a matching placebo tablet were used in the study (**Table 4**). For children 3 to 16 years of age, the study drug was administered as a tablet which was chewed and swallowed without water. For children 1 to <3 years of age, the tablet was placed on a teaspoon and approximately half spoonful (2 to 3 mL) of drinking water was added using a dosing syringe onto the tablet. The resulting soft mass with a semi-solid consistency was administered.

Study Endpoints

The two primary efficacy endpoints were cure rates (CR) for *A. lumbricoides* and *T. trichiura* infections at the end of the double-blind period for subjects with positive corresponding egg counts at baseline.

Secondary efficacy endpoints were egg count reductions (ER) for *A. lumbricoides* and *T. trichiura* infections at the end of the double-blind period.

The baseline value for efficacy analyses was the average positive egg count for the respective STH from the screening visit.

Protocol Amendments

There were four non-substantive protocol amendments. Please refer to the clinical study report for details.

Data Quality and Integrity: Sponsor's Assurance

The Applicant reports appropriate steps taken to ensure the accuracy and reliability of the data.

Reviewer Comment: On 06 September 2016, the Division received a communication from the Applicant regarding their pre-FDA site inspection results conducted on August 1 and 2, 2016. The Applicant identified a deviation from the Quality Control (QC) procedure at the study sites and two protocol deviations in the PK sub-study.

The protocol deviation for QC involved failure of accurate transcription of results to case report forms when a new consensus value was documented. This 'QC transcription deviation' was noted in 11 QC check samples from 9 subjects and impacted the outcome of cure in 3 subjects (251001043, 251002044 and 251002101). Re-analysis of efficacy using the updated results based on QC did not significantly change the results. Please refer to the relevant Applicant submissions submitted to the NDA for details.

In the PK sub-study, a patient who spit out the dose or vomits within 4 h after treatment was considered to be no longer PK evaluable. However, there were two children included in their analysis who should not have been. There was one child (251001272) who spit out part of the mebendazole 500 mg chewable tablet administered as a semi-solid mass on a spoon at Visit 3. The child was re-dosed in a similar manner and spit out part of the second dose. This child was considered to have received at least 50 % of the dose and therefore described as "treatment compliant". There was a second child (251002233) in the PK substudy who spit out part of the mebendazole 500 mg chewable tablet administered as a semi-solid mass on a spoon at Visit 3. The child was considered to have received at least 50 % of the dose and therefore described as "treatment compliant". Excluding these two subjects (251001272 and 251002233) from the PK analysis decreased the mean values for mebendazole C_{max} and AUC_{last} for the 1-3 year age class (**Table 3**). Please refer to the Clinical Pharmacology Review for additional details.

Both the 'QC transcription deviation' and 'PK sub-study protocol deviations' were reviewed in detail at several internal Division meetings (September 6, 13, 27, and 30, 2016). In addition the Division discussed these findings with the Applicant via teleconference on 13 September 2016.

It was ultimately determined that the pre-inspection site results did not alter the final conclusions of the study or labeling, and should be noted in the Clinical Study Report as errata.

Please refer to Section 4.1 for information regarding inspections conducted by the Office of Scientific Investigations.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in compliance with Good Clinical Practice.

Financial Disclosure

The Applicant did not disclose any financial conflicts of interest.

Efficacy Results – Primary and Secondary Endpoints

Efficacy results based on the intent-to-treat population, defined as all randomized subjects with pretreatment stool sample positive for 1 or more worms of interest, are summarized in Table 5 and Table 6.

Table 5 Cure rates at the end of the double-blind period (Day 19) – ITT Population

Infection Type	Mebendazole n/N (%)	Placebo n/N (%)	Difference ¹ (95% CI)
Large Roundworm	72/86 (83.7)	9/81 (11.1)	72.6 (62.3, 82.7)
Whipworm	42/124 (33.9)	9/119 (7.6)	26.2 (16.7, 35.6)

(b) (4)

¹Difference in cure rates, expressed in percentages, and based on Mantel Haenzel methods to account for stratification by site, for large roundworm and whipworm; (b) (4)

Failures include patients who tested positive for the worm at Day 19 or positive for the worm at baseline and had missing stool sample at Day 19.

Source: Created by the statistical reviewer using dataset “adeff.xpt”

Source: NDA 208398 Statistics Review, Table 1, Janelle Charles, PhD.

Table 6 Egg Reduction Rates for *A. lumbricoides* at the end of the double-blind period (Day 19) – ITT Population

	Mebendazole	Placebo
<u>Baseline, (eggs/g)</u>		
N	86	81
Geometric Mean	5801.3	6259.0
Median (Range)	9389.6 (48; 117384)	10560.0 (36; 90840)
<u>Post-treatment, (eggs/g)</u>		
N	81	76
Geometric Mean	1.9*	2116.4
Median (Range)	0 (0; 20064)	5932.9 (0; 143040)
Egg Count Reduction Rate	100%	30%

Geometric mean, median, and range calculated from log transformed data. Egg count reduction rate based on median of the individual relative change in egg count from baseline to post-treatment; see definition in Section 3.2.1.2. *p-value<0.001 for difference in mean egg counts, based on analysis of covariance in which the log transformed post-treatment egg count is the dependent variable with site and treatment as fixed effects and the log transformed baseline egg count as a covariate.

In the ANCOVA model and egg count reduction rate, the baseline egg count is used for 10 patients (5 mebendazole and 5 placebo) with missing data at Day 19.

Source: Created by the statistical reviewer using “dataset adeff2.xpt”

Source: NDA 208398, Statistical Review, Table 5, Janelle Charles, PhD.

Table 7 Egg Reduction Rates for *T. trichiura* at the end of the double-blind period (Day 19) – ITT Population

	Mebendazole	Placebo
<u>Baseline, (eggs/g)</u>		
N	124	119
Geometric Mean	209.2	270.8
Median (Range)	168 (12; 8808)	264 (12; 5916)
<u>Post-treatment, (eggs/g)</u>		
N	118	112
Geometric Mean	23.4*	150.2
Median (Range)	53.7 (0; 10536)	209.9 (0; 7704)
Egg Count Reduction Rate	81.2%	27.4%

Geometric mean, median, and range calculated from log transformed data. Egg count reduction rate based on median of the individual relative change in egg count from baseline to post-treatment; see definition in Section 3.2.1.2. *p-value<0.001 for difference in mean egg counts, based on analysis of covariance in which the log transformed post-treatment egg count is the dependent variable with site and treatment as fixed effects and the log transformed baseline egg count as a covariate.

In the ANCOVA model and estimation of egg count reduction rate, baseline egg count is used for 13 patients (6 mebendazole and 7 placebo) with missing data at Day 19.

Source: Created by the statistical reviewer using “dataset adeff2.xpt”

Source: NDA 208398, Statistical Review, Table 6, Janelle Charles, PhD.

Reviewer Comment: *Treatment with the new mebendazole 500 mg chewable tablet results in cure rates and egg reduction rates for *T. trichiura* and *A. lumbricoides* which are superior to placebo. Cure rates and egg reduction rates for *T. trichiura* are lower than *A. lumbricoides*. These results are consistent with the published literature. For example, one large published study (n=5830) evaluating efficacy of mebendazole in 6 countries on 3 continents confirmed findings from previous studies that mebendazole reduces fecal egg counts; however it is less efficacious for *T. trichiura* compared to *A. lumbricoides* (b) (4).¹¹⁻¹³ *T. trichiura* infections frequently require 3 days of treatment to achieve cure, rather than single-dose treatment.^{6, 13}*

Because the environment where target populations reside may not change, the goal of public health mass drug administration programs for STH infections is to decrease worm burden, rather than eliminate infection, in order to reduce morbidity and minimize severe complications caused by STH in at-risk populations.^{2, 9}

*Please refer to the relevant sub-section of **Section 8.4 Safety Results** for a description of patient disposition and demographic characteristics.*

Please refer to the Statistical Review for details regarding the efficacy analysis.

In the Applicant's proposed label, (b) (4) This reviewer suggests displaying data using geometric means in the proposed label.

Efficacy Results – Exploratory Endpoint

Thirteen randomized subjects had hookworm infection in addition to *Ascaris lumbricoides* and/or *Trichuris trichiura* infections. (b) (4)

Reviewer Comment: *The numbers are too small to make efficacy conclusions for the new mebendazole 500 mg chewable tablet and cure of hookworm infection solely from Study GAI3003. Please see **Section 7.2.3** for additional details.*

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Please refer to **Section 7.2.1.**

7.1.2. Secondary and Other Endpoints

Please refer to **Section 7.2.1.**

7.1.3. Subpopulations

Subpopulation analyses by age and sex evaluated cure rates for *A. lumbricoides* and *T. trichiura* after treatment with the new mebendazole 500 mg chewable tablet. Cure rates were similar between females and males, as well as across age groups.

Reviewer Comment: Please refer to the Statistical Review for details.
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7.1.4. Dose and Dose-Response

The Applicant develops a new mebendazole 500 mg chewable tablet intended for single-dose mass drug administration STH public health programs. The new formulation complies with WHO recommendations that only chewable deworming tablets should be given to children under 5 years old, and that chewable tablets be mixed with water in children under 3 years old.¹⁴ In the United States, a multi-dose mebendazole regimen (100 mg twice daily for 3 days) is approved.⁸

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The antihelminthic effect is directly related to the presence of mebendazole in the gastrointestinal tract. Using the same benzimidazole drugs for STH infections can theoretically place selection on the β -tubulin gene, leading to resistance.^{15, 16} Resistance has not yet been described in STH mass drug administration programs.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting - *A. lumbricoides*, *T. trichiura* (b) (4) Infections

The Applicant conducted a literature review summarizing efficacy data for a single-dose mebendazole 500 mg regimen (any formulation). Cure rates [CRs] and egg reduction rates

[ERs]) were abstracted for each study. Weighted means, where the treatment group results were weighted proportionally to the number of subjects treated, were used to calculate overall cure rates and egg reduction rates.

The Applicant's summary of efficacy for *A. lumbricoides*, *T. trichiura*, (b) (4) are summarized in **Table 8**, **Table 9**, and **Table 10**.

Table 8 Literature Summary of Efficacy of 500-mg Single-Dose Mebendazole Against *Ascaris lumbricoides* – All Studies, Including Placebo-Controlled Trials

Arm	Studies Reporting Results	Individuals with Cure Rate Data	Overall Cure Rate, %*	Range of Cure Rates, %	Individuals with Egg Reduction Data	Overall Egg Reduction, %*	Range of Egg Reduction, %
All Studies							
MBZ	22	2,771	92.5	72.5 – 100	3,689	98.5	89.8 - 100
PCT							
MBZ	4	611	84.6	72.5 - 98	611	98.1	96.1 - 99
PBO	3	285	21.0	0 – 27.9	285	23.9	6.0 – 33.9

Note: Average Egg Reduction Rates were determined inconsistently across studies including by using individual mean, group geometric mean and group arithmetic mean.

Key: MBZ=mebendazole, PCT=placebo-controlled trial, PBO=placebo

*Weighted means (Mod2.7.3/Sec3.2.1/Table 7)

Source: NDA 208398, Module 2.5, Clinical Overview, Table 5.

Table 9 Literature Summary of Efficacy of 500-mg Single-Dose Mebendazole Against *Trichuris trichiura* - All Studies, Including Placebo-Controlled Trials

Arm	Studies Reporting Results	Individuals with Cure Rate Data	Overall Cure Rate, %*	Range of Cure Rates, %	Individuals with Egg Reduction Data	Overall Egg Reduction, %*	Range of Egg Reduction, %
All Trials							
MBZ	23	4,407	27.6	8.4 – 100	5,417	72.9	31.6 - 93.0
PCT							
MBZ	5	1,147	33.4	22.9 - 77.6	1,147	86.8	81.0 – 92.8
PBO	4	704	9.5	0 – 18.6	704	16.4	-11.7 – 21.2

Note: Average Egg Reduction Rates were determined inconsistently across studies including by using individual mean, group geometric mean and group arithmetic mean.

Key: MBZ=mebendazole, PCT=placebo-controlled trial, PBO=placebo

*Weighted means (Mod2.7.3/Sec3.2.2/Tab9)

Source: NDA 208398, Module 2.5, Clinical Overview, Table 6.

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(b) (4)

Source: NDA 208398, Module 2.5, Clinical Overview, Table 7.

Reviewer Comment: Overall cure rates and egg reduction rates from the literature indicate that a single 500 mg mebendazole dose is superior to placebo for *A. lumbricoides* and *T. trichiura*. This is consistent with findings in Study GAI3003. (b) (4)

(b) (4)

The Statistics Reviewer, Janelle Charles, PhD, identified 6 placebo-controlled trials from the Applicant's literature review, where a total of 571 mebendazole patients and 557 placebo patients were evaluated for clearance of hookworm eggs at the end of the respective treatment periods (**Table 11**).¹⁷⁻²² Treatment follow-up varied from 2 weeks up to 4 weeks and ages of patients ranged from 2 to 71 years. Reported clinical cure rates ranged from 2.9% to 91.1% for mebendazole and 0% to 33% for placebo across all studies. Please refer to the Statistics Review by Janelle Charles, PhD for details.

7.2.2. Considerations on Benefit in the Postmarket Setting - Adults

The Applicant seeks approval of the new mebendazole 500 mg chewable tablet for both pediatric and adult populations. Although the Phase 3 study, GAI3003, only enrolled children up to 16 years of age, the Applicant submits a review of the literature for each STH indication, where studies with adults are included.

Reviewer Comment: *This reviewer recommends labeling the new mebendazole chewable tablet for populations ≥ 1 year of age (i.e. both pediatric and adult populations).*

*The current application (NDA 208398) is considered a 505(b)2 submission. The Applicant submits information cited in published literature regarding efficacy of single-dose mebendazole 500 mg (any formulation) against STH infections (*A. lumbricoides*, *T. trichiura*, *N. americanus* and *A. duodenale*) (**Section 7.2.1**). These publications include studies where both adults and children were enrolled. Higher efficacy rates were observed with the 500-mg singledose mebendazole regimens as compared to the placebo arm with respect to both cure rates and egg reduction rates in each of these studies.*

A. lumbricoides: *4 of the 22 studies were placebo controlled studies (age range 2 to 70 years), with 3 studies reporting results for a placebo-control group (**Table 8**).^{17, 18, 23, 24} Two of these studies^{17, 24} enrolled adults, with the age of enrollees ranging from 2 to 70 years of age. One of the studies reported results for a placebo group (age range 2 to 70 years).¹⁷ Cure rates for the mebendazole arm were 93.4% (n=61) and 0% (n=44) in the placebo arm.¹⁷ The second study²⁴ was conducted only in adults (age range 18 to 44 years), with cure rates in the mebendazole arm reported at 72.5% (n=302).*

T. trichiura: *5 of the 23 studies included a placebo control group (age range 2 to 70 years), with 4 studies reporting results for a placebo-control group (**Table 9**).^{17-19, 23, 24} Two of these studies^{17, 24} enrolled adults, with the age of enrollees ranging from 2 to 70 years of age. One of the studies reported results for a placebo group (age range 2 to 70 years).¹⁷ Cure rates for the mebendazole arm were 77.6% (n=67) and 0% (n=38) in the placebo arm.¹⁷ The second study²⁴ was conducted only in adults (age range 18 to 44 years), with cure rates in the mebendazole arm reported at 39.1% (n=391).*

(b) (4)

There are additional reasons to support the labeling of the new mebendazole 500 mg chewable tablet for both adult and pediatric populations. Current labeling for the mebendazole 100 mg tablet indicates the same dosage schedule for adults and children, with no upper age limit restrictions.⁸ Mebendazole (both the new chewable 500 mg tablet and the approved 100 mg tablet) acts locally within the gastrointestinal tract and has poor systemic absorption. Although different doses and durations are used for each formulation, both the mebendazole 500 mg and 100 mg tablets use the same dosing regimen for adults and children. Furthermore, mebendazole would have the same mechanism of action on the soil transmitted helminth, irrespective of whether the host is an adult or a child. Finally, labelling for both the pediatric and adult populations will support its intended use as part of WHO single dose mass drug administration STH public health programs. Restricting the drug to only the pediatric population may have a significant negative public health impact.

7.2.3. Other Relevant Benefits – Mixed species infections

The Applicant proposes that the new mebendazole 500 mg chewable tablet will be used for treatment of single and mixed STH infections. However, in the original NDA application, no data were submitted to support the mixed species aspect of the indication. In response to an Information Request sent to the Applicant on 09 June 2016, additional information was provided.

The Applicant provided an analysis of cure rates and egg count reduction rates by single, double, and triple worm infections at the end of the double blind period for Study GAI3003. Of the 295 randomized subjects, 49 subjects had single infections with *A. lumbricoides* (placebo, $n=25$; mebendazole, $n=24$); 124 subjects had single infections with *T. trichiura* ($n=62$ in each group); 109 subjects had double species infections with *A. lumbricoides* and *T. trichiura* (placebo, $n=50$; mebendazole, $n=59$). Cure rates and egg count reduction rates for subjects with single and double infections of *A. lumbricoides* and *T. trichiura* in the mebendazole group are similar. Sample sizes were too small to make any conclusions about mixed-species infections with hookworm. Note that the study design for GAI3003 excluded patients with only hookworm infections. Thirteen patients had hookworm infection in addition to *Ascaris lumbricoides* and/or *Trichuris trichiura* infection.

(b) (4)

Table 12 Analysis of Cure Rate by STH Infection at Baseline (Single- and Double-Worm Infections)

Type of Infection at Baseline	Cure* Rate		% Difference (95% CI)
	Mebendazole n/N (%)	Placebo n/N (%)	
Single-Worm Infection¹			
Large Roundworm Only	21/24 (87.5)	0/25 (0)	87.5 (66.2, 97.3)**
Whipworm Only	20/62 (32.3)	3/62 (4.8)	27.4 (9.2, 44.3)**
Mixed-Worm Infection²			
Large Roundworm & whipworm	22/59 (37.2)	3/50 (6.0)	31.3 (12.7, 48.2)**

17 patients with missing Day 19 Kato Katz measurements treated as failures for these analyses.
*For patients with mixed-worm infections, cure means all worms present at baseline have been cleared at Day 19.
¹By study design, there were no patients with only hookworm randomized in Trial GAI3003.
**CI based on exact method.
Source: Created by the statistical reviewer using dataset “adeff2.xpt”

Source: NDA 208398 Statistical Review, Table 11, Janelle Charles, PhD.

The Applicant also reviewed the literature and reported that effectiveness for single- and mixed-species infections is not described; although the majority of the patients in the studies have mixed- species infections.

Reviewer Comment: Results from Study GAI3003 are sufficient to support labeling of the new mebendazole 500 mg chewable tablet for (b) (4) STH infections. The relationship of mixed species STH infections and efficacy of any antihelminthic drug is not well described. Nevertheless, populations receiving STH treatment through mass drug administration public health programs frequently have mixed-species infections and benefit from regular antihelminthic treatment.^{2,9}

Please refer to the Statistics Review by Janelle Charles, PhD for additional details.

7.3. Integrated Assessment of Effectiveness

The new mebendazole 500 mg chewable tablet is effective for the treatment of single- and mixed- species soil transmitted helminth infections caused by roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) (b) (4) populations greater than 1 year of age.

The Applicant conducted one Phase 3, randomized, double-blind, placebo-controlled, study

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(GAI3003) at three African sites to assess the efficacy and safety of a single dose of a 500-mg chewable mebendazole tablet for the treatment of *A. lumbricoides* and *T. trichiura* infections in children between the ages of 1 and 16 years. At the end of the double-blind period (Day 19), cure rates for subjects in the new mebendazole 500 mg chewable tablet treatment arm were superior to placebo for *A. lumbricoides* (mebendazole, 72/86 [83.7%]; placebo, 9/81 [11.1%]) and *T. trichiura* (mebendazole, 42/124 [33.9%]; placebo, 9/119 [7.6%]). In addition, cure rates for subjects with single and double infections of *A. lumbricoides* and *T. trichiura* in the mebendazole group were similar and superior to placebo.

The Applicant conducted a literature review summarizing efficacy data for a single-dose mebendazole 500 mg regimen (any formulation) for the treatment of STH infections. Overall cure rates abstracted from the literature indicate that a single 500 mg mebendazole dose is superior to placebo for *A. lumbricoides*, *T. trichiura*, (b) (4) in children and adults.

In both Study GAI3003 and the literature review, cure rates and egg reduction rates were not as high for *T. trichiura* (b) (4) in comparison to *A. lumbricoides* with single dose mebendazole 500 mg treatment (any formulation). However, cure rates and egg reduction rates were superior to placebo for all STH infections studied.

Single dose benzimidazole treatment (with mebendazole or albendazole) is a key component of periodic mass drug administration STH public health programs.^{2, 9} It is well known that reductions in STH worm burden, even with lower cure rates, can reduce morbidity and transmission.^{2, 6, 9, 15} Findings from Study GAI3003 and the literature review support the use of the new mebendazole 500 mg chewable tablet for treatment of single- and mixed species STH infections in children and adults.

8 Review of Safety

8.1. Safety Review Approach

The four clinical studies conducted by the Applicant were reviewed for safety issues. In addition, because mebendazole has been marketed since 1971, reports from internal clinical studies, postmarketing, and the literature were reviewed. Note that when safety analyses conducted by the clinical reviewer produced the same results as the Applicant, tables created by the Applicant are presented in the review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across the four clinical studies, there were 536 children who received one 500 mg dose of mebendazole and 176 subjects (141 children and 35 adults) who received two 500 mg doses (**Table 13**).

Table 13: Clinical Studies - Summary of Exposure

Study Number (Mebendazole Formulation)	Study Objective	Number of 500-mg Doses	Number of Subjects/ Demography
MEBENDAZOLGAI1001 (solid 500-mg tablet vs. previous 500-mg chewable tablet)	Bioavailability and Safety (cross-over)	2	19 Men (20 – 41 years)
MEBENDAZOLGAI1002 (new 500-mg chewable tablet)	Food Effect and Safety (cross-over)	2	7 Men and 9 Women (18 – 55 years)
MEBENDAZOLGAI3002 (previous 500-mg chewable tablet)	Safety	1	206 Boys and 190 Girls (2 – 10 years)
MEBENDAZOLGAI3003 (new 500-mg chewable tablet)	Efficacy and Safety with Pharmacokinetics	2 – 141 1 – 140 ^a	143 Boys and 152 Girls (1 – 15 years)

^a Among the 295 randomized subjects, 11 did not take any study medication (placebo or mebendazole), hence only 284 subjects were included in the safety analysis set (140 in placebo, and 144 in mebendazole). Three of the 140 subjects in the placebo group did not complete the DB phase and did not enter into the OL phase. These subjects, therefore, were not exposed to mebendazole. In total, 14 of the 295 randomized subjects were not exposed to mebendazole.

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 1.

8.2.2. Relevant characteristics of the safety population

Demographic characteristics of the safety population for Studies GAI3002 and GAI3003 are briefly summarized in **Table 22**. In GAI3002, the median age of subjects was 4 years (range 4 – 10 years) with 48.0% females. In GAI3003, the median age of subjects was 8 years (range 1 – 15 years) with 51.5% females. In both GAI3002 and GAI3003, the majority of subjects were Black or African American (98.7% and 100%, respectively).

Reviewer Comment: The Applicant enrolls children under 3 years of age in their studies which is a key component to assess safety of the mebendazole chewable 500 mg chewable tablet. The new rapidly-disintegrating mebendazole 500 mg chewable tablet was specifically developed for use in the youngest age groups where chewing and swallowing may be difficult. In GAI3002, 62/396 (15.7%) of the subjects were under 3 years of age. In GAI3003, 13/149 (8.7%) subjects in the mebendazole arm and 14/146 (9.6%) subjects in the placebo arm were under 3 years of age.

8.2.3. Adequacy of the safety database

The Applicant provides an adequate safety database with respect to exposure, demographics and dose.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the submission was adequate for the clinical safety review. The Office of Computational Sciences (OCS) conducted a Data Fitness Assessment which included whether the data could be loaded into analytic tools for reviewer use, whether certain common analyses could be performed, availability of appropriate variables, and appropriate use of standard terminology. No major issues were identified through the Data Fitness Assessment.

8.3.2. Categorization of Adverse Events

The Applicant's categorization of adverse events was adequate.

TEAEs for GAI3002 were recorded on Day 1 (30 minutes postdose) and 3 days (± 1 day) after study drug administration.

TEAEs for GAI3003 were recorded on Day 1 (up to 3 hours following administration of a 500-mg chewable mebendazole tablet or matching placebo); Day 19 (up to 3 hours following administration of an open-label 500-mg chewable mebendazole tablet); and Day 26 (7 days following administration of the open-label dose).

Reviewer Comment: *There are two points regarding datasets and analyses to note for adverse events.*

First, when TEAEs were first reported at the last study visit (i.e. Day 3 for GAI3002 or Day 26 for GAI3003) or when TEAEs were not completely resolved by the last study visit, there were no end dates to report in the AEENDTC variable of the dataset. In these cases, the Applicant recorded the outcome as 'RECOVERING/RESOLVING' or 'NOT RECOVERED/NOT RESOLVED' in the AEOUT variable of the ADAE analysis datasets. For both GAI3002 and GAI3003, all TEAEs with end dates (AEENDTC) had the AEOUT of RECOVERED/RESOLVED.

Second, the Applicant used MedDRA 12.1 for GAI3002 and MedDRA 18.0 for GAI3003 to analyze TEAEs. This clinical reviewer used MedDRA version 18.0 to analyze TEAEs for both GAI3002 and GAI3003. AE Term Matching reports did not reveal inconsistencies in Applicant AE reporting for GAI3002 and GAI3003.

8.3.3. Routine Clinical Tests

No clinical laboratory assessments were conducted for GAI3002 and GAI3003.

8.4. Safety Results

8.4.1. Deaths

In the four clinical studies (GAI1001, GAI1002, GAI3002 and GAI3003), there were no deaths reported.

8.4.2. Serious Adverse Events

In the four clinical studies (GAI1001, GAI1002, GAI3002 and GAI3003), there were no serious adverse events reported.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Disposition of subjects in Studies GAI3002 and GAI3003 are presented in **Table 23**.

In Study GAI3002, 6 subjects were withdrawn from the study due to non-compliance of study drug (failure to consume the study medication).

For Study GAI3003, 295 of the 792 subjects screened were enrolled and randomized. Two hundred seventy-eight subjects (94.2%) completed the double-blind phase and continued into the open-label phase of the study. Overall, 17 (5.8%) of 295 subjects were withdrawn during the double-blind phase. Reasons for discontinuation included subject choice ($n=12$), lost to follow-up ($n=3$), protocol violation ($n=1$; significant wasting), and physician decision ($n=1$). All 278 subjects who completed the double-blind phase and entered the open label phase completed the study.

Reviewer Comment: *Reasons for subject discontinuation from Study GAI3003 were similar in both treatment arms.*

8.4.4. Significant Adverse Events

In the four clinical studies (GAI1001, GAI1002, GAI3002 and GAI3003), there were no other significant adverse events reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

8.4.5.1. Study GAI1001

There were no TEAEs reported in Study GAI1001.

8.4.5.2 Study GAI1002

Results are discussed in **Section 8.5.1**.

8.4.5.3 Study GAI3002

In Study GAI3002, 11% (44/396) of the subjects reported at least 1 TEAE (**Table 14**). The most common TEAEs were reported in the Gastrointestinal Disorders SOC (14/396 [4%]) and General Disorders and Administration Site Conditions SOC (11/396 [2.8%]). TEAEs reported in greater than or equal to 5 subjects included pyrexia (11 [2.8%]), diarrhea (10 [2.5%]), lymphadenopathy (8 [2.0%]), and cough (5 [1.3%]). There was one TEAE of epistaxis considered severe. The remainder of TEAEs was mild or moderate in severity.

8.4.5.4 Study GAI3003

In Study GAI3003, the incidence of TEAEs in the double-blind phase was similar in the mebendazole (9/144 [6.3%]) and placebo (8/140 [5.7%]) treatment groups (**Table 14**). The most common TEAEs were reported in the Infections and Infestations SOC (mebendazole 3/144 [2.1%] versus placebo 4/140 [2.9%]). One TEAE occurred in more than one subject (abdominal pain, $n=2$ [1.4%]). All TEAEs were mild or moderate in severity.

In the open label phase of the study, the incidence of TEAEs was higher in the subjects who received mebendazole in the double-blind phase (6/141 [4.3%]) versus placebo (1/137 [0.7%]) (**Table 15**). The most common TEAEs were reported in the Gastrointestinal Disorders SOC (3/278 [1.1%]). No TEAE occurred in more than one subject. All TEAEs were mild or moderate in severity.

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Table 14 Treatment-Emergent Adverse Events by Body System (GAI3002 and GAI3003 [Double-Blind Phase]) - Safety Population.

Body System Or Organ Class Dictionary-Derived Term	GAI3002 Mebendazole (n=396)	GAI3003 Placebo (N=140)	GAI3003 Mebendazole (N=144)
Total no. subjects with any TEAE	44 (11%)	8 (5.7%)	9 (6.3%)
Gastrointestinal disorders	14 (4%)	2 (1.4%)	3 (2.1%)
Abdominal distension	1 (<1%)	1 (0.7%)	2 (1.4%)
Abdominal pain	2 (1%)	1 (0.7%)	1 (0.7%)
Aphthous stomatitis	1 (<1%)	0	0
Diarrhea	10 (3%)	0	0
Nausea	1 (<1%)	0	0
Oral Pain	1 (<1%)	0	0
General Disorders and Administration Site Conditions	11 (3%)	0	0
Pyrexia	11 (3%)	0	0
Blood and Lymphatic System Disorders	8 (2%)	0	0
Lymphadenopathy	8 (2%)	0	0
Infections and infestations	3 (1%)	4 (2.9%)	3 (2.1%)
Bronchitis	2 (1%)	0	0
Gastroenteritis	0	0	1 (0.7%)
Nasopharyngitis	0	2 (1.4%)	1 (0.7%)
Tinea infection	0	0	1 (0.7%)
Conjunctivitis	0	1 (0.7%)	0
Conjunctivitis bacterial	0	1 (0.7%)	0
Tonsillitis	0	1 (0.7%)	0
Upper respiratory infection	1 (<1%)	0	0
Urinary tract infection	1 (<1%)	0	0
Metabolism and Nutrition Disorders	0	0	1 (0.7%)
Vitamin A deficiency	0	0	1 (0.7%)
Respiratory, Thoracic and Mediastinal Disorders	8 (2%)	2 (1.4%)	1 (0.7%)
Cough	5 (1%)	2 (1.4%)	1 (0.7%)
Asthma	1 (<1%)	0	0
Dyspnea	1 (<1%)	0	0
Epistaxis	1 (<1%)	0	0
Rhonchi	1 (<1%)	0	0
Investigations	4 (1%)	0	0
Respiratory rate increased	2 (1%)	0	0
Cardiac murmur	1 (<1%)	0	0
Respiratory Rate	1 (<1%)	0	0
Skin and Subcutaneous Tissue Disorders	3 (1%)	0	1 (0.7%)
Rash pruritic	0	0	1 (0.7%)
Rash Papular	3 (1%)	0	0
Nervous System Disorders	2 (1%)	0	0
Dizziness	1 (<1%)	0	0
Headache	1 (<1%)	0	0
Hepatobiliary Disorders	1 (<1%)	0	0
Jaundice	1 (<1%)	0	0

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Body System Or Organ Class Dictionary-Derived Term	GAI3002 Mebendazole (n=396)	GAI3003 Placebo (N=140)	GAI3003 Mebendazole (N=144)
Eye disorders	0	1 (0.7%)	0
Night blindness	0	1 (0.7%)	0

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

NOTE: In Study GAI3003, Only subjects who experienced adverse events during the double-blind period were included in this table.

3002 is based on dictionary version: MedDRA 12.1

3003 is based on dictionary version MedDRA 18.0

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 4.

Table 15 Treatment-Emergent Adverse Events by Body System Open-Label Follow-Up Phase (GAI3003) - Safety Population.

Body system or organ class Preferred term	OL Mebendazole Subjects on Placebo during DB (N=137)	OL Mebendazole Subjects on Mebendazole during DB (N=141)	OL Mebendazole Total (N=278) ^a
Total no. subjects with any TEAE (%)	1 (0.7)	6 (4.3)	7 (2.5)
Gastrointestinal disorders	1 (0.7)	2 (1.4)	3 (1.1)
Abdominal pain	0	1 (0.7)	1 (0.4)
Diarrhoea	1 (0.7)	1 (0.7)	2 (0.7)
Vomiting	0	1 (0.7)	1 (0.4)
Infections and infestations	0	1 (0.7)	1 (0.4)
Malaria	0	1 (0.7)	1 (0.4)
Pneumonia	0	1 (0.7)	1 (0.4)
Injury, poisoning and procedural complications	0	1 (0.7)	1 (0.4)
Soft tissue injury	0	1 (0.7)	1 (0.4)
Nervous system disorders	0	1 (0.7)	1 (0.4)
Headache	0	1 (0.7)	1 (0.4)
Skin and subcutaneous tissue disorders	0	1 (0.7)	1 (0.4)
Pruritus	0	1 (0.7)	1 (0.4)

Key: DB=double-blind; OL=open-label; TEAE=treatment-emergent adverse events

^a 17 subjects dropped out before Visit 3 (3 lost to follow-up, 12 withdrew consent, 1 withdrawn for protocol violation, 1 withdrawn by physician decision)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Note: Follow-up phase includes data collected on or after the 2nd drug administration at visit 3.

Dictionary version MedDRA 18.0

[TSFAE01B.RTF] [JNJ-108329\GAI3003\DBR_FINAL\RE_CSR\PROD\TSFAE01B.SAS] 28OCT2015, 12:31

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 5.

Reviewer Comment: Please see **Section 8.7** for discussion about Applicant's proposed labeling.

8.4.6. Laboratory Findings

No clinically significant changes in laboratory findings (hematology, chemistry and urinalysis) were reported after study drug administration in Study GAI1001 and GAI1002. No clinical laboratory assessments were conducted for Study GAI3002 and GAI3003.

8.4.7. Vital Signs

There were no clinically significant changes in vital signs (blood pressure, pulse, respiratory rate, and temperature) over time for subjects in all four clinical studies (GAI1001, GAI1002, GAI3002 and GAI3003). In Study GAI3002, three subjects reported a TEAE of increase in respiratory rate on Study Day 1 ($n=1$) or Study Day 4 ($n=2$). All three TEAEs were considered mild in intensity.

8.4.8. Electrocardiograms (ECGs)

This section is not applicable.

8.4.9. QT

This section is not applicable.

8.4.10. Immunogenicity

Please see **Section 8.9.1** regarding Stevens-Johnson Syndrome described in Postmarketing.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Feeding Status

In Study GAI1002, the incidence of TEAEs was higher in the fasted state (5/16 [31.3%]) versus the fed state (1/16 [6.3%]) (**Table 24**). There was no TEAE reported in more than two subjects in either group.

In Study GAI3003, there was a higher incidence of TEAEs in the fasted state for both treatment arms of the double-blind phase of the study [mebendazole, fed 4/85 [4.7%], fasted 5/59 [8.5%]) versus placebo, fed 2/81 [2.5%], fasted 6/59 [10.2%]) (**Table 25**).

In the open-label phase of the study, the incidence of TEAEs was similar in the fed (3/138 [2.2%]) and fasted (4/140 [2.9%]) states (**Table 26**). None of the TEAEs were reported in more than 2 subjects in either the double-blind or open-label phase of the study in both the fed and fasted groups.

Reviewer Comment: *Despite findings described in the Clinical Pharmacology studies regarding increased systemic exposures of the mebendazole chewable tablet, observed in comparison to the non-chewable formulation in the fasted state (GAI1001) or with the concomitant ingestion of a high fat meal (fed state) (GAI1002), there was no correlation between feeding status and a particular TEAE. Furthermore, in the Phase 3 Study GAI3003, the incidence of TEAEs was higher in the fasted state; however, there was no correlation between feeding status and a particular TEAE. These findings are consistent with the published literature and suggest that the new mebendazole 500 mg chewable tablet can be administered without regard to feeding status.*

Published Clinical Pharmacology studies indicate that systemic bioavailability of a solid oral 500 mg dose of mebendazole is less than 10%. The majority of the dose of any mebendazole formulation remains in the gastrointestinal tract where it is active against STH.

Systemic mebendazole exposures were examined through a bioavailability study (GAI1001) and food effect study (GAI1002). Note that systemic mebendazole exposures for the previous 500 mg chewable formulation and the new 500 mg chewable formulation are similar. Administration of the previous chewable formulation under fasted conditions resulted in about a 2-fold increase in mean systemic mebendazole exposure compared to the non-chewable formulation. In addition, administration of the new mebendazole 500 mg chewable tablet to adults with a high fat meal resulted in about a 2.4 to 4 fold increase in mean systemic mebendazole exposures compared to fasted conditions. In Study GAI1002, the number of subjects (n=16) enrolled are too small to draw any meaningful safety conclusions. The distribution of TEAEs did not reveal a particular safety signal.

Please refer to the Clinical Pharmacology Review for additional details.

The literature reports increased mebendazole serum concentrations with meals. One published study examined serum mebendazole concentrations in patients treated with 1 gram mebendazole for hydatid disease. Serum mebendazole levels in 7 patients were higher when administered with a 'rich meal' in comparison to administration on an empty stomach; however these differences were not statistically significant.²⁵

The clinical relevance of higher mebendazole exposures associated with a high fat meal is not clear.

In the Phase 3 Study GAI3003, the incidence of TEAEs was higher in the fasted state for both the mebendazole and placebo treatment arms. However, it should be noted that the total number of TEAEs are small overall and it is difficult to make substantive conclusions (Double blind phase: mebendazole, n=9 [6.3%] and placebo n=8 [5.7%]; Open-label phase: n=7 [2.5%]). TEAEs occurring in both treatment arms of the fasted state in the double-blind phase included

‘abdominal distention’, ‘nasopharyngitis’ and ‘cough’. TEAEs occurring in both treatment arms of the fed state included ‘abdominal pain’.

There are many published studies where higher doses or longer durations of mebendazole are used. It is acknowledged that mebendazole formulations other than the proposed product were used in these studies, and systemic absorptions may be different. Systemic exposures to mebendazole and its metabolites at higher doses or longer durations (i.e. 40 mg/kg/day for 21 days, 2 grams 3 times a day) are similar to, or higher than, exposures observed with the new chewable mebendazole 500 mg tablet.^{25, 26} In addition, higher mebendazole serum concentrations with meals are noted when a higher than the proposed dose of mebendazole (i.e. 1.5 gram, 10 mg/kg) is used for the treatment of hydatid disease.^{27, 28} Furthermore, in a review of 121 patients, including children, receiving mebendazole treatment (30 to 100 mg/kg/day for 3 to 12 months) for hydatid disease, the most frequent side effects noted were elevated SGOT and SGPT (n=14) and abdominal pain (n=14).²⁹

Current labeling for the mebendazole 100 mg chewable tablet states that ‘the tablet may be chewed, swallowed, or crushed and mixed with food’.⁸ In addition, the label states that ‘No special procedures, such as fasting or purging, are required’.⁸

In the Applicant’s proposed labelling for the mebendazole 500 mg chewable tablets, the Applicant does not make any recommendations regarding the administration of the drug during fasting or fed conditions in Section 2, Dosage and Administration, of the label. In Section 12.3 Pharmacokinetics, the Applicant states that “Dosing with a high fat meal increases the bioavailability of mebendazole, but has limited impact on the amount of drug in the gastrointestinal tract.” This approach is reasonable.

8.5.2. Age

8.6.2.1 GAI 3002

The frequency of TEAEs was similar across all age groups in Study GAI3002 (<3 years [9/62, 14.5%], ≥3 to ≤ 6 years [26/271 [9.6%], and ≥7 to ≤ 10 years [9/63, 14.3%]) (**Table 27**).

TEAEs reported at greater than or equal to three percent in any age group included the following:

- o Less than 3 years: diarrhea 5/62 (8%), pyrexia 3/62 (5%)
- o Three to 6 years: pyrexia 7/271 (3%)
- o Seven to 10 years: lymphadenopathy 2/63 (3%)

8.6.2.2 GAI3003

Overall, the frequency of TEAEs was similar in both treatment arms across all age groups for Study GAI3003. Detailed adverse event listings by System Organ Class and Preferred Terms for the double-blind and open-label phase of the study can be found in **Table 28** and **Table 29** located in the **Appendices**.

Table 16 Frequency of Treatment Emergent Adverse Events by Age Group for Study GAI3003 (Overall) - Safety Population

Age Group (years)	MEBENDAZOLE (N=144)		PLACEBO (N=140)	
	n (%)	Total, N	n (%)	Total, N
	13 (9.0)	144	9 (6.4)	140
< 3	0 (0.0)	12	1 (8.3)	12
≥ 3 to < 7	3 (9.7)	31	0 (0.0)	24
≥ 7 to ≤ 16	10 (9.9)	101	8 (7.7)	104

During the double-blind phase of Study GAI3003, there were zero TEAEs noted in either treatment arm for the youngest age group, less than 3 years ($n=12$ for each treatment arm). Although TEAEs occurred in the 3 to 6 year and 7 to 16 year age groups for the mebendazole treatment arm in the double-blind phase of Study GAI3003, small numbers preclude the ability to make any meaningful conclusions in comparison to the placebo arm (**Table 28**). No TEAE was reported in more than 1 subject in any age group in the mebendazole treatment arm.

In the open-label phase of Study GAI3003, the incidence of TEAEs was similar across age groups (less than 3 years, 1/22 [4.5%]; 3 to 6 years, 2/55 [3.6%]; greater than 6 to 16 years, 4/201 [2.0%]) (**Table 29**). No TEAE was reported in more than 1 subject in any age group in the open-label phase.

Reviewer Comment: *There is no discernible pattern of TEAEs and age group for Studies GAI3002 and GAI3003, despite the higher PK exposures observed in the youngest age group. It should be noted that sample sizes are small for all age groups in Studies GAI3002 and GAI3003, especially the youngest age cohort, thus preventing definitive conclusions from being made. Published literature provides supportive safety evidence regarding the use of a single mebendazole 500 mg dose in children 12 months to less than 24 months of age.*

*In the PK substudy of Study GAI3003, approximately 4-fold higher mean C_{max} values and 3-fold higher mean AUC values were seen in the youngest children compared to older age groups and adults (**Table 2** and **Table 3**). This may be due to differences in mg/kg dose received by the younger subjects, as well as differences in absorption or metabolism relative to the older age*

groups. In the older pediatric subjects enrolled in Study GAI3003, mebendazole exposures were similar to adult subjects in Study GAI1002. Please refer to the Clinical Pharmacology review for additional details.

It should be noted that capillary fingerstick whole blood samples were obtained in the PK substudy of Study GAI3003. Although results suggest that there is a reasonable correlation of concentrations in capillary fingerstick whole blood and venous sampling methods, the fingerstick sampling technique tended to overestimate mebendazole plasma concentrations. The Applicant proposes that contamination during sample collection may have led to these results. However, this reviewer disagrees and interprets the results as reported.

One published study examined plasma levels of mebendazole over a 6 hour period post-dose in 24 children with hydatid disease (age range 18 months to 16 years).³⁰ Children received a 17 mg/kg dose of mebendazole with food (overall treatment 50 mg/kg daily in 3 divided doses for 9 months to 2 years). The mean (SD) mebendazole level 4 hours after dosing was 25.76 (9.81) ng/ml and was similar to adults in the study. In addition, the mean C_{max} values for the 3 to 7 and 7 to 16 year age groups in Study GAI3003 were similar to results of the published study. It should be noted that the C_{max} in the 1 to 3 year age group in Study GAI3003 was higher than the results from the published study. A different formulation of mebendazole was used for the published study and Study GAI3003.

Two additional studies show that systemic exposures to high-dose mebendazole and its metabolite are higher in the youngest age group of Study GAI3003 compared to adults (**Table 30**).^{25, 26}

The clinical relevance of the higher exposures noted in the youngest age groups is not clear. In GAI3003, the frequency of TEAEs was similar between treatment arms across all age groups. This observation is reassuring despite a potentially higher systemic mebendazole exposure in the youngest age group.

Supportive evidence of safety of mebendazole in the youngest age group can be gathered from published literature. For example, in a 1 year anti-helminthic drug study of children less than 24 months of age receiving mebendazole 500 mg chewable tablets (different than proposed formulation) (n=317) or placebo (n=336), no differences between the incidence of adverse effects in the 2 groups were observed 1 week following treatment.³¹ Although the study collected data on a limited number of adverse events, the most frequent adverse events recorded in both treatment arms were fever (mebendazole, 45/317 [12.1%], placebo 49/336 [14.5%]), cough (mebendazole, 32/317 [10.0%], placebo 37/336 [11.0%]) and diarrhea (mebendazole, 18/317 [5.7%], placebo 12/336 [3.6%]).³¹

In addition, there is a recently published report of a randomized, multi-arm, placebo controlled trial of single-dose mebendazole 500 mg tablet (crushed and mixed with fruit juice) administered at different times and frequencies in children 12 to 24 months. There was no difference in the frequency of serious or minor adverse events in the mebendazole treatment groups (n=1,686) and the placebo group (n=1,760).³²

Current labeling in the Pediatric Use Section of the mebendazole 100 mg chewable tablets states that “The drug has not been extensively studied in children under two years; [REDACTED] (b) (4)

The Applicant’s proposed labelling for the new mebendazole 500 mg chewable tablet, Section 8.4 Pediatric Use, states the following, “The safety and effectiveness of VERMOX™ Chewable 500 mg tablets have been established in children [REDACTED] (b) (4) years of age, [REDACTED] (b) (4)

The Applicant’s approach is reasonable.

*Please see **Section 8.7** for information regarding safety data identified through Internal Clinical Study Reports, which includes both pediatric and adult populations (age range, 0 to 70 years). Please see **Section 8.9.1** for additional information regarding Postmarketing concerns and Pediatric labeling.*

8.6.2.3 Postmarketing

The Applicant reports two cases of convulsions in infants exposed to mebendazole identified through postmarketing.^{33, 34} Although a causal relationship cannot be established, the timing between mebendazole intake and the convulsion is convincing.

A description of the two cases follows:

Case 1: A previously healthy 8-week-old Caucasian boy was prescribed mebendazole (50 mg b.i.d. for 3 days) for prevention of pinworm infection.³³ Twenty-four hours after starting mebendazole, the infant developed transient staring attacks and arching of the back. After 3 days’ medication, the patient developed generalized convulsions resulting in status epilepticus and respiratory arrest. The infant was ventilated in an intensive care unit, and received treatment with double-volume exchange transfusion. Convulsions continued on the second day and treatment with phenobarbitone and phenytoin was given. The subject was extubated, neurologically normal and discharged from the hospital within days on a phenobarbitone taper within days. The child was neurologically normal at the 6 month follow-up visit.

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Case 2: In the second case report,³⁴ a 4-week old boy was administered a total dose of 600-mg mebendazole over 3 days. Mebendazole was prescribed to the whole family for treatment of worm infections. Approximately 24 hours after the last mebendazole dose, the child developed a seizure. The next morning, the child was brought to the physician's office and was reported to be in status epilepticus. The child was transferred to a hospital and admitted for 2 days. The child recovered and was seizure-free at an unknown time of follow-up. An EEG was performed 2 weeks after the event and was normal.

Reviewer Comment: *The association of mebendazole exposure and convulsions in infants is a potential safety concern. In both reported postmarketing cases, convulsions developed soon after mebendazole treatment was given. Both infants likely experienced higher than expected systemic mebendazole exposures given their relatively smaller body mass and immature liver function. Although an exact mechanism is unknown, the higher mebendazole systemic exposures may have contributed to higher plasma concentrations, penetration into the central nervous system and subsequent neurotoxicity.*

The number of reported postmarketing cases in children less than 1 year of age exposed to mebendazole may be small and difficult to identify. WHO does not recommend single dose mebendazole 500 mg treatment for children less than 1 year of age. In addition, current labeling in the Pediatric Use Section for the mebendazole 100 mg tablet states that (b) (4)

The label for the mebendazole 100 mg tablet does not describe any contraindications or warnings for use in children less than one year of age.

In the Applicant's proposed label, the risk of convulsions with the new mebendazole 500 mg chewable tablet, especially in children below the age of 1 year, is noted in Section 5.1 Warnings. (b) (4)

On 22 August 2016, the Division sent an Information Request to the Applicant (b) (4)

*In their response dated 25 August 2016, the Applicant refers to the two aforementioned cases. In addition, the Applicant refers to the WHO guidelines recommending use of 500 mg mebendazole in children 1 year of age or older as part of large-scale treatment programs without diagnosis.*¹⁴ (b) (4)

.

For labeling, the Applicant's approach to include information about the risk of convulsions with mebendazole exposure in children less than one year of age in Section 5.1 Warnings is acceptable. There is limited data to support contraindicating (i.e. to never use) mebendazole in children less than one year of age.

8.6. Safety Analyses by Demographic Subgroups

8.6.1 Sex

8.6.1.1 GAI3002

In Study GAI3002, the frequency of TEAEs was similar in females (19/ 190 [10.0%]) and males (25/ 206 [12.1%]).

8.6.1.2 GAI3003

Overall, the frequency of TEAEs by sex was similar in both the mebendazole and placebo treatment arms [mebendazole, female 6/75 [8.0%], male 7/69 [10.1%]) versus placebo, female 5/72 [6.9%], male 4/68 [5.9%]]. Similarly, during the double-blind phase of Study GAI3003, the frequency of TEAEs by sex was similar in both the mebendazole and placebo treatment arms [mebendazole, female 5/75 [6.7%], male 4/69 [5.8%]) versus placebo, female 4/72 [5.6%], male 4/68 [5.9%]]. No TEAEs were reported in more than one subject in either female or male groups. Results were similar for the open label phase of the study (female, 3/146 [2.1%] versus male, 4/132 [3.0%]).

Reviewer Comment: *There is no discernible pattern of TEAEs and sex for Studies GAI3002 and GAI3003.*

8.6.2 Age

Please see **Section 8.5.2.**

8.7. Specific Safety Studies/Clinical Trials – Internal Clinical Studies

The Applicant completed an analysis of Adverse Drug Reactions from in-house confidential, unpublished clinical trial reports for subjects treated with any dose of mebendazole for intestinal helminth infections. Only studies with the following characteristics were included: 1.) an available English translation; 2.) conducted in study populations corresponding to the labeled indication or the labeled indication could not be determined; and 3.) study contained a sample size of at least 40 subjects or sample size could not be determined. The Applicant identified 67 reports of which 39 (including 6 double-blind placebo-controlled studies) contained sufficient information to assess adverse drug reactions in the currently marketed

mebendazole. A summary of these 39 unpublished clinical studies can be found in *Module 2.7.4, Summary of Clinical Safety, Table 7*.

Adverse events reported in these internal clinical studies are summarized in **Table 17**. Actual numbers of TEAEs in every unpublished study are not reported. Although exact numbers are difficult to determine from these internal studies, there were more than 4500 female and male subjects total exposed to mebendazole ranging in age from 0 to 70 years. Mebendazole dosing regimens ranged from 20 mg single dose to 400 mg for 14 days. No adverse events were reported in 27 of the 39 studies. In general, according to the Applicant, adverse events were reported in less than 5% of subjects, were typically mild or moderate in intensity, and resolved spontaneously.

One study reported moderately severe abdominal cramps in 47 of 98 subjects (48%).

In 5 of the 6 placebo controlled studies, no adverse events were reported. There was one placebo controlled trial comparing various dosages of mebendazole ($n=68$) with levamisole ($n=24$), pyrantel pamoate ($n=23$), thiabendazole ($n=22$), piperazine citrate ($n=21$) and placebo ($n=20$). In this trial, anorexia, nausea, vomiting, abdominal cramps, headache, and diarrhea were reported by subjects in the mebendazole treatment groups.

Table 17 Number of internal clinical studies reporting an adverse event

Adverse Event	Number of studies reporting adverse event* ($n=39$)
Vomiting	8
Diarrhea	5
Abdominal pain	4
Nausea	4
Abdominal cramps	3
Anorexia	2
Flatulence	2
Headache	2
Rash	2
Abdominal discomfort	1
Dizziness	1
Erratic migration	1
Feeling cold	1
Fever	1
Pains in the cardiac region	1

**Note that no adverse events were reported in 12 of the 39 internal studies.*

Reviewer Comment: Based on summary safety results of the Applicant's 39 internal clinical study reports (**Table 17**), this reviewer suggests that the following adverse reactions be incorporated into Section 6.1, Adverse Reactions in Clinical Studies, of the Applicant's proposed label: 'vomiting', 'diarrhea', 'nausea', 'abdominal pain', 'rash' and 'anorexia'.

In Section 6.1, Adverse Reactions in Clinical Studies, of the proposed label, the Applicant lists 4 adverse reactions reported by less than 1% of mebendazole-treated subjects in their 39 internal studies. These adverse reactions include 'abdominal discomfort', 'diarrhea', 'flatulence', and 'rash'. The Applicant does not include all adverse reactions which were reported in several clinical studies, including 'vomiting', 'diarrhea', 'nausea', 'abdominal pain', and 'anorexia'. Furthermore, the Applicant does not provide sufficient data to support the incidence of TEAEs as less than 1% in their Summary of Clinical Safety. Hence, this reviewer recommends removal of the adverse reaction incidence in Section 6.1 of the label.

In addition, the Applicant proposes a statement that the safety profile of the mebendazole chewable 500 mg tablet is consistent with the safety profile reported in the internal clinical studies. This approach is acceptable if the Applicant incorporates labeling changes as proposed by this reviewer.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Previous genotoxicity studies indicate that mebendazole is not mutagenic or clastogenic. Mebendazole is aneugenic *in vitro* in mammalian somatic cells at a threshold concentration of 115 ng/mL. In the youngest age group (< 3 years) and fed adults, the Applicant notes that the aneugenic threshold is transiently exceeded. Lifetime studies in mice and rats showed an absence of carcinogenicity with mebendazole exposure.

Reviewer Comment: The safety risk with single-dose administration is considered low with regards to carcinogenicity or tumor development. This is further supported by post-marketing data with repeated doses and prolonged treatment durations, where an increased risk for carcinogenicity was not observed.

8.8.2. Human Reproduction and Pregnancy

Mebendazole has embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg (approximately 0.2 fold the MRHD, based on mg/m²).⁸ Doses up to 40 mg/kg in rats (0.8 fold MRHD, based on mg/m²), given to males for 60 days and to females for 14 days prior to gestation, were associated with maternal toxicity, but no effects on fetuses and offspring were observed. Several large clinical studies suggest that there is no impact on pregnancy outcome and short term mebendazole exposure.³⁵⁻⁴⁰

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In the Applicant's Periodic Benefit Risk Evaluation Report/ Periodic Safety Report (NDA 208398 SD7) covering 04 May 2015 through 03 May 2016 for mebendazole and mebendazole/quinfamide, 7 cases reported drug exposure during pregnancy. Of these seven cases, pregnancy outcomes were live birth ($n=1$) and not reported ($n=4$). One case concerned a 36-year old female with a history of alcohol consumption who experienced a spontaneous abortion. The remaining case reported a 27 year old female who experienced malaise when treated with mebendazole for a helminthic infection during the eleventh week of her pregnancy.³⁶

The Applicant provides a review of several studies published in the literature. The Applicant concludes that mebendazole use for treatment of STH infections in pregnant women after their first trimester is safe and does not result in increased miscarriages, malformations, stillbirths, early neonatal deaths and premature babies.^{35, 37, 38}

Reviewer Comment: *The published literature, including prospective pregnancy registries, case-control retrospective cohorts and randomized-controlled studies, have reported no association with mebendazole use and a potential risk of major birth defects or miscarriage (Table 31).*

Furthermore, the WHO Recommendations on Preventive Chemotherapy in Human Helminthiasis⁴¹ state the following: Several studies have failed to find a statistically significant difference in the occurrence of congenital abnormalities between babies born to women treated with single dose mebendazole or albendazole during pregnancy and those born to untreated women. Similarly, no significant difference has been found in the occurrence of adverse birth outcomes (abortion, stillbirth, birth defects) between women inadvertently exposed to praziquantel, ivermectin, or the combination of ivermectin and albendazole (during large-scale chemotherapy interventions), and women not exposed to the drugs. These studies include approximately 6000 documented exposures to mebendazole, but the number of documented exposures to the other anthelmintic drugs is much lower (approximately 50–200).

Regarding treatment of adolescent girls, women of reproductive age and pregnant women, the WHO⁴¹ states the following: In areas where schistosomiasis and soil-transmitted helminthiasis are endemic, risk–benefit analyses have revealed that the health advantages of treating women of reproductive age and pregnant women far outweigh the risks to their health and to the health of their babies. The benefits of treating pregnant women include reduced maternal anemia and improved infant birth weight and survival. The proven benefits of antenatal deworming in the absence of any evidence indicative of drug teratogenicity or embryotoxicity in humans provides compelling evidence to support the treatment with albendazole or mebendazole of women for STH after the first trimester of pregnancy.

The WHO⁴¹ goes on to recommend the following: For soil-transmitted helminthiasis, this

manual recommends that albendazole or mebendazole be offered to pregnant women in the 2nd and 3rd trimesters of pregnancy and to lactating women in preventive chemotherapy interventions targeting areas where the prevalence of any soil-transmitted helminth infection (ascariasis, trichuriasis and hookworm infection) exceeds 20%.

Based on evidence from published literature, as well as WHO recommendations, the new mebendazole 500 mg chewable tablet should be safe to use in pregnant women beyond the first trimester.

The Division of Pediatrics and Maternal Health was consulted for input regarding labeling for Sections 8.1 Pregnancy and 8.2 Lactation to be consistent with the Agency's Pregnancy, Labeling and Lactation Rule (PLLR). Specifically, Dr. Tamara Johnson provided input regarding labeling and the Division incorporated her suggestions into the revised label to be sent to the Applicant.

8.8.3. Pediatrics and Assessment of Effects on Growth

Both Studies GAI3002 and GAI3003 were conducted exclusively in children.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are several published studies where mebendazole has been administered at higher doses and longer durations than that proposed by the Applicant. In a study of mebendazole treatment for hydatid disease, 118 of the 121 patients (males and females, 1 to 60 years old) received a mebendazole dose of 50 mg/kg/day.²⁹ The most frequent adverse events were elevated transaminases (14/121 [11.6%]) and abdominal pain (14/121 [11.6%]). Eight patients stopped treatment due to adverse events. Another literature review examining treatment for hydatid disease notes allergic reactions, prolonged fevers, alopecia and reversible neutropenia can be associated with high dose mebendazole treatment at longer durations.⁴² Additional adverse events to note include agranulocytosis and glomerulonephritis.⁴³⁻⁴⁵

Drug abuse potential, withdrawal and rebound are not issues with the proposed single-dose regimen.

Reviewer Comment: *The Applicant's overall approach to labeling in Section 10, Overdose is acceptable. However, minor changes are suggested.*

(b) (4)

In the proposed label for the new mebendazole 500 mg chewable tablet, the Applicant describes the following adverse events in Section 10, Overdosage: ‘alopecia’, (b) (4) ‘hepatitis’, ‘agranulocytosis’, ‘neutropenia’, and ‘glomerulonephritis’. This is approach is acceptable. ‘Reversible liver function disturbances’ could be changed to ‘Transaminase elevation’ or ‘Abnormal liver function tests’. The Applicant can consider including ‘glomerulonephritis’ in Section 6.2 Postmarketing Adverse Events Section of the label as well.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant submitted a Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report (PBRER/PSUR) (NDA 208398 SD7) covering 04 May 2015 through 03 May 2016 for mebendazole and mebendazole/ quinfaide. Interval exposure to mebendazole and mebendazole/quinfaide from 01 May 2015 to 30 April 2016 was approximately 35 million treatment courses (**Table 32**). Approximately 4 million treatment courses were dispensed as a 500 mg chewable tablet (different than proposed) and 5 million treatment courses were dispenses as an oral solution, suspension or syrup. Cumulative exposure to mebendazole and mebendazole/ quinfaide from 1988 to 30 April 2016 was approximately 845 million treatment courses for all formulations (**Table 33**). (b) (4)

During the 04 May 2015 through 03 May 2016 reporting period, 47 spontaneous cases (46 initial, 1 follow-up) were identified involving pediatric patients whose age was between 2 and 18 years. One ‘case’ was a literature case of a study with 50 children receiving 300 mg ‘simple dose’ mebendazole. Adverse events of nausea and vomiting (12% and 2%, respectively), were reported. Of the remaining 46 cases, the most frequent MEDRA PT reported included abdominal pain ($n=7$), diarrhea ($n=6$) and drug ineffective ($n=6$). Nausea was reported in 4 cases and vomiting was reported in 4 cases. There were no cases reporting use in children < 2 years during the reporting period.

Important identified risks, important potential risks and missing information were evaluated by the Applicant (**Table 18**). No new safety information was identified during the most recent PBRER/PSUR reporting period.

Table 18 Important Identified Risks, Important Potential Risks, and Missing Information

Important Identified Risks	Convulsions in children
	Hypersensitivity
	Haematologic abnormalities including neutropenia
	Stevens-Johnson syndrome (in co-administration with metronidazole)
	Liver function disturbances including hepatitis
Important Potential Risks	Drug interactions with metronidazole and cimetidine
	Chocking with solid formulations
Missing Information	Use in children < 2 years
	Use in elderly (>65 years)
	Pregnancy and lactation
	Use in patients with renal dysfunction
	Use in patients with hepatic dysfunction

Source: NDA 208398 SD7, Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report, Table 3.

Reviewer Comment: With the exception of ‘agranulocytosis’ and ‘glomerulonephritis’, the Applicant adequately addresses important identified risks, important potential risks, and missing information in the proposed label for the new mebendazole 500 mg chewable tablet. The Applicant should also consider adding ‘agranulocytosis’ and ‘glomerulonephritis’ to Section 6.2, Postmarketing, of the label. In addition, ‘abdominal pain’ and ‘diarrhea’ should be included in Section 6.1 Clinical Studies and deleted from Section 6.2 Postmarketing to avoid redundancy.

‘Convulsions’, ‘Hypersensitivity including anaphylactic reaction and anaphylactoid reaction’, ‘Exanthema’, ‘Angioedema’, ‘Urticaria’, ‘Toxic epidermal necrolysis’, ‘Stevens-Johnson Syndrome’, ‘Hepatitis’, ‘Abnormal liver function tests’, ‘Neutropenia’ are listed in Section 6.2 of the Postmarketing Adverse Reactions section of the Applicant’s proposed label. The Warning and Precautions Section of the proposed also label also includes the risk of convulsions in children less than 1 year of age, as well as the risk of concomitant mebendazole use and serious skin reactions.

This reviewer suggests inclusion of ‘agranulocytosis’ in Section 6.2 Postmarketing Adverse Reactions Section of the label. The Warnings Section of the current label for the mebendazole 100 mg chewable tablet includes ‘agranulocytosis’ and ‘neutropenia’ associated with higher doses and longer duration of treatment.⁸ However, it should be noted that ‘agranulocytosis’ and ‘neutropenia’ are not included in the Warnings and Precautions Section of the Applicant’s proposed label for the new mebendazole 500 mg chewable tablet. Furthermore, in the proposed label for the new mebendazole 500 mg chewable tablet, Section 6.2 Postmarketing Adverse Reactions, includes ‘neutropenia’ but not ‘agranulocytosis’. Both adverse events are well-described in the literature.^{42, 43, 45-49}

This reviewer suggests inclusion of ‘glomerulonephritis’ in Section 6.2 Postmarketing Adverse Reactions Section of the label. In the currently proposed label, the Applicant includes ‘glomerulonephritis in Section 10, Overdose, of the label. ‘Glomerulonephritis’ is not included in the current label for the mebendazole 100 mg chewable tablet. ‘Glomerulonephritis’ has been reported in the literature and in post-marketing reports and could be included in Section 6.1 of the label.⁴⁴ Mesangiocapillary glomerulonephritis has been described on pathology of patients who had received mebendazole treatment for hydatid disease.⁴⁴

*(b) (4)
this reviewer recommends that these adverse events should be included in Section 6.1 Clinical Studies and would not be repeated in Section 6.2 Postmarketing.*

Choking is not included in the proposed label. This is acceptable. The intent of the new mebendazole 500 mg chewable formulation is to minimize choking by its rapidly disintegrating characteristics. There were no TEAEs of choking reported in GAI3002 and GAI3003. Cough was reported in 5 subjects (1%) in GAI 3002, and equally in both arms of GAI3003 [mebendazole, n=1 (0.7%); placebo, n=2 (1.4%)].

*The Applicant’s proposed label states that there is no data for pediatric patients under 1 year of age in Section 8.4 Pediatric Use Section of the label. This is acceptable and supported by the Applicant’s clinical trials. Please see **Section 8.5.2** for additional information regarding mebendazole exposure in children less than 1 year of age and labeling for Section 4 Contraindications and Section 5.1 Warnings.*

In addition, the Applicant’s proposed label states that there insufficient data in subjects aged 65 years and over in Section 8.5 Geriatric Use Section of the label. This is acceptable. Furthermore, the target population for mass drug administration programs for STH treatment is children.

The Applicant does not comment on patients with renal dysfunction in the proposed label. In Section 12.3 Pharmacokinetics, the Applicant’s proposed label addresses the fact that higher plasma levels of mebendazole levels may result in patients with impaired hepatic function, impaired metabolism, or impaired biliary elimination.

8.10. Expectations on Safety in the Postmarket Setting

This section is not applicable.

8.11. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines. Please refer to discipline-specific reviews for additional details.

8.12. Integrated Assessment of Safety

The new mebendazole 500 mg chewable tablet is safe for the treatment of single- and mixed-species soil transmitted helminth infections caused by roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) (b) (4) in populations greater than 1 year of age.

Safety results from 712 subjects enrolled in four Applicant-conducted clinical studies (GAI1001, GAI1002, GAI3002, and GAI3003), showed that subjects exposed to the mebendazole 500mg chewable tablet had few non-serious TEAEs which were consistent with what has been reported through the Applicant's internal study reports and more than 40 years of post-marketing surveillance. In addition, there was no discernible relationship of TEAEs and feeding status, age or sex in the clinical studies. Furthermore, there was no association of TEAEs in circumstances where higher mebendazole systemic exposures have been described, such as high fat meals and administration to children less than 3 years old. In addition, the safety profile of the new mebendazole 500 mg chewable tablet is consistent with postmarketing surveillance reports where different formulations, doses and duration of treatments have been used for over 845 million estimated treatment courses since 1988.

9 Advisory Committee Meeting and Other External Consultations

The Division of Pediatrics and Maternal Health was consulted regarding the Pregnancy Labeling and Lactation Rule (PLLR) and proposed labeling for Sections 8.1 and 8.2. Please see Section 8.8.2 of this review for details.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling recommendations by the Clinical reviewer are summarized in Table 19.

Table 19 Summary of Labeling Recommendations

Section of Label	Applicant	Recommendation	Rationale
4 Contraindications	(b) (4)	(b) (4)	See Section 8.5.2.

		(b) (4)	
6.1 Adverse Reactions from Clinical Studies	Reports adverse reactions from 39 internal clinical studies: 'abdominal (b) (4) 'diarrhea', 'flatulence', and 'rash'	Report the following: 'vomiting', 'diarrhea', 'nausea', 'abdominal pain', 'rash' and 'anorexia' Remove (b) (4) rom Section 6.2 Postmarketing.	See Section 8.7.
6.1 Adverse Reactions from Clinical Studies	(b) (4)	(b) (4)	See Section 8.7.
6.2 Adverse Reactions from Postmarketing	Lists the following adverse reactions: 'Convulsions', 'Hypersensitivity including anaphylactic reaction and anaphylactoid reaction', 'Exanthema', 'Angioedema', 'Urticaria', 'Toxic epidermal necrolysis', 'Stevens-Johnson Syndrome', 'Hepatitis', 'Abnormal liver (b) (4) tests', 'Neutropenia'	The following should be added: 'Agranulocytosis' and 'Glomerulonephritis'	See Section 8.9.
8.1 Pregnancy	Risk summary, clinical considerations, human data, and animal data described.	Changes incorporated per DPMH consult to reflect PLLR.	See Section 8.8.2.
8.2 Lactation	Risk summary described.	Changes incorporated per DPMH consult to reflect PLLR.	See Section 8.8.2.
10 Overdosage	Lists the following adverse reactions: 'alopecia', 'reversible (b) (4)	(b) (4) could be changed to	See Section 8.8.4.

	(b) (4) 'hepatitis', 'agranulocytosis', 'neutropenia', and 'glomerulonephritis'.	'Transaminase elevation' or 'Abnormal liver (b) (4) tests'.	
14.1 Clinical Studies	Describes clinical trial data for <i>Trichuris trichiura</i> (whipworm) and/or <i>Ascaris lumbricoides</i> (large roundworm)	Suggest additional section for mixed species infection.	See Section 7.2.3.
14.1 Infestations with <i>Trichuris trichiura</i> (whipworm) and/or <i>Ascaris lumbricoides</i> (large roundworm) in Pediatric Patients	Arithmetic means for egg count reduction rates are used.	Displaying data using geometric means.	See Section 6.2.2.
General	Use of the term (b) (4) to denote STH infections.	Suggest using 'infection' to denote STH infections	(b) (4)

			(b) (4)
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10.2. Patient Labeling

A separate patient instruction sheet is not required.

Section 17 Patient Counseling Information, includes the following: 1. Recommends that the tablet be chewed before swallowing; 2. Provides instructions on adding water to turn the chewable tablet into semi-solid mass if the patient cannot chew; 3. Advises the patient to not swallow the tablet whole; 4. Explains that the drug may be taken with or without food; and 5. Cautions against the concomitant use of metronidazole.

10.3. Nonprescription Labeling

This section is not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required. Given the known safety profile of the various mebendazole formulations, the risks for the new mebendazole 500 mg chewable tablet can be managed through labeling.

12 Postmarketing Requirements and Commitments

No post-marketing requirements or commitments are recommended.

13 Appendices

13.1. References

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13.2. Financial Disclosure

The Applicant adequately disclosed financial arrangements with clinical investigators.

Covered Clinical Study (Name and/or Number): MEBENDAZOLGAI3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>3 Principal Investigators, 9 Sub-Investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>Not applicable</u> Significant payments of other sorts: <u>Not applicable</u> Proprietary interest in the product tested held by investigator: <u>Not applicable</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>Not applicable</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) Not applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) Not applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>The Applicant's Senior Financial Director, Ryan Koors, submits a Form 3454 for all 3 Primary Investigators and 9 Sub-Investigators.</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Current Treatment Options for Soil Transmitted Helminth Infections

Table 20 Current Treatment Options for Soil Transmitted Helminth Infections

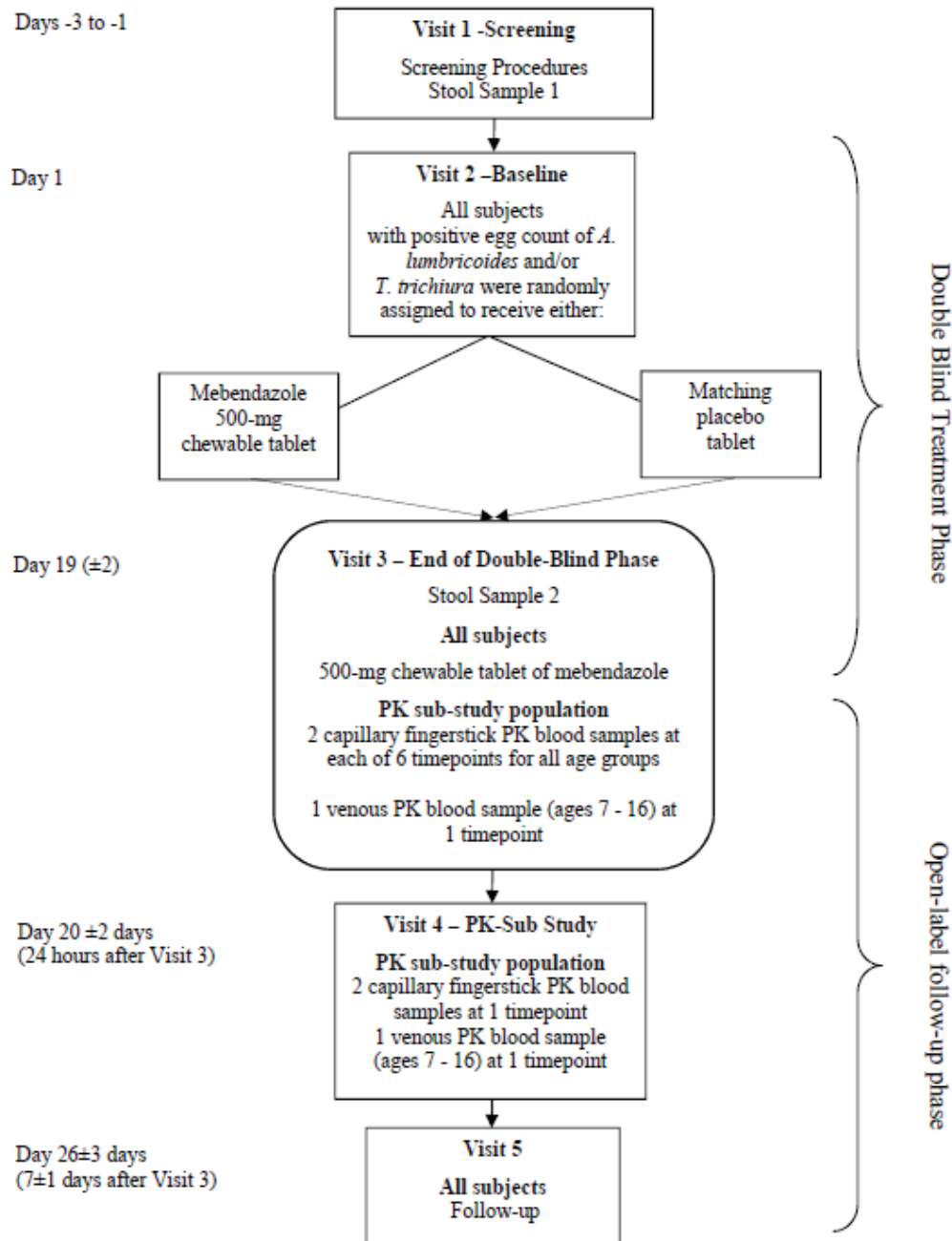
Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatment						
Mebendazole – tablet, chewable 100 mg	Treatment of Enterobius vermicularis (pinworm), Trichuris trichiura (whipworm), Ascaris lumbricoides (common roundworm), Ancylostoma duodenale (common hookworm), Necator americanus (American hookworm) in single or mixed infections	1974	1 tablet morning and evening for 3 consecutive days. If the patient is not cured three weeks after treatment, a second course of treatment is advised.	Not on current label.	<i>Occasional:</i> Diarrhea, abdominal pain <i>Rare:</i> Leukopenia, agranulocytosis, hypospermia	Multi-dose regimen not practical for mass drug administration in STH public health programs.
Other Treatments⁷						
Mebendazole – 500 mg	STH infections as described for mebendazole 100 mg.	Not approved in the U.S. Solid oral tablet approved 1971 in Belgium	Ascaris, Hookworm: 500 mg orally once or 100 mg orally twice daily x 3 days Trichuris: 100 mg orally twice daily x 3 days	Single-dose mebendazole less efficacious for hookworm than single-dose albendazole. ⁶	<i>Occasional:</i> Diarrhea, abdominal pain <i>Rare:</i> Leukopenia, agranulocytosis, hypospermia	Single-dose regimen preferred for mass drug administration in STH public health programs. ⁹
Albendazole	FDA-Approved for neurocysticercosis and hydatid disease.	Not approved for STH	Ascaris, Hookworm: 400 mg orally once Trichuris: 400 mg orally x 3 days	Single-dose albendazole more efficacious for hookworm than single-dose mebendazole or pyrantel pamoate. ⁶	<i>Frequent:</i> abdominal pain, increased transaminases <i>Occasional:</i> reversible alopecia, leukopenia <i>Rare:</i> Rash, hepatic toxicity,	Same as mebendazole 500 mg.

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					renal toxicity	
Levamisole	FDA-Approved for veterinary treatment of adult nematode infections in cattle and sheep.	Not approved for STH	Single dose, weight-based dosing	Single-dose levamisole less efficacious for hookworm than single-dose albendazole. ⁶	Not evaluated in randomized placebo controlled trial at recommended doses. ⁶	None.
Pyrantel pamoate	FDA-Approved for over-the-counter use for Enterobius vermicularis (pinworm) treatment.	Not approved for other STH	Hookworm: 11 mg/kg base (max 1 g) po daily x 3 days	Single-dose pyrantel pamoate less efficacious for hookworm than single-dose albendazole. ⁶	<i>Occasional:</i> GI disturbance, headache, dizziness, rash, fever	None.
Ivermectin	FDA approved for Strongyloidiasis, onchocerciasis	Not approved for STH	(b) (4) Trichuris: 200 mcg/kg/d orally x 3 days	Not efficacious against hookworm.	<i>Occasional:</i> Cutaneous, systemic or ophthalmologic reactions when used as microfilaricidal treatment. <i>Rare:</i> Hypotension	Not used for WHO STH control programs.

13.4. Overall Study Design for GAI3003

Figure 1 Overall Study Design for GAI3003.



Note: Figure revised from the MEBENDAZOLGAI3003 Study Report.¹⁴

Source: NDA 208398, Module 2.7.3, Summary of Clinical Efficacy, Figure 1.

13.5. Time and Events Schedule for GAI3003

Table 21 Time and Events Schedule for GAI3003

Phase	Screening	Treatment			Posttreatment	Early Withdrawal ^a
Period	Screening	Baseline	Double-Blind	PK Visit	Follow-up	
Visit	1 ^b	2 ^c	3 ^{c,d}	4 (PK subject subset only)	5 (All subjects)	
Day	-3 to -1	1	19 ^e	20 ^f	26 ^g	
Screening/Administrative						
Informed consent	X					
Informed assent ^a	X					
Inclusion/exclusion criteria	X					
Medical history	X					
Urine pregnancy test ⁱ	X		X			
Hemoglobin ^j	X					
Study Drug						
Randomization		X				
Drug Administration		X ^k	X ^l			
Study Drug Accountability		X	X			
Stool sample collection for egg count analysis	X ^m		X ^a			X ^o
Safety						
Physical examination	X		X		X	X
Height	X					
Weight	X		X		X	X
BMI	X		X		X	X
Vital signs ^p	X	X	X	X	X	X
Blood samples for PK analysis			X ^{q,r}	X ^s		
Adverse event monitoring ^t	X	X	X	X	X	X
Concomitant therapy ^u	X	X	X	X	X	X

- a Every effort will be made to perform final assessments for all subjects who withdraw from the study at any time before Visit 3.
b Only subjects with a positive egg count for any STH will be enrolled in the study.
c Subjects will be observed 3 hours posttreatment for safety evaluations.
d Subjects who come for Visit 3 and have their stool sample collected will be considered as “completers” for the study efficacy analysis.
e Day listed is an approximation. Actual day is Day 19±2 days.
f Day listed is an approximation. Actual day occurs 1 day after Visit 3.
g Day listed is an approximation. Actual day occurs 7±1 days after Visit 3.

Source: NDA 208398, Clinical Protocol Amendment INT-4 MEBENDAZOLGAI3003, Time and Events Schedule.

13.6. Demographic Characteristics of Subjects in Studies GAI3002 and GAI3003

Table 22 Demographic Characteristics of Subjects in Studies GAI3002 and GAI3003 – Safety Population.

		GAI3002		GAI3003					
Demographic Baseline Characteristics		Mebendazole		Mebendazole		Placebo		Overall	
		N=396		N=144		N=140		N=284	
Age	Mean (SE)	4.6 (1.9)		8.0 (3.3)		7.8 (3.0)		7.9 (3.2)	
	Min	2		1		1		1	
	Median	4		8		8		8	
	Max	10		15		15		15	
		Count	%	Count	%	Count	%	Count	%
Age Group	Under 3 years	62	15.7	12	8.3	12	8.6	24	8.5
	Between 3 and less than 7 years	271	68.4	31	21.5	24	17.1	55	19.4
	Between 7 and 17 years	63	15.9	101	70.1	104	74.3	205	72.2
Sex	F	190	48.0	75	52.1	72	51.4	147	51.8
	M	206	52.0	69	47.9	68	48.6	137	48.2
Race	Black Or African American	391	98.7	144	100.0	140	100.0	284	100.0
	Unknown	1	0.3	0	0	0	0	0	0
	White	4	1.0	0	0	0	0	0	0

13.7. Disposition of Subjects in Studies GAI3002 and GAI3003

Table 23 Disposition of Subjects in Studies GAI3002 and GAI3003 (Double-Blind Phase) – All Subjects.

		GAI3002		GAI3003			
Category of Disposition Event	Disposition Event	Mebendazole		Mebendazole		Placebo	
		Subject Count	%	Subject Count	%	Subject Count	%
Protocol Milestone	Informed Consent Obtained	396	100	149	100.0	146	100.0
	Randomized	-	-	149	100.0	146	100.0
Disposition Event	Completed	390	98.5	141	94.6	137	93.8
	Withdrawal By Subject	0	0	7	4.7	5	3.4
	Lost To Follow-Up	0	0	0	0.0	3	2.1
	Physician Decision	0	0	0	0.0	1	0.7
	Protocol Violation	-	-	1	0.7	0	0.0
	Non-Compliance With Study Drug	6	1.5	-	-	-	-
Other Event	Subject Assent Obtained	-	-	121	81.2	122	83.6

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13.8. Treatment Emergent Adverse Events by System Organ Class and Dictionary-derived Terms for Study GAI1002 - Safety Population

Table 24 Treatment Emergent Adverse Events by System Organ Class and Dictionary-derived Terms for Study GAI1002 - Safety Population

	MEBENDAZOLE 500 mg		Total ^a
	Fasted	Fed	
	(N=16)	(N=16)	(N=16)
All safety subjects	16	16	16
Total no. subjects with any TEAE (%)	5 (31.3)	1 (6.3)	5 (31.3)
Gastrointestinal Disorders	4 (25.0)	1 (6.3)	5 (31.3)
Toothache	2 (12.5)	1 (6.3)	3 (18.8)
Diarrhoea	1 (6.3)	1 (6.3)	2 (12.5)
Abdominal Pain	0	1 (6.3)	1 (6.3)
Nausea	1 (6.3)	0	1 (6.3)
Injury, Poisoning And Procedural Complications	1 (6.3)	0	1 (6.3)
Contusion	1 (6.3)	0	1 (6.3)
Respiratory, Thoracic And Mediastinal Disorders	1 (6.3)	0	1 (6.3)
Rhinorrhoea	1 (6.3)	0	1 (6.3)

Reported dictionary version: MedDRA 16.1.

^aIncidence is based on number of subjects, not the number of events.

Note: Percentages calculated with the number of subjects in each group as denominator.

Treatment A: Mebendazole 500 mg fast-disintegrating chewable tablet - Fasted

Treatment B: Mebendazole 500 mg fast-disintegrating chewable tablet - Fed

[TSFAE01.rtf] [JNJ-108329\GAI1002\DBR_FINAL\RE_CSR\PROD\tsfae01.sas] 04MAY2014, 02:50

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 3.

13.9. Treatment Emergent Adverse Events by Food State for Study GAI3003 Double Blind Phase - Safety Population

Table 25 Treatment Emergent Adverse Events by Food State for Study GAI1003 Double Blind Phase - Safety Population.

	Total 140	Placebo (N=140) Food State <a>		Total 144	Mebendazole 500 mg (N=144) Food State <a>	
		Fed 81	Fasted 59		Fed 85	Fasted 59
Number of subjects						
Total no. subjects with any TEAE	8 (5.7%)	2 (2.5%)	6 (10.2%)	9 (6.3%)	4 (4.7%)	5 (8.5%)
Body System or Organ Class						
Preferred term						
Gastrointestinal disorders	2 (1.4%)	1 (1.2%)	1 (1.7%)	3 (2.1%)	1 (1.2%)	2 (3.4%)
Abdominal distension	1 (0.7%)	0	1 (1.7%)	2 (1.4%)	0	2 (3.4%)
Abdominal pain	1 (0.7%)	1 (1.2%)	0	1 (0.7%)	1 (1.2%)	0
Infections and infestations	4 (2.9%)	1 (1.2%)	3 (5.1%)	3 (2.1%)	2 (2.4%)	1 (1.7%)
Gastroenteritis	0	0	0	1 (0.7%)	1 (1.2%)	0
Nasopharyngitis	2 (1.4%)	0	2 (3.4%)	1 (0.7%)	0	1 (1.7%)
Tinea infection	0	0	0	1 (0.7%)	1 (1.2%)	0
Conjunctivitis	1 (0.7%)	0	1 (1.7%)	0	0	0
Conjunctivitis bacterial	1 (0.7%)	0	1 (1.7%)	0	0	0
Tonsillitis	1 (0.7%)	1 (1.2%)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (0.7%)	0	1 (1.7%)
Vitamin A deficiency	0	0	0	1 (0.7%)	0	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	2 (1.4%)	1 (1.2%)	1 (1.7%)	1 (0.7%)	0	1 (1.7%)
Cough	2 (1.4%)	1 (1.2%)	1 (1.7%)	1 (0.7%)	0	1 (1.7%)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.7%)	1 (1.2%)	0
Rash pruritic	0	0	0	1 (0.7%)	1 (1.2%)	0
Eye disorders	1 (0.7%)	0	1 (1.7%)	0	0	0
Night blindness	1 (0.7%)	0	1 (1.7%)	0	0	0

KEY: MedDRA=Medical Dictionary of Regulatory Activities; TEAE=treatment-emergent adverse event

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Food State <a>: Fed state is defined as eating anything within 2 hours of the drug administration (from 2 hours before to 2 hours after). Fasted state is defined as eating nothing within 2 hours of the drug administration

Dictionary version MedDRA 18.0

Food state is based on Day 1 information.

[TSFAE07A.RTF] [JNJ-108329\GAI3003\DBR_FINAL\RE_CSR\PROD\TSFAE07A.SAS] 18MAR2016, 17:04

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 13.

13.10. Treatment Emergent Adverse Events by Food State for Study GAI3003 Open Label Phase - Safety Population

Table 26 Treatment Emergent Adverse Events by Food State for Study GAI1003 Open Label Phase - Safety Population.

	All OL Mebendazole 500 mg (N=278)		
	Food State <a>		
	Total	Fed	Fasted
Number of subjects	278	138	140
Total no. subjects with any TEAE	7 (2.5%)	3 (2.2%)	4 (2.9%)
Body system or organ class			
Preferred term			
Gastrointestinal disorders	3 (1.1%)	1 (0.7%)	2 (1.4%)
Abdominal pain	1 (0.4%)	0	1 (0.7%)
Diarrhoea	2 (0.7%)	1 (0.7%)	1 (0.7%)
Vomiting	1 (0.4%)	0	1 (0.7%)
Nervous system disorders	1 (0.4%)	0	1 (0.7%)
Headache	1 (0.4%)	0	1 (0.7%)
Skin and subcutaneous tissue disorders	1 (0.4%)	0	1 (0.7%)
Pruritus	1 (0.4%)	0	1 (0.7%)
Infections and infestations	1 (0.4%)	1 (0.7%)	0
Malaria	1 (0.4%)	1 (0.7%)	0
Pneumonia	1 (0.4%)	1 (0.7%)	0
Injury, poisoning and procedural complications	1 (0.4%)	1 (0.7%)	0
Soft tissue injury	1 (0.4%)	1 (0.7%)	0

KEY: MedDRA=Medical Dictionary of Regulatory Activities; TEAE=treatment-emergent adverse event

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Note: Follow-up phase includes data collected on or after the 2nd drug administration at visit 3.

Food State <a>: Fed state is defined as eating anything within 2 hours of the drug administration (from 2 hours before to 2 hours after). Fasted state is defined as eating nothing within 2 hours of the drug administration

Dictionary version MedDRA 18.0

Food state is based on day 19 information.

[TSFAE07B.RTF] [JNJ-108329\GAI3003\DBR_FINAL\RE_CSR\PROD\TSFAE07B.SAS] 18MAR2016, 17:04

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 13.

13.11. Treatment Emergent Adverse Events by Age for Study GAI3002 - Safety Population

Table 27 Treatment Emergent Adverse Events Occurring at Greater Than or Equal to 1% by System Organ Class and Dictionary Derived Term by Age Group for GAI3002 - Safety Population.

	< 3 years (n=62) n (%)	3 to 6 years (n=271) n (%)	7 to 10 years (n=63) n (%)	Total (n=396) n (%)
Total number of subjects with adverse events	9 (14.5)	26 (9.6)	9 (14.3)	44 (11.1)
<i>Gastrointestinal disorders</i>	6 (9.7)	8 (3.0)	0	14
Abdominal distention	1 (1.6)	0	0	1 (0.3)
Diarrhea	5 (8.1)	5 (1.9)	0	10 (2.5)
Nausea	1 (1.6)	0	0	1 (0.3)
<i>General disorders and administration site conditions</i>	3 (4.8)	7 (2.6)	1 (1.6)	11 (2.8)
Pyrexia	3 (4.8)	7 (2.6)	1 (1.6)	11 (2.8)
<i>Respiratory, thoracic and mediastinal disorders</i>	1 (1.6)	6 (2.2)	1 (1.6)	8 (2)
Asthma	0	0	1 (1.6)	1 (0.3)
Cough	1 (1.6)	4 (1.5)	0	5 (1.3)
Dyspnea	1 (1.6)	0	0	1 (0.3)
<i>Blood and lymphatic system disorders</i>	1 (1.6)	5 (1.8)	2 (3.2)	8 (2)
Lymphadenopathy	1 (1.6)	5 (1.8)	2 (3.2)	8 (2)
<i>Investigations</i>	1 (1.6)	3 (1.1)	0	4 (1)
Respiratory rate increased	1 (1.6)	1 (0.4)	0	2 (0.5)
<i>Skin and subcutaneous tissue disorders</i>	0	2 (0.8)	1 (1.6)	3 (0.8)
Rash popular	0	2 (0.8)	1 (1.6)	3 (0.8)
<i>Infections and Infestations</i>	0	2 (0.7)	1 (1.6)	3 (0.8)
Bronchitis	0	1 (0.4)	1 (1.6)	2 (0.5)
<i>Nervous system disorders</i>	0	0	2 (3.2)	2 (0.5)
Dizziness	0	0	1 (1.6)	1 (0.3)
Headache	0	0	1 (1.6)	1 (0.3)
<i>Hepatobiliary Disorders</i>	0	0	1 (1.6)	1 (0.3)
Jaundice	0	0	1 (1.6)	1 (0.3)

13.12. Treatment Emergent Adverse Events by Age for Study GAI1003 Double-Blind Phase - Safety Population

Table 28 Treatment Emergent Adverse Events by Age for Study GAI3003 Double Blind Phase - Safety Population.

	Placebo (N=140)				Mebendazole 500 mg (N=144)			
	Total	Age Categories (year)			Total	Age Categories (year)		
		<3	3 to 6	7 to 16		<3	3 to 6	7 to 16
Number of subjects	140	12	24	104	144	12	31	101
Total no. subjects with any TEAE	8 (5.7%)	0	0	8 (7.7%)	9 (6.3%)	0	3 (9.7%)	6 (5.9%)
Body system or organ class								
Preferred term								
Gastrointestinal disorders	2 (1.4%)	0	0	2 (1.9%)	3 (2.1%)	0	1 (3.2%)	2 (2.0%)
Abdominal distension	1 (0.7%)	0	0	1 (1.0%)	2 (1.4%)	0	1 (3.2%)	1 (1.0%)
Abdominal pain	1 (0.7%)	0	0	1 (1.0%)	1 (0.7%)	0	0	1 (1.0%)
Infections and infestations	4 (2.9%)	0	0	4 (3.8%)	3 (2.1%)	0	2 (6.5%)	1 (1.0%)
Gastroenteritis	0	0	0	0	1 (0.7%)	0	1 (3.2%)	0
Nasopharyngitis	2 (1.4%)	0	0	2 (1.9%)	1 (0.7%)	0	0	1 (1.0%)
Tinea infection	0	0	0	0	1 (0.7%)	0	1 (3.2%)	0
Conjunctivitis	1 (0.7%)	0	0	1 (1.0%)	0	0	0	0
Conjunctivitis bacterial	1 (0.7%)	0	0	1 (1.0%)	0	0	0	0
Tonsillitis	1 (0.7%)	0	0	1 (1.0%)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)
Vitamin A deficiency	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)
Respiratory, thoracic and mediastinal disorders								
Cough	2 (1.4%)	0	0	2 (1.9%)	1 (0.7%)	0	0	1 (1.0%)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)
Rash pruritic	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)
Eye disorders	1 (0.7%)	0	0	1 (1.0%)	0	0	0	0
Night blindness	1 (0.7%)	0	0	1 (1.0%)	0	0	0	0

KEY: MedDRA=Medical Dictionary of Regulatory Activities; TEAE=treatment-emergent adverse event

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

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[TSFAE09A.RTF] [JNJ-108329\GAI3003\DR_FINAL\RE_CSR\PROD\TSFAE09A.SAS] 18MAR2016, 17:04

Source: NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 11.

13.13. Treatment Emergent Adverse Events by Age for Study GAI1003 Open Label Phase - Safety Population

Table 29 Treatment Emergent Adverse Events by Age for Study GAI3003 Open Label Phase - Safety Population.

	DB Placebo (N=137)				DB Mebendazole 500 mg (N=141)				All OL Mebendazole 500 mg (N=278)			
	Total	Age Categories (year)			Total	Age Categories (year)			Total	Age Categories (year)		
		<3	3 to 6	7 to 16		<3	3 to 6	7 to 16		<3	3 to 6	7 to 16
Number of subjects	137	12	24	101	141	10	31	100	278	22	55	201
Total no. subjects with any TEAE	1 (0.7%)	1 (8.3%)	0	0	6 (4.3%)	0	2 (6.5%)	4 (4.0%)	7 (2.5%)	1 (4.5%)	2 (3.6%)	4 (2.0%)
Body system or organ class / preferred term												
Gastrointestinal disorders	1 (0.7%)	1 (8.3%)	0	0	2 (1.4%)	0	1 (3.2%)	1 (1.0%)	3 (1.1%)	1 (4.5%)	1 (1.8%)	1 (0.5%)
Abdominal pain	0	0	0	0	1 (0.7%)	0	1 (3.2%)	0	1 (0.4%)	0	1 (1.8%)	0
Diarrhoea	1 (0.7%)	1 (8.3%)	0	0	1 (0.7%)	0	0	1 (1.0%)	2 (0.7%)	1 (4.5%)	0	1 (0.5%)
Vomiting	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Injury, poisoning and procedural complications	0	0	0	0	1 (0.7%)	0	1 (3.2%)	0	1 (0.4%)	0	1 (1.8%)	0
Soft tissue injury	0	0	0	0	1 (0.7%)	0	1 (3.2%)	0	1 (0.4%)	0	1 (1.8%)	0
Infections and infestations	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Malaria	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Pneumonia	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Nervous system disorders	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Headache	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)
Pruritus	0	0	0	0	1 (0.7%)	0	0	1 (1.0%)	1 (0.4%)	0	0	1 (0.5%)

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Note: Follow-up phase includes data collected on or after the 2nd drug administration at visit 3.

Dictionary version MedDRA 18.0

Source [Mod274](#)

Source: NDA 208398, Module 2.7.2, Summary of Clinical Pharmacology Studies, Appendix 9.

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13.14. Systemic Exposure (AUC) to Mebendazole and its Metabolites – Clinical Studies and Literature

Table 30 Systemic Exposure (AUC) to Mebendazole and its Metabolites After Single or Repeated Oral Doses

Dose	Children (Phase 3 GAI3003)			Adults (Phase 1 GAI1002)		Adults (Braithwaite, et al.)	
	500 mg Single dose	500 mg Single dose	500 mg Single dose	500 mg Single dose	10 mg/kg Single dose	40 mg/kg/day (10 mg/kg/ q6h) Repeated dosing	6,000 mg/day Repeated dosing
<u>Formulation</u>		<u>New Chewable Formulation</u>			<u>Unspecified formulation supplied by Janssen</u>		<u>500-mg tablet Janssen</u>
Age (N)	1-<3 y (22)	3-<7 y (12)	7-16y (10)	23-55 y (16)	29-77 y (5)	32-77 y (6)	Adults (8)
Fast/Fed	Mostly Fed	Mostly Fed	Mostly Fed	Fasted	Fasted/Fed	Fasted/Fed	Fed
AUC (h.ng/mL)	AUC ₂₄ ^a	AUC ₂₄ ^a	AUC ₂₄ ^a	AUC ₂₄ ^a	AUC ₁₂ ^b	AUC ₆ ^b	AUC ^{b,c}
MBZ ^d	1,320 (206-4,076)	416 (161-874)	387 (116-747)	111 (39.9-218)	210 (62-497)	650 (479-997)	2089 (438-6296)
R-MBZ ^d	2,466 (489-6,507)	2,027 ^b (830-3,386)	1,630 (566-3,147)	715 (117-1,349)	970 (183-3,104)	3,503 (1,988-5,212)	ND
H-MBZ ^d	2,027 (387-6,361)	1,682 ^b (597-2,838)	1,992 (458-3,797)	680 (217-1,833)	856 (651-1,392)	2,160 (1,894-2,401)	ND

R-MBZ = reduced mebendazole; H-MBZ = hydrolyzed mebendazole ; ND = Not determined

^a Based on whole blood concentrations from fingerstick samples

^b Based on plasma or serum concentrations

^c Interval not specified

^d Values are Mean (range)

Cross reference: [Mod5.3.1.1\GAI1002](#), [Mod5.3.5.1\GAI3003](#), Braithwaite, et al ⁸, Bekhti et. Al ⁴.

Source: NDA 208398, Module 2.7.2, Summary of Clinical Pharmacology, Table 23.

13.15. Pregnancy Outcomes with Mebendazole Exposure

Table 31 Pregnancy Outcomes and Mebendazole Exposure

	Author Country Journal Year PMID	Study Type	Subjects Enrolled	Mebendazole (MBZ) Dose	Pregnancy Outcome			
					Major Congenital Defect	First Trimester Exposure and Major Congenital Defects	Stillbirths and Perinatal deaths	Low Birth Weight Babies
1*	De Silva NR ³⁵ Sri Lanka Lancet 1999 10209979	Cross- sectional	MBZ: 5,275 Control: 1,737	600 mg (100 mg twice daily for 3 days)	MBZ (97 [1.8%] of 5275 vs control 26 [1.5%] of 1737 OR 1.24 [95% CI 0.8-1.91], p=0.39)	MBZ 10/407 (2.5%) (OR vs controls 1.66 [0.81-3.56], p=0.23	Stillbirth and perinatal death: MBZ vs control (1.9 vs 3.3%, OR 0.55 [95% CI 0.4-0.77]),	MBZ vs. control (1.1 vs 2.3%, OR 0.47 [95% CI 0.32-0.71])
2*	Diav- Citrin O ³⁶ Israel Am J Obstet Gynecol 2003 12548230	Prospective	MBZ: 192 Matched control: 192	100 mg (single treatment) OR 100 mg dose repeated after an interval OR 100 mg dose for 3 days	MBZ: 5/150 (3.3%) Control: 3/175 (1.7%) P = 0.478; relative risk [RR], 1.94; 95% CI, 0.47- 8.00	MBZ: 4/92 (4.3%) vs 3/175 (1.7%; control); P = .238; RR, 2.54; 95% CI, 0.58-11.09	Stillbirth: MBZ: 0/192 Control: 2/175 (1.1%)	Median Birthweight MBZ: 3222 (2880-3655) Control: 3257.5 (2900-3637.5)
3*	Acs N ³⁷ Hungary Congenit Anom 2005 16131365	Population- based case- control	Congenital Abnormalities: 22,843 Normal: 38,151	100 mg (single dose)	Congenital Abnormalities and MBZ exposed: 14/ 22,843 (0.06%) Normal and MBZ exposed: 14/38,151 (0.04%)	No data.	No data.	Normal and MBZ exposure group had longer mean gestational age and larger birthweight compared to non-exposed

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	Author Country Journal Year PMID	Study Type	Subjects Enrolled	Mebendazole (MBZ) Dose	Pregnancy Outcome			
					Major Congenital Defect	First Trimester Exposure and Major Congenital Defects	Stillbirths and Perinatal deaths	Low Birth Weight Babies
4	Gyorkos TW ³⁸ Canada Peru Pediatr Infect Dis J 2005 16940835	Randomized, double-blind, placebo control	MBZ + Iron: 522 Iron: 520	500 mg (single dose)	MBZ: 7/500 (1.4%) Placebo: 8/496 (1.61%) P=0.783	No data.	Stillbirths: MBZ + Iron: 8/522 (1.5%) Iron: 4/520 (0.77%)	No data.
5	Larocque R ²⁴ Canada Peru Trop Med Int Health 2006 17002722	Randomized, double-blind, placebo control	MBZ + Iron: 522 Iron: 520	500 mg (single dose)	MBZ: 4/479 (0.84%) Placebo: 5/471 (1.06%)	No data.	Stillbirths: MBZ: 8/479 (1.67%) Placebo: 4/471 (0.85%)	Low birthweight (<2500 g): MBZ: 39/479 (8.1%) 41/471 (8.7%) P=0.755 OR 0.93 (95% CI: 0.59, 1.47 Very low birthweights (<1500 g) MBZ: 0/479 (0%) 7/471 (1.5%) P=0.007 OR 0.10 (95% CI: 0.0, 0.68
6	Torp- Pedersen A ³⁹ Denmark J Obstet Gynaecol	Danish fertility database analysis (10 years)	Total births: 713,667 MBZ: 2,567 Pyrvinium: 1,588	Not reported.	No data.	Unexposed: 22,580/708,982 (3.2%) MBZ exposed: 24/1022 (2.3%) Adjusted OR 0.7 (95% CI 0.4, 1.1)	Stillbirths: Unexposed: 2548/708,982 (0.4%) MBZ exposed: 7/2567 (0.3%) Adjusted OR	Small for gestational age: Unexposed: 70,005/708,982 (9.9%) MBZ exposed: 198/2567 (7.7%)

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	Author Country Journal Year PMID	Study Type	Subjects Enrolled	Mebendazole (MBZ) Dose	Pregnancy Outcome			
					Major Congenital Defect	First Trimester Exposure and Major Congenital Defects	Stillbirths and Perinatal deaths	Low Birth Weight Babies
	2016 27189319					Pyrvinium exposed: 10/445 (2.2%) Adjusted OR 0.8 (0.4, 1.5)	0.9 (0.4,2.1) Pyrvinium exposed: 5/1588 (0.3%) Adjusted OR 1.0 (0.4,2.8) Neonatal mortality: Unexposed 2055/708,982 (0.3%) MBZ exposed: 5/2567 (0.2%) Adjusted OR 0.8 (0.3, 2.2) Pyrvinium exposed: 5/1588 (0.3%) Adjusted OR 1.1 (0.3, 3.3)	Adjusted OR: 1.0 (0.8, 1.1) Pyrvinium exposed 127/1588 (8.0%) Adjusted OR 0.9 (0.8, 1.1)
7	Satya Deepti ⁴⁰ India Res J Pharm Biol Chem Sci 2015 No PMID	Randomized, double- blinded, placebo control	Total: 500 2x2 factorial design Albendazole and MBZ	600 mg (100 mg twice daily for 3 days)	No data.	Study excluded pregnant women in first trimester.	No data.	No overall effect of either anthelmintic treatment on mean birth weight or proportion of newborns with low birth weight. Data not shown.

Adapted from NDA 208398, Module 2.7.4, Summary of Clinical Safety, Table 15. Pregnancy outcome data added.

**Referenced in WHO Preventive Chemotherapy in Human Helminthiasis⁴¹*

13.16. Interval and Cumulative Postmarketing Exposure

Table 32 Exposure to mebendazole and mebendazole/quinfamides (01 May 2015 to 30 April 2016)

Formulation	Grams	Assumed treatment	Treatment courses
100, 200, 300 mg tablets	8,613,227.0	600 mg	14,355,378
500 mg tablets	5,760,051.5	500 mg	11,520,103
500 mg chewable tablets	1,816,082.0	500 mg	3,632,164
Oral Solution, Suspension, Syrup	3,190,710.3	600 mg	5,317,851
Combination Packs	0.0	550 mg	0
Total	19,380,070.8		34,825,496

Source: NDA 208398 SD7, Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report, Table 2.

Table 33 Exposure to mebendazole and mebendazole/quinfamides (1988 to 30 April 2016)

Formulation	Grams	Assumed treatment	Treatment courses
100, 200, 300 mg tablets	212,675,310.5	600 mg	354,458,851
500 mg tablets	116,825,762.6	500 mg	233,651,525
500 mg chewable tablets	18,730,733.7	500 mg	37,461,467
Oral Solution, Suspension, Syrup	131,251,848.0	600 mg	218,753,080
Combination Packs	500,773.3	550 mg	910,497
Total	479,984,428.1		845,235,420

Source: NDA 208398 SD7, Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report, Table 3.

Clinical Review

Sheral S. Patel, M.D.

NDA 208398 – 505(b)(2)

VERMOXTM CHEWABLE (mebendazole 500 mg chewable tablets)

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/s/

SHERAL S PATEL
10/06/2016

HALA H SHAMSUDDIN
10/06/2016

Clinical Inspection Summary

Date	October 3, 2016
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation (DCCE)
To	Alison Rodgers, Regulatory Project Manager Sheral Patel, M.D., Medical Officer Hala Shamsuddin, M.D., Clinical Team Leader Sumathi Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 208398
Applicant	Janssen Pharmaceuticals, Inc.
Drug	Mebendazole Chewable Tablet (Vermox®)
New Molecular Entity	No
Review Priority	Priority
Proposed Indication	Treatment of gastrointestinal infestation by <i>Trichuris trichiura</i> (whipworm), <i>Ascaris lumbricoides</i> (large roundworm), and <i>Ancylostoma duodenale</i> (b) (4)
Consultation Date	May 23, 2016
CIS Goal Date	September 15, 2016
Action Goal Date	October 19, 2016
PDUFA Due Date	October 19, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

A randomized controlled trial (Study GAI3003) of chewable mebendazole (Vermox®) was audited at good clinical practice (**GCP**) inspection of the largest (of three) participating clinical investigator (**CI**) site with 156 (of 295) subjects (53%, Site 251002 at Jimma, Ethiopia). No significant GCP deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the sNDA.

II. BACKGROUND

Mebendazole is an anti-helminthic indicated for the treatment of gastrointestinal infestation by the whipworm *Trichuris trichiura*, the roundworm *Ascaris lumbricoides*, and/or the hookworms *Ancylostoma duodenale* and *Necator americanus*. Under an orphan designation (granted 2014) for neglected tropical diseases, Janssen Research and Development (**JRD**) developed a chewable formulation of mebendazole (Vermox®) to improve treatment compliance in young children. The pivotal study GAI3003 was a randomized, double-blind, placebo-controlled trial in 295 children (age 1-16 years) completed over nine months (2015) at three CI sites in areas endemic for soil-transmitted helminth (**STH**) infestation (two in Ethiopia, one in Rwanda).

Study GAI3003: A Double-Blind, Randomized, Multi-Center, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of a 500-mg Chewable Tablet of Mebendazole in the Treatment of Soil-Transmitted Helminth Infestations (Ascaris lumbricoides and Trichuris trichiura) in Pediatric Subjects

The primary study objective was to compare chewable mebendazole (single 500 mg tablet) with placebo in clearing (as assessed at end of blinded period) *Ascaris lumbricoides* and *Trichuris trichiura* infestations (co-primary efficacy endpoints/analyses of cure rates). The study included five visits: (1) screening, collection and examination of stool sample for STH egg counts (Kato-Katz method); (2) Day 1, randomization and single-dose oral treatment with either chewable mebendazole or matching placebo; (3) Day 19, end of blinded period, repeat collection and examination of stool sample for STH egg counts followed by open-label active therapy; (4) Day 20 (day after Visit 3), collection of samples for pharmacokinetic evaluation; and (5) Day 26 (one week after Visit 3), end of open-label follow-up, final safety evaluations. This study was audited on-site at GCP inspection of the largest of the three participating CI sites (156 of 295 subjects, 53%).

III. INSPECTION OUTCOME: Audit of Study GAI3003 at Site 251002

Clinical Investigator Site	Site / Enrollment	Outcome
Netsanet Workenh Gidi, M.D. Jimma University Hospital Jimma, Ethiopia	Site 251002 156 subjects	September 19-21, 2016 NAI

NAI: No Action Indicated (no significant deviations from GCP regulations)

The establishment inspection report (**EIR**) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. At EIR receipt and review, an addendum may be forwarded to the review division if new significant findings are discovered; otherwise, OSI's written post-inspection correspondence with the CI (copied to review division) indicates EIR review completion with confirmation of the findings as reported in this clinical inspection summary (**CIS**).

The *Request for Clinical Inspections* lists three CI sites, of which the two in Ethiopia were to be inspected. Site 251001 (Emias Diro; Gondar, Ethiopia) could not be inspected due to travel restriction to Gondar, Ethiopia.

Netsanet Workenh Gidi, M.D.

Site 251002: 4175 subjects were screened, 156 were enrolled, 8 were withdrawn, and 148 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for efficacy evaluations and adverse event monitoring.

No significant GCP deficiencies were observed and a Form FDA 483 was not issued. Verbal discussion included not rigorously following the quality control procedures in determining STH egg counts (three subjects), which appeared minor and unlikely to be significant to the study outcome.

Study conduct appeared GCP-compliant overall, including sponsor oversight of study conduct. All audited data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the sNDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
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Kassa Ayalew, M.D., M.P.H.
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CC:

DAIP / Division Director / Sumathi Nambiar
DAIP / Clinical Team Leader / Hala Shamsuddin
DAIP / Medical Officer / Sheral Patel
DAIP / Regulatory Health Project Manager / Alison Rodgers

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OSI / DCCE / GCPAB / Team Leader / Janice Pohlman
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
10/03/2016

JANICE K POHLMAN
10/03/2016

KASSA AYALEW
10/03/2016

Request for Priority Review Designation

NDA Supporting Document Number:	NDA 208398 SD1
Reference IND:	IND 115959
Sponsor:	Janssen Pharmaceutical Research & Development, LLC
Drug:	VERMOX® (mebendazole) 500 mg chewable tablet
Proposed Indication:	Single dose for the treatment of (b) (4) gastrointestinal (b) (4) by Trichuris trichiura (whipworm), Ascaris lumbricoides (large roundworm), (b) (4)
Correspondence Date:	April 19, 2016
Date Received / Agency:	April 19, 2016
Date Review Completed:	April 25, 2016
Reviewer:	Sheral S. Patel, M.D. (DAIP/OAP/OND/CDER)
Team Leader:	Hala Shamsuddin, M.D. (DAIP/OAP/OND/CDER)
Materials Reviewed:	Request for Priority Review Designation

1. Introduction

The Sponsor submits an NDA application for VERMOX Chewable (mebendazole) 500 mg chewable tablets seeking the indication of treatment of soil transmitted helminths in adults and pediatrics (b) (4) and concurrently submits a request for designation of Priority Review.

2. Recommendations

This reviewer recommends granting the Sponsor's request for Priority Review.

Soil transmitted helminth infections are considered a serious condition. The mebendazole 500 mg chewable provides significant improvement over the mebendazole 100 mg chewable tablet for the following reasons.

- The mebendazole 500 mg chewable tablet allows for administration to a broader age range of children, a special population. The mebendazole 500 mg chewable tablet has been studied in children as young as 1 year of age, while the currently approved mebendazole 100 mg chewable tablet has only been studied in children greater than 2 years of age.
- The mebendazole 500 mg chewable tablet is a single dose regimen which improves compliance over the mebendazole 100 mg tablet dosing regimen (100 mg BID for 3 days), potentially contributing to improved effectiveness.
- The rapidly disintegrating formulation allows for dosing to individuals who may have difficulty chewing or swallowing the 100 mg tablet, such as young children, potentially minimizing adverse events such as choking.

3. Drug Product

Mebendazole is a synthetic broad-spectrum anthelmintic agent for oral administration belonging to the class of benzimidazole derivatives. Mebendazole has low systemic bioavailability, with 90% of the drug remaining in the gastrointestinal tract, where it exerts activity against soil-transmitted helminths (STH).

The proprietary name (VERMOX Chewable [mebendazole] 500 mg Tablets) was conditionally accepted by the Agency on 18 December 2015.

Orphan Drug Designation was granted on 08 September 2014.

4. Proposed Indication

Mebendazole (Vermox) 100 mg chewable tablets were approved on 28 June 1974 (NDA 17-481) for the treatment of *T. trichiura* (whipworm), *A. lumbricoides* (large roundworm), *Enterobius vermicularis* (pinworm), and *A. duodenale* and *N. americanus* (hookworm) in single or mixed (b) (4). In 2006, marketing in the US was discontinued for commercial reasons. However, the NDA has not been withdrawn and annual safety reporting continues.

The proposed indications for VERMOX Chewable (mebendazole) 500-mg chewable tablets are treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); and *Ancylostoma duodenale* (b) (4).

Reviewer comment: The Sponsor is not seeking an indication for the treatment of *Enterobius vermicularis* (pinworm), which is approved for the mebendazole 100 mg chewable tablets.

5. Justification for Priority Review

According to the FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, qualifying criteria for priority review include:¹

1. An application (original or efficacy supplement) for a drug that treats a serious condition

AND,

2. If approved, would provide a significant improvement in safety or effectiveness

This review will focus on the justification provided for the two aforementioned criteria to determine priority review.

5.1 Whether soil transmitted helminthiasis is a serious condition, and whether mebendazole treats this condition

A serious disease or condition is defined in the expanded access regulations as follows:¹

. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Soil transmitted helminth (STH) infections are considered a neglected tropical disease. STH infections are caused by four main species of parasitic worms (*Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); and *Ancylostoma duodenale* (b) (4)). In areas of poor sanitation, people are infected through soil contaminated with helminth eggs passed through human feces.

According to the World Health Organization (WHO), STH infections are found in more than 1.5 billion people, or 24% of the world's population.² Furthermore, there are over 270 million preschool-age children and over 600 million school-age children living in areas where these parasites are intensively transmitted.²

Morbidity from STH infections is associated with worm burden. Clinical presentation can range from asymptomatic to intestinal manifestation (diarrhea, abdominal pain), malaise, and weakness.^{3,4} Impaired cognitive and physical development can occur with soil-transmitted infections in children.^{3,4} Hookworm infection specifically can lead to chronic intestinal blood loss and anemia.

In addition, STH infections lead to impaired nutritional status through worms feeding on host tissue, including blood, and increased malabsorption of nutrients in the host.^{3,4} Furthermore, infected individuals may experience gastrointestinal symptoms, such as loss of appetite, diarrhea, and abdominal pain, which can lead to decreased food intake.

The WHO recommends control of STH infections to decrease morbidity through periodic treatment of at-risk individuals living in endemic areas.² At-risk individuals include preschool children, school-age children, women of childbearing age (including pregnant women in the second and third trimesters and breastfeeding women), as well as adults in certain high-risk occupations such as tea-pickers or miners. Periodic treatment decreases worm burden, which can decrease morbidity.

Mebendazole 100 mg chewable tablet is the only FDA approved therapy for STH.

Reviewer comment: Periodic treatment to reduce worm burden is especially important in the pediatric population. Children with high burdens of intestinal helminths will experience long term cognitive and physical delays if not treated. The proposed indication, for which the Sponsor's drug is intended to treat, meets the criteria for a serious condition.

5.2 Significant improvement in safety or effectiveness over other available FDA-approved therapies

According to the Guidance, the proposed drug should be a significant improvement over available therapies in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition.¹

The approved therapy for the treatment of STH in the United States is mebendazole 100 mg chewable tablet, which is administered bid for 3 days. The label states that 100 mg tablets have not been studied in children less than 2 years of age.

A 500 mg solid oral mebendazole tablet, used for single dose administration to treat STH, is not available in the United States. Although the solid oral tablet can be crushed and administered with a small amount of potable water, if available, for children less than 5 years old, this is not a preferred method for several reasons: 1.) additional work required for crushing the tablet, 2.) unpleasant taste of the medication, 3.) possible choking hazard if the medication is not completely crushed, and 4.) chance of insufficient dosing if part of the medication is lost.

Given these reasons, the WHO recommends that only chewable deworming tablets should be given to children under 5 years old, and that chewable tablets be crushed and mixed with water in children under 3 years old. The WHO recommends a 500-mg chewable dose for all ages ≥ 1 year, with no adjustment in dosage needed based on age, weight or surface area.⁵

The Sponsor's proposed 500 mg chewable tablet would be administered as a single dose. It is a rapidly disintegrating formulation which turns into a soft semi-solid mass when mixed with a small amount of water. In addition, the 500 mg chewable tablet has been studied in children as young as 1 year old.

The Sponsor reports results from a Phase 3 study (GAI3003) which showed that a single dose of mebendazole 500 mg chewable tablet is more effective than placebo in the treatment of *A. lumbricoides* (83% vs. 11%, respectively) and *T. trichura* (34% vs. 7%, respectively) in pediatric subjects as young as one year. The Sponsor reports that results from the 712 subjects in the 4 studies submitted for the application for the mebendazole 500 mg chewable tablets showed a safety profile consistent with what has been reported in the literature and in postmarketing surveillance in adults and children.

Reviewer comment: *The Sponsor's proposed mebendazole 500 mg chewable tablets meet the criteria for significant improvement in safety or effectiveness. It offers several improvements over existing therapy including:*

- 1. Improved patient compliance by single dose administration (which may indirectly contribute to improved efficacy)*
- 2. Ability to administer drugs to individuals who may have difficulty chewing a tablet, such as young children (possibility of less adverse events such as choking)*
- 3. Potential to treat children as young as 1 year of age (special populations)*

6. References

1. U.S. FDA Guidance for Industry: Expedited Program for Serious Conditions - Drugs and Biologics, 2014. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
2. World Health Organization. Soil-transmitted Helminth Infections Fact Sheet. 2016. <http://www.who.int/mediacentre/factsheets/fs366/en/> (accessed April 25 2016).
3. World Health Organization. Soil-transmitted helminthiasis: eliminating soil-transmitted helminthiasis as a public health problem in children: progress report 2001-2010 and strategic plan 2011-2020., 2012.
4. U.S. Centers for Disease Control and Prevention. Parasites - Soil-transmitted Helminths (STHs). 2013. <http://www.cdc.gov/parasites/sth/> (accessed April 25 2016).
5. World Health Organization. Controlling disease due to helminth infections, 2002.

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SHERAL S PATEL
05/16/2016

HALA H SHAMSUDDIN
05/16/2016

CLINICAL FILING CHECKLIST FOR NDA 208398

NDA Number: 208398

Applicant: Janssen
Pharmaceuticals, Inc.

Stamp Date: 19 April 2016

Drug Name: VERMOX™
Chewable (mebendazole) 500 mg
chewable tablets

NDA Type: 505(b)(1)

PDUFA Goal Date:
19 October 2016

The Sponsor develops mebendazole 500 mg chewable tablets for donation to the World Health Organization single-dose mass drug administration programs for soil-transmitted helminths. The proposed indication is the treatment of single or mixed gastrointestinal infestations by Trichuris trichiura (whipworm); Ascaris lumbricoides (large roundworm); (b) (4) The mebendazole 500 mg chewable tablet would be administered as a single dose. The intended population is adults and pediatrics ((b) (4) year of age). For individuals who have difficulty swallowing, water is added to the tablet which changes the tablet into a soft mass with semi-solid consistency. The Sponsor submits results from an open label, single-center, single-dose, single arm safety study (GAI3002, n=396) and a double-blind, randomized, parallel group, placebo-controlled multicenter pediatric study (GAI3003, n=295) to support their application.

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).			X	eCTD submission
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?			x	Per agreement at pre-NDA meeting 08 March 2016, all safety information from various data sources summarized in

CLINICAL FILING CHECKLIST FOR NDA 208398

	Content Parameter	Yes	No	NA	Comment
					Module 2.7.3 Summary of Clinical Safety.
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	Per agreement at pre-NDA meeting 08 March 2016, all efficacy information for the one pivotal trial summarized in Module 2.7.3 Summary of Clinical Efficacy.
10.	Has the applicant submitted a benefit-risk analysis for the product?			x	
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			x	
14.	Describe the scientific bridge (e.g., BA/BE studies)			x	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?	x			1. GAI1001 Phase1 Relative Bioavailability Study Healthy adults (n=18) 2. GAI1002 Phase 1 Food effect Healthy adults (n=16) 3. GAI3003 Phase 3 Pediatrics subjects, PK substudy (n=44)
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			GAI3003: Phase 3 randomized, multi-center, double-blind, parallel-group, placebo-controlled study (n=295)
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		The drug is intended to be used for a WHO drug donation program to treat a neglected tropical disease, and is

CLINICAL FILING CHECKLIST FOR NDA 208398

	Content Parameter	Yes	No	NA	Comment
					not intended to be marketed for commercial purposes in the U.S.
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?			x	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
25.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	There were no deaths, serious adverse events, or adverse events leading to discontinuation in the Sponsor conducted clinical studies.
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	The Sponsor submits data from a Phase 3 study conducted in children.

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 208398

	Content Parameter	Yes	No	NA	Comment
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	x			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		The drug is intended to be used for a WHO drug donation program to treat a neglected tropical disease, and is not intended to be marketed for commercial purposes in the U.S.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			In studies GAI3002 and GAI3002, adverse event end dates are missing in 78% and 33% of records respectively. AEOU (“Outcome of Adverse Event”) variable provides some clarification. In study 3002, 44 of 45 adverse events that were missing end dates had an outcome of “Not Recovered/Not Resolved”. In study 3003, 4 of 10 adverse events that were missing end dates had an outcome of “Not Recovered/Not

CLINICAL FILING CHECKLIST FOR NDA 208398

	Content Parameter	Yes	No	NA	Comment
					Resolved” and 6 of 10 had an outcome of “Recovering/Resolving”.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

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

Information Requests to be communicated to the Sponsor:

1. In studies 3002 and 3003, adverse event end dates are missing in 78% and 33% of records, respectively. Please clarify and submit an updated dataset for both studies, as needed. The variable AEENRF (“End Relative to Reference Period”) could be utilized to denote whether an event was still ongoing at the end of a subject’s participation in a trial or if this information is unknown.

2. From Office of Scientific Investigations: The clinsite.xpt file that you submitted in NDA 208398 for Study Mebendazolgai3003 failed the quality control check for load to CDER’s Clinical Investigator Site Selection Tool because you have entered “-1” for all arms at all sites for the following variables: TRTEFFR, TRTEFFS, SITEEFFE, and SITEEFFS. Please provide a corrected clinsite.xpt file for Study Mebendazolgai3003.

Sheral S. Patel, M.D.

16 May 2016

Reviewing Medical Officer

Date

Hala Shamsuddin, M.D.

16 May 2016

Clinical Team Leader

Date

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/s/

SHERAL S PATEL
05/16/2016

HALA H SHAMSUDDIN
05/16/2016