

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208398Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 5, 2016
From	Hala Shamsuddin MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208398/S1
Supplement#	
Applicant	Janssen Pharmaceuticals, Inc.
Date of Submission	April 19, 2016
PDUFA Goal Date	October 19, 2016
Proprietary Name / Non-Proprietary Name	Vermox™ CHEWABLE/ Mebendazole
Dosage form(s) / Strength(s)	Chewable Tablet/500 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of single or mixed gastrointestinal infestations by <i>Ascaris lumbricoides</i> (roundworm), <i>Trichuris trichiura</i> (whipworm), and (b) (4) in patients 1 year of age and older
Recommendation on Regulatory Action	Approval for adult and pediatric patients 1 year of age and older

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ascaris lumbricoides (roundworm), *Trichuris trichiura* (whipworm), *Necator americanus* and *Ancylostoma duodenale* (hookworm) are soil transmitted helminths that reside in the intestines and are estimated to infect approximately 24% of the world's population, mainly children living in poor underserved communities. These infections result in nutritional and cognitive impairment. The World Health Organization (WHO) periodically (once or twice per year depending on the prevalence of STH infections in the community) administers a single 500 mg mebendazole or 400 mg albendazole dose to all at-risk people living in endemic areas to decrease the morbidity of STH infections. An oral solid mebendazole tablet is donated by the Applicant for use in WHO deworming campaigns. (b) (4)

The Applicant conducted a randomized, double-blind study showing that a single 500 mg chewable tablet was significantly more effective than placebo in achieving clinical cure (stool egg reduction to zero) at Day 19 in children infected with *A. lumbricoides* and/or *T. trichiura*, as well as the small subset of patients also infected with hookworm. In addition, mebendazole was significantly more effective in reducing egg counts. Similar to the findings in this study, published literature indicates higher responses in ascariasis compared to trichiuriasis or hookworm (in this order). Although published reports of placebo-controlled trials show very high variability in response in the treatment of hookworm infections (likely affected by geographic location, dosage, patient age and worm infection density), single dose mebendazole generally resulted in higher cure and egg reduction rates compared to placebo across the studies. In general, mebendazole is poorly bioavailable, however, bioavailability was higher in the fed state compared to fasted state, and higher in children 1 to 3 years of age compared to older children and adults. The safety profile of mebendazole was mainly related to the gastrointestinal tract, and the frequency or severity of adverse reactions did not seem to correlate with systemic exposure or age.

The Phase 3 trial supporting this NDA was conducted in pediatric patients, however, the pathophysiology of STH infections is similar in adults and children and the local antihelminthic effect of mebendazole is expected to be the same whether the worm resides in the intestines of a child or an adult. Published literature for mebendazole in the treatment of STH in adults is limited, as most studies enrolled only children or did not specify responses by age. However, the reported response rates seemed similar in adults and children. Additionally, mebendazole 100 mg chewable is currently FDA approved for patients 2 years of age and older without specifically stating that the use should be limited to children.

Overall, the single 500 mg mebendazole chewable tablet has demonstrated substantial evidence of efficacy in the treatment of *Ascaris lumbricoides* and *Trichuris trichiura* and the risk-benefit profile is highly favorable. (b) (4)

I also highly recommend approval in patients one year of age or older, **without** restricting the indication to pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> • <i>Ascaris lumbricoides</i> (roundworm), <i>Trichuris trichiura</i> (whipworm), <i>Necator americanus</i> and <i>Ancylostoma duodenale</i> (hookworms) are soil transmitted helminths (STH) that reside intraluminally in the gastrointestinal tract and cause nutritional impairment due to nutrient and vitamin malabsorption, loss of appetite, diarrhea, dysentery, or intestinal complications that require surgical intervention (intestinal obstruction, rectal prolapse). Nutritional impairment adversely impacts growth and physical development and causes cognitive impairment and worsening school performance. • The WHO estimates that more than 1.5 billion people, or 24% of the world's population, have STH infections. Over 270 million preschool children and over 600 million school-age children live in areas of intense transmission and are in need of treatment and prevention interventions. STH affect the poorest communities and are considered neglected tropical infections. 	<ul style="list-style-type: none"> • STH are serious infections that cause significant morbidity, affecting a large number of people, mainly preschool and school age children living in poor, underserved communities.
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> • In the United States, only mebendazole is FDA approved for the treatment of STH. The approved dosing regimen is 100 mg chewable tablet daily for 3 or 5 days (depending on the infecting species). Albendazole and ivermectin may be used off-label. Outside the US, solid oral mebendazole tablet and oral suspension are available. • The WHO provides periodic treatment to all at-risk people living in endemic areas to decrease morbidity of STH infections. Treatment is given once or twice a year depending on the prevalence of STH infections in the community. The recommended treatments are single dose mebendazole (500 mg) or albendazole (400 mg). 	<ul style="list-style-type: none"> • There is a need for a single dose regimen that can be conveniently used in WHO mass deworming campaigns and that can administered to very young children. The proposed mebendazole formulation is a single dose regimen of a rapidly disintegrating chewable 500 mg tablet that can be given to children as young as one year of age.
<u>Benefit</u>	<ul style="list-style-type: none"> • In a randomized, placebo-controlled study in children 1-16 years of age (Study GAI3003), a single 500 mg mebendazole rapidly disintegrating chewable tablet compared to placebo resulted in superior cure rates for <i>A. lumbricoides</i> (difference in cure rate 72.6%, 95% CI 62.3, 82.7) and <i>T. trichiura</i> (difference in cure rate 26.3%, 95% CI 16.7, 35.6) on Day 19. Cure rates for single or double infections were similar. Cure rates were highest for ascariasis. (b) (4) <p>Overall cure rates abstracted from the literature indicate that a single 500 mg</p>	<ul style="list-style-type: none"> • Evidence of efficacy in children is demonstrated in a randomized, placebo-controlled trial for ascariasis and trichuriasis. Published literature, despite significant limitations, is supportive. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>mebendazole dose results in cure rates that are similar to what is reported in the Phase 3 trial for ascariasis and trichuriasis. However, there was significant variability, likely related to different populations, different geographic locations, patient age, timing of assessment and methods used. Overall, cure rates are highest for ascariasis (b) (4).</p> <p>(b) (4)</p> <ul style="list-style-type: none"> • In patients not achieving cure, mebendazole significantly reduced egg count compared to placebo. • Study GAI3003 was conducted in children 1 to 16 years of age. Published literature in adults is limited, as most studies were either done in children or did not specify response rates by age. However, overall, despite these limitations, similar response rates (cure and egg reduction) in adults seems to be similar to those in children. STH pathophysiology is the same in children and adults. Mebendazole acts intraluminally; the local effects on the worm are not expected to be different whether the worm resides in the intestines of a child or an adult. Additionally, 100 mg dosing regimen is already FDA-approved in adults. 	<p>(b) (4)</p> <p>(b) (4)</p> <ul style="list-style-type: none"> • Evidence of efficacy in adults is limited as most published studies enrolled children (consistent with higher prevalence of STH in children). However, response rates seem similar in children and adults. Additionally, disease pathophysiology is similar and expected local antihelminthic effects of mebendazole are expected to be the same. I recommend approval in adults.
<p><u>Risk</u></p>	<ul style="list-style-type: none"> • There were no deaths and no serious adverse events across four clinical studies submitted in support of this application • Overall treatment emergent adverse events (TEAEs) were not frequent (6.3% mebendazole compared to 5.7% placebo) and mainly related to the gastrointestinal tract • TEAEs were similar to those reported in the literature, and similar to those reported in 39 internal studies in the Applicant's database and in extensive 	<ul style="list-style-type: none"> • The risk/benefit profile of mebendazole chewable 500 mg tablet is highly favorable. • Labeling will include a Warning regarding risk of seizures in infants and a similar statement in Pediatric use.

Cross Discipline Team Leader Review
 NDA 208398 Mebendazole Chewable Tablet 500 mg

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>postmarketing experience of over 845 million doses.</p> <ul style="list-style-type: none"> • Two cases of status epilepticus were reported in infants postmarketing. Both recovered without neurologic sequelae. • Systemic exposure is low. Although systemic exposure was higher in children less than 3 years of age compared to older children and adults and higher if given with a high fat meal compared to fasted stated, there was no relationship between the occurrence of TEAE and age or feeding status. 	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> • There are no specific risks that require initiation of risk management strategy beyond product labeling. 	<ul style="list-style-type: none"> • No risk evaluation and mitigation strategies, post-marketing requirements or commitments are recommended.

2. Background

Mebendazole is an antihelminthic synthetic benzimidazole derivative that was initially approved in 1974 as chewable 100 mg tablets (Vermox™ - NDA 017841 – Janssen Pharmaceuticals) for the 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. The approved dosing regimen for adults and children older than the age of 2 years is 100 mg once daily for 3 days for *Trichiuris* and hookworm infections and for 5 days for *Ascaris* infection.

In this submission, the Applicant seeks approval for a new mebendazole oral formulation and new dosing regimen for the same previously approved indications except the pinworm treatment indication. The proposed product is a rapidly disintegrating 500 mg chewable tablet. The proposed dosing regimen is a single 500 mg dose. Of note, the Applicant had previously developed a chewable 500 mg tablet that was used in some of the studies submitted in this application.

In support of this application, the Applicant submitted the following:

- An open label, single dose, randomized, cross over design, relative bioavailability study comparing single 500 mg solid mebendazole tablet to a previous chewable 500 mg version of the current product in 19 healthy adult subjects (MEBENDAZOLGAI1001, referred to as GAI1001)
- Phase 1, open-label, randomized, cross over design study to evaluate the food effect on systemic absorption of the currently proposed 500 mg rapidly disintegrating chewable tablet in 16 healthy adult subjects (MEBENDAZOLGAI1002, referred to as GAI1002)
- Open-label, single center study to evaluate the safety and tolerability of previous version of 500 mg chewable tablet in 396 children 2 to 10 years of age, inclusive (MEBENDAZOLGAI3002).
- Randomized, multicenter, double-blind, parallel group, placebo-controlled study to evaluate efficacy and safety of a single dose of the currently proposed rapidly disintegrating 500 mg chewable tablet compared to placebo in the treatment of *A. lumbricoides* and *T. trichiura* in 295 pediatric subjects 1 to 16 years of age, with PK assessment in a subpopulation (MEBENDAZOLGAI3003, referred to as GAI3003).
- Published literature evaluating single 500 mg dose of mebendazole in the treatment of STH, including published reports from placebo-controlled trials

Data from study GAI3003 and the published literature were used to support efficacy in the treatment of *A. lumbricoides* and *T. trichiura*, (b) (4)

Regulatory History

A pre-IND meeting was held on October 26, 2012 to discuss the development program for the currently proposed formulation. IND 115,959 was submitted on January 14, 2014. The product was granted Orphan Designation for the same indication sought in this NDA on September 2, 2014, and a pre-NDA meeting was held on March 8, 2016. At the time of this submission, the Applicant requested, and was granted, Priority Review because this product is intended for the treatment of a serious disease (soil transmitted helminths) and offers advantages over the existing mebendazole product in that it is given as a single dose (thus enhancing adherence and feasibility for use in mass deworming campaigns), and it can be administered to children as young as one year of age.

Mebendazole (Vermox™) 100 mg chewable tablet was first approved in the United States in 1974 (NDA 017841 – Janssen Pharmaceuticals). Marketing was discontinued in 2006 due to commercial reasons, however, the NDA remained active. This NDA (208398) was submitted under the 505(b)(2) regulatory pathway. The Applicant cross referenced NDA 017481, and DMF 30325 for information pertaining to the drug substance. The proposed proprietary name “Vermox™ Chewable” was conditionally accepted under IND 115,959 on December 18, 2015 by the Office of Medication Error Prevention and Risk Management.

Mebendazole is licensed in 123 countries around the world. Outside the United States, the registered formulations of mebendazole include 100-mg, 200-mg, and 500-mg solid oral tablets, 100 mg and 500-mg chewable tablets, and oral suspensions of 20 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, and 100 mg/mL. 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. The Applicant is currently donating the 500-mg mebendazole (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. The Applicant does not plan to market the proposed 500 mg rapidly disintegrating chewable tablet in the United States if approved, but intends to donate it to the WHO for use in mass deworming programs for STH.

Disease Background^{1,2}

The main species of soil transmitted helminths (STH) that infect people are *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm) and *Necator americanus* and *Ancylostoma duodenale* (hookworms). They are transmitted by eggs present in human feces which in turn contaminate soil in areas where sanitation is poor. For roundworm and whipworm, infection occurs when the eggs are ingested. For hookworm, infection occurs primarily by walking barefoot on contaminated soil.

STH are among the most common infections worldwide. The WHO estimates that more than 1.5 billion people, or 24% of the world’s population, are infected with STH. Infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in

¹ <http://www.who.int/mediacentre/factsheets/fs366/en/>

² http://www.who.int/intestinal_worms/more/en/

sub-Saharan Africa, the Americas, China and East Asia. Over 270 million preschool children and over 600 million school-age children are estimated to live in areas of intense transmission.

Morbidity from STH infections is related to worm burden. STH infections cause nutritional impairment by many ways: loss of appetite, chronic intestinal blood loss, nutrient and vitamin malabsorption, diarrhea, dysentery, or intestinal complications that require surgical intervention (e.g., intestinal obstruction and rectal prolapse). Nutritional impairment significantly and adversely impacts growth and physical development causing cognitive impairment and worsening school performance.

The WHO has endorsed a strategy to decrease morbidity of STH infections by providing periodic treatment (deworming) to all at-risk people living in endemic areas without previous individual diagnosis. These include preschool and school-age children, women of childbearing age (including pregnant women in the second and third trimester and breastfeeding women) as well as adults in certain high-risk occupations, such as tea pickers and miners. Treatment is given once a year when the prevalence of STH infections in the community is over 20%, and twice a year when the prevalence is over 50%. The recommended treatments are single dose mebendazole (500 mg) or albendazole (400 mg).

Background Information for Mebendazole

Overall, mebendazole has absolute bioavailability of (b) (4) but inter-individual systemic exposure after oral administration is highly variable. The low bioavailability is postulated to be due to poor solubility and high first pass metabolism. The plasma protein binding is reported to be $\geq 90\%$, and the estimated volume of distribution after intravenous administration is 1.23 L/kg (range: 1 to 2 L/kg).

Mebendazole is mainly metabolized in the liver into two inactive metabolites, a hydrolyzed form and a reduced form. The mean estimates for mebendazole elimination half-life ranges from 3 (b) (4) to (b) (4) hours. Generally, (b) (4) of mebendazole and its metabolites are excreted in urine and the remainder in the feces.

3. Product Quality

Geatan Landouceur conducted the review for the drug substance and George Lunn for the drug product. Facility review was by Quallyna Porte. Their findings are summarized.

The chemical name of mebendazole is methyl-5-benzoyl-1Hbenzimidazol-2-yl carbamate. The molecular weight is 295.30 and a molecular formula $C_{16}H_{13}N_3O_3$. The mebendazole drug substance is manufactured (b) (4) a white to off-white powder (b) (4) practically insoluble in water and various organic solvents (b) (4). The currently proposed mebendazole chewable tablets is polymorph C. The proposed acceptance criteria for the content of polymorph C, impurities and the drug substance specification was found adequate. The detailed chemistry, manufacture and control information for the mebendazole drug substance was provided via a reference to DMF (b) (4). This DMF was reviewed and found to be adequate.

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

The drug product specification for appearance, identity, assay, uniformity of dosage units, degradation products, dissolution, disintegration, water content, and microbial limits (release and end of shelf-life) was found to be adequate.

Stability information was provided to (b) (4). In-use studies for the soft mass that forms after addition of water met the acceptance criteria with respect to assay, degradants, and polymorphic form. Additional stability study on a bottle with no seal and only a loosely fitted cap supported a statement on the product label that opened bottles should be discarded after one month. The stability information, including the proposed expiration dating period of 24 months with the storage statement “Store below 30°C” was found acceptable.

The proposed in vitro dissolution method was validated in terms of accuracy, analysis repeatability, linearity, range, reproducibility, robustness, stability of solution, and filtration study and found acceptable.

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

The reviewers from the Office of Pharmaceutical Quality concluded that sufficient chemistry, manufacturing and controls information to assure the identity, strength, purity, and quality of the drug product, mebendazole chewable tablets were provided and recommended approval of this NDA.

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Nostrandt, DVM, PhD., conducted the nonclinical pharmacology/toxicology review. Her findings are summarized.

(b) (4)
(b) (4)
(b) (4)
Polymorph C
was used (b) (4) formulations of the 500-mg chewable tablet.

(b) (4)

The Applicant provided a summary of the previous findings that were submitted to NDA 017481 for general nonclinical toxicology. In 13-week study in rats, the no observed adverse event level (NOAEL) doses of mebendazole were 10 mg/kg [human equivalent dose (HED) = 1.7 mg/kg]. Toxicities were dose-related at higher doses, and included decreased food consumption and body weight, decreased albumin, increased alkaline phosphatase, small testicles correlating histologically to inhibition of spermatogenesis, and increased liver weight. In 13-week study in dogs, the NOAEL was 2.5 mg/kg/day (HED = 1.25 mg/kg). Findings at higher doses were liver weight increases. Twenty two- and 24-month studies in mice and rats, respectively, were negative for carcinogenicity at dosage levels up to 40 mg/kg/day (0.4-fold and 0.8-fold the maximum recommended human dose on a mg/m^2 basis (500 mg; 60 kg adult) for mice and rats, respectively.

The Applicant submitted study reports evaluating cardiovascular toxicity, mutagenesis, and development and reproductive toxicology. Mebendazole resulted in no relevant electrophysiological effects in isolated Langendorff-perfused female rabbit hearts and in 5.4% reduction of the the membrane K^+ current (IKr) in HERG assay at concentrations up to 10 μM . This concentration is estimated to be 140-fold higher than the highest exposure noted in the Phase 3 study. In anaesthetized guinea pigs, mebendazole up to 1.25 mg/kg IV had no statistically significant effects on cardiovascular parameters.

No safety pharmacology studies of the respiratory or central nervous systems were performed. Ex vivo or in vivo evaluations of alimentary tract effects indicated that mebendazole has no anticholinesterase activity.

Two Ames assays were negative for mutagenicity under the conditions tested. However, mebendazole was considered to be mutagenic in the absence of S9 when tested using continuous (24 hour) incubation in the mouse lymphoma assay, and induced aneuploidy via nondisjunction in cultured human peripheral blood lymphocytes in an in vitro micronucleus assay. In an in vivo micronucleus assay, mebendazole induced aneuploidy in polychromatic erythrocytes (PCEs) in the bone marrow of treated mice. These effects in dividing cells are postulated to be related to interference with microtubule function.

No effects on either male or female fertility in rats were reported when males were treated for at least 60 days prior to mating or when females were treated for 14 days prior to mating and through Day 21 of gestation with oral doses up to 40 mg/kg/day (HED = 6.7 mg/kg).

No embryotoxicity or teratogenicity were noted in hamsters and rabbits at doses up to 40 mg/kg/day (1.6-fold the maximum recommended human dose - MRHD - based on mg/m²). In mice, mebendazole was teratogenic at 10 mg/kg/day (approximately 0.1-fold the MRHD, based on mg/m²) and embryo-lethal at 40 mg/kg/day. In rats, fetal anomalies were noted at 2.5 mg/kg/day, and higher doses resulted in fetal resorption and decreased litter size. Fetal anomalies in both species were mainly skeletal involving ribs, limbs (especially hindlimbs), tail, skull, vertebrae and sternum. Other anomalies included soft or mixed tissue anomalies including exencephaly, facial cleft/cleft palate, anophthalmia/ small/displaced eyes, hydrocephalus, gastroschisis, coelosomy, enlarged atrio-ventricular valve, and unilateral renal and adrenal agenesis.

I agree with Dr. Nostrandt's recommendation to approve this NDA for a single dose of mebendazole in the treatment of STH, with labeling recommendations to include the a description of embryofetal toxicities in the Pregnancy/Animal Data section of labeling and to update the Nonclinical Toxicology section. Pregnancy labeling will be discussed later in this review.

5. Clinical Pharmacology

Dr. Abhay Joshi, Ph.D reviewed the clinical pharmacology for this application. His findings are summarized.

The Applicant conducted two PK studies in healthy adults, one to compare the bioavailability of the solid 500 mg oral tablet to the previous chewable tablet (Study GAI1001), and one to compare the bioavailability of the new chewable tablet under fed and fasted conditions (Study GAI1002). Administration of previous chewable tablet resulted in geometric mean ratios of C_{max} and AUC_{last} that were 1.6 and 2-fold higher than following the administration of solid oral tablet. 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. The relative PK results between solid oral tablet, the previous chewable table and the new chewable tablet under fasted conditions are shown in Table 1. Mebendazole systemic exposures from the previous chewable tablet and the new chewable tablet were similar, and both higher that the exposure resulting from the solid tablet. In comparison, mean C_{max} and AUC_{last} under fed conditions were 56.2 (35.8) ng/mL and 456 (249) ng.h.mL respectively.

Table 1: Comparison of Exposure Parameters Derived from Venous Plasma Sampling (Mean (SD), Range) Resulting from Different Formulations in Adults - Fasted

	500 mg Solid Tablet N = 18	500 mg Previous Chewable N = 18	500 mg New Chewable N = 16
C_{max} (ng/mL)	9.36 (7.74)	14.1 (10.3)	14.0 (9.17)
Range	1.31 – 29.6	3.07 – 37.1	3.95 – 40.6
AUC last (ng.h/mL)	79.9 (59.7)	134 (88.5)	175 (129)
Range	2.01 – 253	32.5 – 388	18.4 - 553

Source: Clinical Pharmacology Review – Table 3

In Study GAI1002, the Applicant also evaluated the reliability of measuring PK parameters obtained by whole blood fingerstick sampling by comparing these parameters measured using plasma venous sampling. Overall, drug concentrations measured by fingerstick were higher compared to venous samples, and some fingerstick samples had much higher mebendazole concentrations than the corresponding concentrations measured by plasma venous sampling, suggesting contamination by site personnel from dosing of the slurry that was prepared by dissolving the drug product on a spoon or subjects from contacting the mouth any time after dosing.

PK of the new/current formulation of chewable tablet was also evaluated in forty-four (44) patients enrolled in the Phase 3 study (GAI3003): Twenty-two were 1-<3 years of age, ten were 3 to 6 years of age and ten were 7 to 16 years of age. In the 1 to < 3 years of age group, the tablet was administered as a soft, semi-solid consistency by placing it on a spoon and adding 2-3 mL of water. Fingerstick samples were obtained in all patients, and venous blood samples were collected in patients in the 7 to 16 years age group.

Similar to the results of Study GAI1002, fingerstick whole blood sampling resulted in higher mebendazole concentrations compared to plasma venous sampling. The mean mebendazole systemic exposure from a single dose of 500 mg mebendazole chewable tablet was approximately 3 to 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 may be partially attributed to the fixed, non-weight normalized dosing and partially attributed to overestimation of mebendazole concentrations when using the fingerstick method. Dr. Joshi noted that because fingerstick measurements overestimate exposure, the highest exposures in children <3 years of age can be considered worst case scenarios. Exposures in older children were similar to exposures in adults.

During a pre-inspection visit(s) conducted by the Applicant on August 1-2 2016, the Applicant identified two children in the <3 years of age group who spit out the mebendazole tablet and should not have been included in the PK substudy. The original and amended mebendazole exposures are shown in Table 2. The amended exposures do not alter the overall conclusions of the PK substudy.

Table 2: Mean Capillary Whole Blood Mebendazole PK Parameters by Age Group and Comparison with the Plasma PK Parameter Estimates in Adults

	Reported Estimates				Compared to Adult Estimates (Fold Increase)		
	1 to <3 years [‡] N = ^{(b) (4)} 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
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)	^{(b) (4)} 739	101	52.1	156	^{(b) (4)} 4.7	0.6	0.3
Mean AUC_{last} (ng.h/mL)	^{(b) (4)} 1196	416	387	456	^{(b) (4)} 2.6	0.9	0.8
Maximum AUC_{last} (ng.h/mL)	^{(b) (4)} 2373	874	747	986	^{(b) (4)} 2.4	0.9	0.8

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

[¥]Adult PK parameter estimates are calculated from plasma samples in fed condition

Source: Adapted from Clinical Pharmacology Review, Table 5

Dr. Abhay notes that although mebendazole was higher in younger children and when administered with high fat food there was no apparent correlation between exposure and safety findings (see safety section). He recommended that Vermox Chewable tablet can be given without regard to meals/food.

Dr. Abhay recommended approval of this NDA. I agree with his recommendation.

6. Clinical Microbiology

Dr. Shukal Bala, PhD, conducted the clinical microbiology review. Her findings are summarized.

Mebendazole is an antihelminthic drug that interferes with cellular tubulin formation in the helminth and causes degenerative changes in its intestine. As a result, its glucose uptake and digestive and reproductive functions are disrupted, leading to immobilization, inhibition of egg production, and death of the helminth. In vitro and ex vivo studies indicate that mebendazole also inhibits the maturation of eggs from hookworms and whipworms. As a direct ovicidal effect of the drug, the eggs of the worms do not progress to the larval stage. However, there

does not appear to be any effect on the infective larvae of *A. duodenale* or *N. americanus* as the larvae incubated with mebendazole retained their ability to infect mice.

In rodents and dogs experimentally infected with different helminth species as well as naturally infected dogs, multiple doses of mebendazole were effective in reducing worm burden. [REDACTED] (b) (4)

There is a potential for development of resistance to mebendazole by helminths. Resistance appears to be due to a single nucleotide polymorphism at codon 200 in the parasite β -tubulin resulting in an amino acid substitution from phenylalanine to tyrosine. However, association between mutations in the β -tubulin of helminths and clinical response in subjects with STH infections has not been evaluated.

In the phase 3 clinical trial (Study GAI3003) to support the efficacy of a single 500 mg dose of mebendazole for the treatment of *A. lumbricoides* and *T. trichiura* infections, the parasitological measurements included identification of helminthic species and egg count in fecal samples by the Kato-Katz method. While *A. lumbricoides* and *T. trichiura* eggs can be identified by direct microscopic examination, the two hookworm species *A. duodenale* and *N. americanus* cannot be differentiated by direct microscopic examination of the eggs. On-site quality control (QC) was performed by experts from the [REDACTED] (b) (4) [REDACTED] at regular intervals on over 10% of the slides in a blinded manner. If there was discrepancy in egg count based on pre-specified criteria, reading of the slides and/or retraining of the technician was performed, under the supervision of the experts from the [REDACTED] (b) (4) [REDACTED] and a consensus value documented on the case report form.

The results of this study indicated mebendazole was superior to placebo in reducing egg counts to zero, but cure rates were higher for *A. lumbricoides* than for *T. trichiura*. Mebendazole was also effective in reducing egg counts for these two helminths, and resulted in clearance of the egg count in the small subset of patients with hookworm mixed infection.

The Applicant submitted published reports evaluating the effectiveness of single 500 mg mebendazole dose in the treatment of STH. The parasitological method used, number and quantity of stool specimens collected and processed for egg count, and time of collection of stool specimens post-treatment varied in different studies. Most of the studies enrolled children, but some also enrolled adults up to the age of 70 years. For *A. lumbricoides*, 22 studies were included, of which 11 were randomized and 4 were placebo-controlled. Cure rates for mebendazole varied between 72.5% and 100% and egg reduction rates varied between 90% and 100%. For *T. trichiura*, 24 studies were included of which 12 were randomized and 5 were placebo-controlled. Cure rates varied between 8.4% and 100%, and egg reduction rates varied between 31.6% and 93%. For hookworm, 24 studies were included, of which 14 were randomized and 8 were placebo controlled (six judged adequate by the statistics reviewer – see Efficacy section). The cure rate varied between 2.9% and 91.1% and egg reduction rate varied between 6.5% and 98.3%. Dr. Bala stated that the variability in response in the published literature was likely due to variability in the methods used, the patient population enrolled in the study including the age of the subjects, intensity of infection (which appears to be higher in

younger children compared to older children and adults), previous drug exposure, and nutritional status. However, both cure rates and egg reduction rates were higher in mebendazole treated subjects compared to the placebo group of patients across published studies.

Dr. Bala concluded that the phase 3 study indicates that a single 500 mg dose of mebendazole is effective in curing and reducing egg counts in patients infected with *A. lumbricoides*, *T. trichiura*, and in the subset of patients with [REDACTED] ^{(b) (4)}. She noted that despite the differences in study design, study population and procedures, the results of the published studies for mebendazole in the treatment of STH are comparable to those of Study GAI3003, and that overall, *A. lumbricoides* appears to be more sensitive compared to *T. trichiura*, [REDACTED] ^{(b) (4)}.

Dr. Bala recommended approval of this NDA. I agree with her recommendation.

7. Clinical/Statistical- Efficacy

Drs. Janelle Charles PhD and Sheral Patel MD conducted the efficacy review. Their findings are summarized.

The Applicant conducted one Phase 3 trial, GAI3003, to evaluate the efficacy of mebendazole chewable 500 mg tablet in the treatment of single or mixed infections due to *A. lumbricoides* and *T. trichiura*. This was a prospective, randomized, double-blind, placebo-controlled trial conducted at three study sites, two in Ethiopia and one in Rwanda.

Two hundred and ninety five (295) patients 1 to 16 years of age with single or mixed infections due to *A. lumbricoides* and *T. trichiura* confirmed by two Kato-Katz stool microscopy examination were randomized in 1:1 ratio to receive a single 500 mg dose of the new/currently proposed mebendazole chewable rapidly disintegrating tablet or matching placebo. Patients with mixed hookworm infection were included, but patients with hookworm only were excluded. Randomization was stratified by site and type of worm (i.e. *Ascaris* or *Trichuris*). If a patient had a mixed infection, the patient was to be assigned to the stratum of *Ascaris* until the desired sample size was achieved for this worm; afterward such patients were to be included in the *Trichuris* stratum.

After collection of stool sample at the test-of-cure visit (Day 19 – end of double-blind period), all patients received a single 500 mg mebendazole chewable tablet (open-label period).

The primary efficacy endpoint was clinical cure, defined as reduction of the egg count of the respective helminth that was present at baseline to zero, on Day 19.

Overall, 149 patients received mebendazole and 146 received placebo. There were 167 patients (86 randomized to mebendazole and 81 to placebo) confirmed with *A. lumbricoides* at baseline and 243 patients (124 randomized to mebendazole and 119 to placebo) confirmed with *T. trichiura* at baseline. Only 13 of the randomized patients were confirmed with hookworm at baseline.

Females accounted for 51.5% of patients. Approximately 5% were less than 2 years of age, 9% were 2 to <5 years of age, 70% of patients were 5 to <11 years of age, and 16% were between 11 and 16 years of age. Approximately 86% were enrolled at the two Ethiopian sites. Patient demographics were balanced in the two study arms. Distribution of egg density on stool examination was also balanced at baseline, with the majority of patients having moderate *Ascaris* infection (5000-49999 eggs/g stool) and light *Trichuris* infection (1-999 eggs/g stool).

Approximately 94% of patients in both study arms completed the double blind period. Reasons for withdrawal were balanced between the two arms.

Efficacy results are presented in Table 3. A single 500 mg mebendazole chewable tablet was superior to placebo for clinical cure for both *A. lumbricoides* and *T. trichiura*. While mebendazole also seemed superior to placebo in patients with mixed hookworm infection, the numbers are small and the confidence interval for the difference large.

Table 3: Cure Rates for Single or Mixed Infection with *A. lumbricoides* and *T. trichiura*, and Mixed Infection with Hookworm - ITT

Infection Type	Mebendazole N = 149	Placebo N = 146	Difference ¹ (95% CI)
<i>A. lumbricoides</i>			
	N = 86 n (%)	N = 81 n (%)	
Cure	72 (83.7)	9 (11.1)	72.6 (62.3, 82.7) ²
Failure	9 (10.5)	67 (82.7)	
Missing	5 (5.8)	5 (6.2)	
<i>T. Trichiura</i>			
	N=124 n (%)	N=119 n (%)	
Cure	42 (33.9)	9 (7.6)	26.2 (16.7, 35.6) ²
Failure	76 (61.3)	103 (86.6)	
Missing	6 (4.8)	7 (5.8)	

(b) (4)

¹Difference in cure rates, expressed in percentages, and based on Mantel Haenzel methods to account for stratification by site.

²P-value <0.001 based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.

Failures include patients who tested positive for the worm at Visit 3 (Day 19, i.e. test-of-cure).

Source: Statistics Review, Tables 1 and 4

Clinical cure rates for *A. lumbricoides* were similar in females and males and similar across the age groups. For *T. trichiura*, cure rates were numerically lower in males compared to females, and numerically lower in 2-5 years age group compared to the other age groups. However, the number of patients in the 2-5 years age group is low. As all patients were black/African, no

analysis by race was done. Cure rates by study site were numerically lower in Rwanda compared to Ethiopia for *A. lumbricoides*, but overall similar for *T. trichiura* (Table 4).

Table 4: Clinical Cure Rates for *A. lumbricoides* and *T. trichiura* by Study Site

	Mebendazole n/N (%)	Placebo n/N (%)	Difference
<i>A. lumbricoides</i>			
Ethiopia	59/68 (86.8)	6/66 (9.1)	77.7 (67.0, 88.3)
Site 251001 (Gondar)	27/33 (81.8)	1/33 (3.0)	78.8 (58.7, 91.3)
Site 251002 (Jimma)	32/35 (91.4)	5/33 (15.2)	76.3 (60.9, 91.6)
Rwanda (Site 250001)	13/18 (72.2)	3/15 (20.0)	52.2 (18.3, 77.3)
<i>T. Trichiura</i>			
Ethiopia	35/103 (34.0)	8/101 (7.9)	26.1 (15.5, 36.6)
Site 251001 (Gondar)	14/31 (45.2)	5/29 (17.2)	27.9 (5.7, 50.2)
Site 251002 (Jimma)	21/72 (29.2)	3/72 (4.2)	25.0 (8.1, 40.8)
Rwanda	7/21 (33.3)	1/18 (5.6)	27.8 (-4.7, 56.7)

Source: Statistics Review, Tables 8 and 9

There were 109 patients (59 mebendazole and 50 placebo) who were infected with both *Ascaris* and *Trichuris*. Among these patients, the clinical cure rate, i.e. percentage of patients with zero egg count for both worms, was 37.2% for mebendazole and 6.0% for placebo, resulting in a difference in cure rate of 31.3%; 95% CI (12.7%, 48.2%).

For the secondary endpoint of reduction in egg count, a logarithmic transformation was first performed on the baseline and post-treatment average patient level egg counts to account for the positively skewed distribution of the egg count data. Because of the skewed distributions of egg counts for each STH worm and the paired nature of the data, Dr. Charles reported the egg count reduction rates based on the geometric mean of the of the relative change of logarithmic transformed egg count from baseline to test of cure rather than based on arithmetic mean as proposed by the Applicant. Egg reduction rates on Day 19 are presented in Table 5.

Table 5: Egg Reduction Rates for *A. lumbricoides* and *T. trichiura*

	Mebendazole	Placebo
<i>Ascaris lumbricoides</i>		
Baseline (eggs/g)		
N	86	81
Geometric Mean	5801.3	6259.0
Median (Range)	9389.6 (48 - 117384)	10560.0 (36 - 90840)
Post-treatment, (eggs/g)		
N	81	76
Geometric Mean	1.9*	2116.4
Median (Range)	0 (0 - 20064)	5932.9 (0 - 143040)
Egg Count Reduction Rate	100%	30%
<i>Trichuris trichiura</i>		
Baseline (eggs/g)		
N	124	119

Geometric Mean	209.2	270.8
Median (Range)	168 (12 - 8808)	264 (12 - 5916)
Post-treatment, (eggs/g)		
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%

*p-value<0.001 for difference in mean egg counts, based on analysis of covariance in which the log transformed posttreatment egg count is the dependent variable with site and treatment as fixed effects and the log transformed baseline egg count as a covariate.

Source: Statistics Review, Tables 5 and 6

Thirteen (13) patients had hookworm infection in addition to *A. lumbricoides* and/or *T. trichiura* infection. (b) (4)

The Applicant submitted published literature evaluating the effectiveness of single 500 mg mebendazole tablet in the treatment of STH. Results as reported by the Applicant are shown in Table 6. These studies were also summarized in the microbiology review that noted that there were differences in the methodology used and timing of assessment.

Table 6: Literature Summary of Efficacy of 500 mg Single Dose Mebendazole Against STH

Arm	N of Studies	N Patients with Cure Rate Data	Cure Rate, %	Range of Cure Rate, %	N Patients with Egg Reduction Data, %	Overall Egg Reduction, %	Range of Egg Reduction, %
<i>A. lumbricoides</i>							
All Studies							
Mebendazole	22	2771	92.5	72.5-100	3689	98.5	89.9 – 100
Placebo-Controlled Studies							
Mebendazole	4	611	84.6	72.5 – 98	611	98.1	96.1 – 99
Placebo	3	285	21.0	0-27.9	285	23.9	6.0 – 33.9
<i>T. trichiura</i>							
All Studies							
Mebendazole	23	4407	27.6	8.4-100	5417	72.9	31.6 - 93
Placebo-Controlled Studies							
Mebendazole	5	1147	33.4	22.9 – 77.6	1147	86.8	81.0 – 92.8
Placebo	4	704	9.5	0 – 18.6	704	16.4	-11.7 – 21.2

(b) (4)

(b) (4)

Dr. Charles concluded that the results of Study GAI3003 indicated the superiority of mebendazole compared to placebo and provided substantial evidence to support the efficacy of mebendazole for the treatment of single- or mixed-infection with *A. lumbrocoides* and *T. trichiura*. She recommended approval for these two helminths. (b) (4)

(b) (4)

Dr. Patel also concluded that the results of Study GAI3003 indicate that mebendazole is effective in the treatment of *A. lumbrocoides* and *T. trichiura*, (b) (4)

(b) (4) She noted that the published literature indicates higher mebendazole efficacy in cure and egg reduction compared to placebo, and that mebendazole has been a key component of periodic deworming campaigns. As already noted in the microbiology review, Dr. Patel acknowledged that the cure rates reported in this study and in the literature indicate that *A. lumbricoides* is more responsive to treatment (b) (4). She recommended approval for mebendazole in the treatment of STH as requested by the Applicant.

I agree with Drs. Charles and Patel that Study GAI3003 has demonstrated substantial evidence of efficacy of single dose 500 chewable mebendazole tablet in the treatment of *A. lumbricoides*

and *T. trichiura*. Cure rates and egg reduction rates reported in this study are in accordance with what is reported in the literature.

(b) (4)

Additionally, although the Phase 3 study enrolled children 1-16 years of age, I recommend that mebendazole 500 mg chewable be approved for patients greater than 1 year of age, with no upper age restriction for several reasons. First, Study GAI3003 did not show a differential response between children as young as one year of age and older children up to the age of 16. Second, although the published literature in adults is quite limited as most of the published studies were conducted in children (who are more commonly affected than adults), did not report age specific treatment response, and/or did not include a control arm. These studies are summarized below.

In the study by Abadi et. al³, 156 patients between 2 and 70 years of age with *A. lumbricoides*, *T. trichiura* and (b) (4) infections were randomized to receive single 500 mg mebendazole dose or placebo. Of the 156 patients, 105 were children (implying that 51 were adults). Cure rates were reported for the entire population and not specifically reported by age. Overall mebendazole cure rates for ascariasis, trichiuriasis (b) (4) were 93.4%, 77.8%, and 91.1% respectively. In comparison, placebo cure rates were zero for all. Mebendazole egg reduction rates for ascariasis, trichiuriasis and hookworm were 99%, 92.8% and 98.3% respectively, whereas placebo egg reduction rates were 6%, 10.7%, and 13.5% respectively. The study by Albonico et al⁴. enrolled 446 patients of “any age” with ascariasis, trichiuriasis (b) (4). Although the number of adults was not specified, the report included graphs showing similar rates of egg reduction in each age group. Cure rates for ascariasis, trichiuriasis (b) (4) were 93.2%, 25.6% and 17.8% respectively. Gorodner et al⁵. reported on 300 patients 5 to 60 years of age who received a single 500 mebendazole for the treatment of STH. Cure rates at Day 15 for ascariasis (b) (4) were 89% and 78% respectively. Cure rates at Day 30 were 89% and 91%. This study did not report the number of adults

³ Abadi K. Single dose mebendazole therapy for soil-transmitted nematodes. Am J Trop Med Hyg 1985;34(1):129-33.

⁴ Albonico M, Renganathan E, Bosman A, et al. Efficacy of a single dose of mebendazole on prevalence and intensity of soil-transmitted nematodes in Zanzibar. Trop Geogr Med 1994a; 46(3):142-6.

⁵ Gorodner JO. Treatment of intestinal parasite infections with a single dose of mebendazole (translation from Spanish). Unpublished internal report, 1987 (LMD 59167/2). (Submitted in NDA 108398)

enrolled or cure rates by age. Jongsuksuntigul et al⁶. reported on 56 patients 3 to 80 years of age from one village who received a single 500 mg dose. The cure rates for ascariasis, trichiuriasis (b) (4) were 100%, 70.3% and 30.2% respectively. Although this study did not report the number of adults enrolled or the cure rate by age, the prevalence of STH infection in that village was 92.9%. Louba et al⁷. reported on 827 pregnant women 14-47 years of age who received single 500 mg mebendazole. Cure rates for ascariasis, trichiuriasis (b) (4) infection were 79%, 70% and 41% respectively. (b) (4)

Larocque et al . randomized 1042 pregnant women 18-44 years of age with STH to receive mebendazole or placebo iron. The study primary objective was to evaluate birth weight. Mebendazole cure rates for ascariasis, trichiuriasis (b) (4) were 72.5%, 39.1% and 30.7% respectively. Mebendazole egg reduction rates were 98.3%, 92.9%, and 60.8% respectively. Placebo rates were not reported. However, the study included graphs of the prevalence of infection showing clear reduction in mebendazole vs. placebo as shown below.

⁶ Jongsuksuntigul P, Jeradit C, Pornpattanakul S, Charanasri U. A comparative study on the efficacy of albendazole and mebendazole in the treatment of Ascariasis, hookworm infection and Trichuriasis. Southeast Asian J Trop Med Publ Health 1993; 24(4):724-9.

⁷ Luoba AI, Geissler PW, Estambale B. Earth-eating and reinfection with intestinal helminths among pregnant and lactating women in western Kenya. Trop Med Int Health 2005; 10(3):220-7.

⁸ Sacko M, De Clercq D, Behnke JM, et al. Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the Southern Region of Mali, West Africa. Trans Roy Soc Trop Med Hyg 1999; 93:195-203.

⁹ Larocque R, Casapia M, Gotuzzo E, et al. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. Trop Med Int Health 2006; 11(10):1485-95.

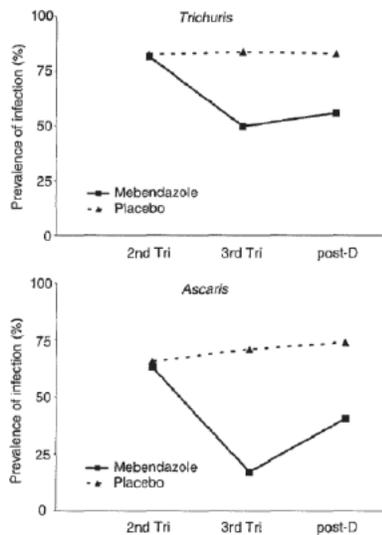


Figure 2 Prevalence of hookworm, *Trichuris* and *Ascaris* infection during pregnancy. 2nd Tri, second trimester (baseline); 3rd Tri, third trimester; post-D, post-delivery.

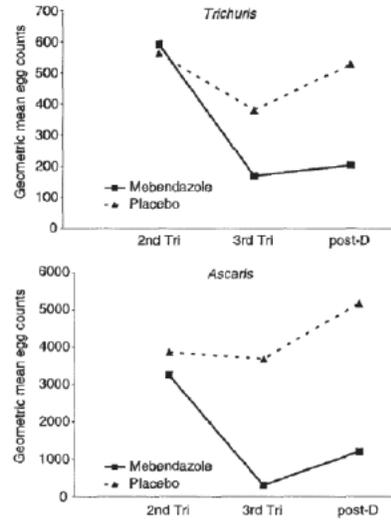


Figure 3 Geometric mean egg counts of hookworm, *Trichuris* and *Ascaris* infection during pregnancy. 2nd Tri, second trimester (baseline); 3rd Tri, third trimester; post-D, post-delivery.

Source: Larocque R, Casapia M, Gotuzzo E, et al. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health* 2006; 11(10):1485-95.

Third, mebendazole acts intraluminally; antihelminthic effect is expected to be the same regardless whether the worm resides in the intestine of a child or an adult. Fourth, the worm burden tends to be higher in children compared to adults. If the drug is effective in the treatment of high worm burden, it stands to reason that it would be effective in the treatment of lower burden. Fifth, there are no safety concerns. Mebendazole has low bioavailability. There is extensive postmarketing safety data, as at least 845 million doses have been dispensed worldwide since 1988, and systemic exposure in adults is lower compared to children 1-3 years of age, and is comparable to children >3 years of age. Sixth, mebendazole 100 mg is already FDA-approved and indicated for the treatment of STH in patients 2 years of age or older, with no upper age restriction and no change in treatment dose or duration.

For products that are studied in adults, approval is extended to children based on similarity of pathophysiology of the disease that justify partial extrapolation of efficacy from the adult studies with further studies to evaluate safety. One can argue for a similar but reverse approach, partial extrapolation of efficacy from children to adults based on similar pathophysiology, and the already existent extensive postmarketing database.

My recommendation is therefore to approve single 500 mg mebendazole chewable tablet for the treatment of patients one year of age or older with *A. lumbricoides*, *T. trichiuris*, ^(b)₍₄₎ [REDACTED] infections without an upper age restriction.

8. Safety

Dr. Sheral Patel MD conducted the safety review. Her findings are summarized.

Safety data were included for the four clinical studies submitted in this NDA (GAI1001, GAI1002, GAI3002 and GAI3003). In Study GAI3003, all enrolled subjects received a dose in the open-label phase after the efficacy visit/at the conclusion of the double blind phase. Overall, 712 subjects received at least one 500 mg mebendazole dose (solid tablet and both versions of the chewable tablet), including 536 children who received one 500 mg dose and 141 children and 35 adults who received two 500 mg doses.

Study GAI1001 used solid and previous chewable tablet formulation, and GAI1002 used previous and current/new chewable formulation. These two studies enrolled a total of 35 adults. Study GAI3002 enrolled children 2 to 10 years of age, used the previous chewable tablet and recorded treatment emergent adverse events (TEAE) on Days 1 and 3 whereas Study GAI3003 enrolled children 1 to 16 years of age, used the current/new chewable tablet and recorded TEAEs on Days 1, 19 and 26. The Applicant and Dr. Patel did not integrate the safety results across studies, but presented them separately due to the differences in age, the formulation used, feeding status and the follow up period.

There were no TEAEs reported in Study GAI1001. TEAEs were more frequent in the fasted versus the fed state in Study GAI1002 (31.3% versus 6.3%). However, no single TEAE was reported in more than one subject. There were no deaths, no serious adverse events and no discontinuations due to an adverse event in either study. Of note, mebendazole exposures were higher in the fed state (see Clinical Pharmacology section).

In Study GAI3002, 396 subjects between 2 and 10 years of age received one 500 mg mebendazole tablet. Median age was 4 years, 190 were female and all were black. 62 were less than 3 years of age, 271 were 3 to 6 years of age and 63 were 7 to 10 years of age. There were no deaths and no serious adverse events. 6 subjects (1.5%) were withdrawn due to failure to consume the study medication. 11% experienced at least one TEAE. The most common TEAEs were pyrexia (2.8%), diarrhea (2.5%), lymphadenopathy (2.0%) and cough (1.3%). The incidence of TEAE was similar across age groups.

In Study GAI3003, 144 subjects received one mebendazole dose in the double-blind phase and a total of 281 received a dose during the open label phase. The median age was 8 years. In the double blind phase, 12 subjects were less than 3 years of age, 31 subjects were 3 to <7 years of age and 101 subjects were 7 to 16 years of age. In the open-label phase, the distribution across the less than 3, 3 to <7 and 7 to 16 years was 22, 55 and 201 subjects respectively. All were black. There were no deaths and no serious adverse events. The frequency of TEAE was

similar in mebendazole and placebo recipients in the double blind phase (6.3% vs. 5.7%), but higher in the open-label phase (4.3% vs. 0.7%). No TEAE occurred in more than one subject.

No laboratory assessments were done for studies GAI30002 and GAI3003.

Dr. Patel analyzed AEs by feeding state and age. In the double blind phase of Study GAI3003, the incidence of TEAEs was higher in the fasted state in both the mebendazole and placebo arms: mebendazole, fed 4.7%/fasted 8.5% versus placebo fed 2.5%/fasted 10.2%. This was similar to the finding of higher incidence of TEAEs in the fasted state in Study GAI1002 in adults. In the open-label phase, AEs were similar in fasted and fed states (2.2% fed, 2.9% fasted). Dr. Patel concluded that the higher systemic exposure noted in the fed state compared to the fasted state did not correlate with increased incidence of AEs.

The frequency of TEAEs was similar in all age subgroups in Studies GAI3002 and GAI3003. Dr. Patel concluded that the higher systemic exposure noted in younger children did not correlate with the frequency of AEs. She also noted that the higher systemic exposure in younger children may be partially due to fingerstick sampling that was employed in the youngest children which may result in contaminated samples from drug residual, and that the published literature supports safety in children 1 to 3 years of age. She concluded that the clinical relevance of higher systemic exposure in the youngest age group is not clear.

In addition to the safety evaluation from the submitted clinical studies, the Applicant submitted an analysis of Adverse Drug Reactions from in-house confidential, unpublished 39 clinical trial reports for subjects treated with any dose of mebendazole for intestinal helminth infections. These studies included more than 4500 female and male subjects 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. AEs were reported in less than 5% of subjects, and included vomiting, diarrhea, abdominal pain/cramps, anorexia, nausea, flatulence, headache and rash.

The Applicant also 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/quinfamide. Interval exposure to mebendazole and mebendazole/quinfamide from 01 May 2015 to 30 April 2016 was approximately 35 million treatment courses. Approximately 4 million treatment courses were dispensed as a 500 mg chewable tablet (different than proposed) and 5 million treatment courses were dispensed as an oral solution, suspension or syrup. Cumulative exposure to mebendazole and mebendazole/quinfamide from 1988 to 30 April 2016 was approximately 845 million treatment courses for all formulations. Approximately 50% of the doses were estimated to be given to children less than 18 years of age. Reported AEs were overall similar to those from the unpublished clinical studies and from the clinical studies supporting this NDA. However, the Applicant identified potential risks that included choking with the solid oral formulation, and two cases of convulsions in infants, 4 and 8 weeks of age, who respectively received mebendazole 600 mg over 3 days and 50 mg bid for 3 days as their siblings were being treated for pinworm infection. Both infants developed status epilepticus and fully recovered without neurologic sequelae. Other identified risks included Stevens-Johnson syndrome when co-administered

with metronidazole, and hematologic abnormalities including neutropenia and liver function abnormalities. Dr. Patel noted that cases of agranulocytosis and glomerulonephritis have been reported in patients administered higher doses of mebendazole for prolonged duration in the treatment of hydatid disease. She recommended adding glomerulonephritis, agranulocytosis and seizures to the postmarketing section of labeling. The 100 mg mebendazole labeling includes neutropenia and agranulocytosis associated with higher doses and longer duration in the Warnings section, and the current label will include a similar warning. Additionally, the current label will include a Warning regarding potential for seizures in infants.

Dr. Patel concluded that the finding of few non-serious TEAEs in the conducted clinical studies is supported by the Applicant's safety evaluation of internal study reports and more than 40 years of postmarketing experience. She also concluded that there was no discernible relationship of TEAEs and feeding status or age in the clinical studies. She recommended approval of this NDA with the above labeling recommendations.

9. Advisory Committee Meeting

An advisory committee meeting was not held.

10. Pediatrics

Mebendazole 500 mg chewable tablet was granted Orphan Designation and is exempt from the Pediatric Research Equity Act (PREA) requirements. However, the Phase 3 study establishing efficacy and safety in the treatment of STH was conducted in children 1 year of age or older. Labeling will include a statement that safety and effectiveness have not been established in children younger than one year of age, however, seizures have been reported in this age group.

11. Other Relevant Regulatory Issues

Financial disclosures were submitted for all investigators and subinvestigators involved in the clinical studies supporting this application, and were deemed adequate.

The Phase 3 study was conducted at 3 clinical site, two in Ethiopia (Jimma and Gondar) and one in Rwanda (Kigali). The Office of Scientific Investigations, Division of Clinical Compliance Evaluation, was consulted on May 23, 2016 to inspect the two Ethiopian sites that enrolled 255 of the 295 subjects in the study. The Gondar site could not be inspected due to security concerns and travel restrictions. Inspection of the Jimma site which enrolled 156/295 subjects (55%) was concluded on September 21, 2016. No significant GCP deficiencies were observed and a Form FDA 483 was not issued. The OSI reviewer, Dr. John Lee MD, stated that the study conduct appeared GCP-compliant, including sponsor oversight of study conduct, and that all audited data were adequately verifiable against source records and CRFs. He concluded that the data from this clinical investigator appear reliable as reported in the NDA.

The Applicant conducted preinspection visits on August 1 and 2, 2016 and identified protocol deviations related to Quality Control (QC) and PK substudy. The protocol deviations regarding

QC involved failure of accurate transcription of the concensus value of the stool egg count to the case report form. This was noted in 11 QC check stool samples from 9 patients, and impacted the outcome of cure in 3 patients. The Applicant also provided documentation regarding QC checks from Rwanda site, as the need for concensus based on predefined specifications seemed higher at that site. Overall, QC checks were done on 74% of the samples and concensus rapidly improved with technician training. The review team (microbiology, statistics and clinical) agreed that these deviations do not affect the efficacy conclusions of the trial and recommended against amending cure rates in labeling or including Clinical Study Report errata. The PK protocol deviations were discussed in the Clinical Pharmacology section of this review, and affected two patients. The clinical pharmacology reviewer indicated that the amended results did not affect the conclusions of the study.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) had conditionally agreed to the proposed proprietary name “Vermox™ Chewable” under IND 115,959 in December 2015. The FDA June 2016 Draft Guidance for Industry entitled, ‘Quality Attribute Considerations for Chewable Tablets’, states that the nomenclature, “[DRUG] Chewable Tablets” is to be used for tablets that *must* be chewed and for which there is no alternative route of administration. As mebendazole chewable tablet may also be given as a semi-solid slurry, the review team discussed the appropriateness of using the word “chewable” to describe this product in labeling with the Office of Product Quality (OPQ) (Yana Mille, RPh and Richard Lostritto, PhD). The term “chewable” was considered appropriate, as the tablet is too large to be swallowed whole and must be chewed, and the semi-solid slurry that may be given is too thick to be considered a suspension and is unlikely to be swallowed without further chewing.

Labeling will include the following:

INDICATIONS AND USAGE: This reviewer recommends granting the indication of treatment of *A. lumbricoides*, *T. trichiura*, (b) (4) to patients one year of age or older (u) (4) (b) (4)

The exact wording of the indication is pending at the time of filing of this review.

DOSAGE AND ADMINISTRATION: will include instructions to chew the tablet, or alternatively, to administer as a slurry after addition of 2-3 mL of water.

WARNINGS AND PRECAUTIONS: Warnings will include the risk of convulsions in infants, agranulocytosis associated with prolonged use and skin reactions with concomitant metronidazole use.

ADVERSE EVENTS: will describe safety findings from Studies GAI3002 and GAI3003, in addition to description of reported postmarketing AEs.

SPECIAL POPULATIONS

Pregnancy and Lactation: The Office of Pediatric and Maternal Health provided input for Pregnancy and Lactation Labeling. The Applicant submitted several published reports, including prospective pregnancy registries, case control retrospective cohorts, cross sectional trials and fertility registries involving several thousand patients evaluating potential mebendazole effects on the fetus, including congenital anomalies, stillbirths and low birth weight. There are no differences in fetal outcomes (teratogenicity or stillbirths) between women exposed to mebendazole during pregnancy and those who were not. The pregnancy section will describe the Animal Data that indicate the potential for teratogenicity and embryoletality noted in mice and rats (but not rabbits and hamsters). A statement that “several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association with mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific pattern or frequency of major birth defects with mebendazole use” will be included under Human Data.

The Lactation section will indicate that a small amount of mebendazole is present in human milk and that the limited data preclude clear determination of risk to the infant.

Pediatric Use: will include a statement that the safety and effectiveness of mebendazole chewable in the treatment of STH was demonstrated in children 1 to 16 years of age, and a statement that convulsions have been reported in infants less than one year of age.

CLINICAL STUDIES: The results of Study GAI 3003 will be described.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The identified safety concerns can be adequately addressed in product labeling. REMS is not required.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are recommended.

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

/s/

HALA H SHAMSUDDIN
10/11/2016