CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208398Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Summary Review
NDA #	208398
Applicant	Janssen Research & Development, LLC
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 tablets/500 mg
Applicant Proposed Indication(s)/Population(s)	For treatment of (b) (4) gastrointestinal (b) (4) by *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), (b) (4)
Action	Approval
Approved Indication/Population(s) (if applicable)	For treatment of patients one year of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sheral Patel MD
Statistical Review	Janelle Charles PhD
Pharmacology Toxicology Review	Amy Nostrandt DVM PhD
OPQ Review (ATL)	Dorota Matecka PhD
Microbiology Review	Shukal Bala PhD
Clinical Pharmacology Review	Abhay Joshi
OPDP	Adam George PharmD
OSI	John Lee MD
CDTL Review	Hala Shamsuddin MD
OSE/DMEPA	Deborah Myers RPh, MBA

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
ATL: Application Technical Lead
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Soil transmitted helminth (STH) infections are a significant cause of morbidity in certain parts of the world and preponderantly affects children. Although these infections can be asymptomatic in some patients, it can lead to long term effects on growth and cognitive functioning. The only FDA approved drug for the treatment of STH including *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale* is mebendazole 100 mg tablets. The current dosing regimen entails use of mebendazole for up to three days.

In this NDA, the Applicant has provided adequate evidence to support the safety and effectiveness of mebendazole chewable 500 mg tablet as a single dose in patients 1 year of age and older for the treatment of gastrointestinal infections due to *A. lumbricoides* and *T. trichiura*. In the placebo-controlled clinical trial (GAI3003), mebendazole chewable tablet 500 mg was superior to placebo for treatment of both *A. lumbricoides* and *T. trichiura* infections either as single or mixed infections. In the ITT population, for both *A. lumbricoides* and *T. trichiura*, the clinical cure rate observed at the test of cure visit in the mebendazole arm was superior to that in the placebo arm. The observed cure rates for *T. trichiura* were lower than that observed for *A. lumbricoides*. For the secondary endpoint of egg count reduction, mebendazole was superior to placebo for both *A. lumbricoides* and *T. trichiura*. The finding of superiority in the single adequate and well-controlled trial is supported by data from the published literature. Cure rates seen in Study GAI3003 are consistent with that reported in the literature. While Study GAI3003 only enrolled pediatric patients 1-16 years of age, the Applicant has provided adequate justification to support the indication in adults. Systemic exposure in children and adults who received the chewable tablet 500 mg was similar with the exception of the youngest cohort, suggesting that similar amounts of mebendazole remain intraluminally. Infections due to STH in adults are expected to have a similar clinical course as in children. In Study GAI3003, efficacy rates were comparable across various age cohorts further suggesting that efficacy is not directly related to systemic exposure or to the dose received in mg/kg. Of the published studies, five enrolled adults and cure rates in these trials were similar to that seen in the pediatric population.

Data on efficacy against hookworm infections in Study GAI3003 were very limited as only 13 patients with hookworm infections were enrolled in this trial and in all 13 patients, hookworm was identified as part of a mixed infection due to *A. lumbricoides* and *T. trichiura*. Patients with single infections due to hookworm were excluded. The primary hypotheses in this study were to evaluate efficacy of mebendazole against *A. lumbricoides* and *T. trichiura* in a sequential manner. Demonstration of efficacy against hookworms was not one of the primary assessments in the trial. (b) (4)

(b) (4)

No new safety signals were identified in Study GAI3003. Safety profile of mebendazole chewable 500 mg tablet was similar to the known safety of mebendazole. In Study GAI3003, safety in the 1-3 year age cohort appeared to be similar to that of older children. Labeling will include a warning about risk of seizures in children less than a year of age based on postmarketing reports, risk of agranulocytosis and neutropenia when mebendazole is used at higher doses and for more prolonged durations, and risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) with the concomitant use of mebendazole and metronidazole.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Soil-transmitted helminth (STH) infections are among the most common infections worldwide and affect the poorest and most deprived communities. Approximately 2 billion people are infected with STH worldwide. They are transmitted by eggs present in human feces which then contaminate soil in areas of poor sanitation. The main species that infect humans are the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*). (http://www.who.int/mediacentre/factsheets/fs366/en/) *A lumbricoides* is the most prevalent of all human intestinal nematodes with more than 1 billion people infected worldwide. Infections with *A. lumbricoides* are often asymptomatic. It can also lead to malnutrition, nonspecific gastrointestinal tract symptoms, and during the larval migratory phase, an acute transient pneumonitis associated with fever and marked eosinophilia. Acute intestinal obstruction has been associated with heavy infections. Worm migration can cause intestinal perforation, peritonitis and common bile duct obstruction resulting in biliary colic, cholangitis, or pancreatitis. *T. trichiura* is the second most common STH in the world. It is co-endemic with round worm and hookworm species. Humans are the natural reservoir. Disease caused by *T. trichiura* can be	STH infections are a significant cause of morbidity in certain parts of the world. It is more common in children and although can be asymptomatic, it can cause significant illness in children with higher worm burden and lead to long term effects on growth and cognitive functioning.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	asymptomatic, result in colitis, abdominal pain, tenesmus, bloody diarrhea, and rectal prolapse. *Necator americanus* is the major cause of hookworm infection worldwide, although *A. duodenale* also is an important hookworm in some regions. Patients with hookworm infection often are asymptomatic. Chronic hookworm infection can cause severe hypochromic, microcytic anemia and in children may lead to physical growth delay, deficits in cognition, and developmental delay.	
Current Treatment Options	Mebendazole tablet is FDA-approved and is indicated 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. It is available as 100 mg chewable tablets and is administered as a single dose for pinworm infections and twice a day for three days for the other three helminthic infections. Albendaazole, ivermectin, pyrantel pamoate, and nitazoxanide are used off-label for treatment of STH. Albendazole and ivermectin are used for treatment of whipworm and roundworm infections. Nitazoxanide is used for treatment of ascariasis. Albendazole and pyrantel pamoate are used for the treatment of hookworm infections. WHO recommendations for treatment include albendazole and mebendazole. As a control strategy, WHO also recommends periodic anthelmintic treatment to all at-risk people living in endemic areas.	There is a need for new therapies for the treatment of STH. Vermox Chewable tablet offers the benefit of being a single dose and allows for administration to young children who cannot swallow by softening it with a small quantity of water.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	In a randomized, placebo-controlled study (Study GAI3003) in children 1-16 years of age, cure rates were higher in children who received a single 500 mg mebendazole chewable tablet compared to placebo for *A. lumbricoides* and *T. trichiura.* In addition to data from this single randomized controlled trial, supportive information was provided from the published literature to support the efficacy of mebendazole for gastrointestinal infections due to *A. lumbricoides* and *T. trichiura.*	In the Phase 3 clinical trial, a single dose of mebendazole 500 mg chewable was superior to placebo for *A. lumbricoides* and *T. trichiura* in children 1-16 years of age. The published studies support the findings from this single adequate and well controlled trial.
Risk	In Study GAI3003, no deaths or serious adverse events were reported. Treatment emergent adverse events were similar between mebendazole and placebo recipients. In addition to data from this clinical trial, the Applicant provided postmarketing safety data and data from internal unpublished studies. There were two reports of young infants (≤2 months of age) who developed seizures after receiving mebendazole. Pharmacokinetic data showed that children 1-3 years of age had higher systemic exposures. There was no difference in the adverse event profile between the younger and older cohorts.	The safety profile of mebendazole is well characterized. There is extensive experience with use of this product (various doses, formulations, and dosing regimens). Product labeling adequately describes the risks associated with mebendazole.
Risk Management	Labeling will include warnings about the risk of seizures, risk of agranulocytosis and neutropenia when mebendazole is used at higher doses and for more prolonged durations, and risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) with the concomitant use of mebendazole and metronidazole.	Besides routine pharmacovigilance, no additional risk mitigation strategies are required at this time.

2. Background

New Drug Application (NDA) 208398 was submitted by Janssen Research and Development, LLC to seek an approval of mebendazole 500 mg chewable tablet as a single dose for the treatment of of gastrointestinal infections caused by *A. lumbricoides* (roundworm), *T. trichiura* (whipworm), and [redacted] (b) (4) This NDA is covered under section 505(b)(2) of the Food Drug and Cosmetic Act as the Applicant is relying in part on the published literature to support the data from the clinical studies conducted by the Applicant.

Mebendazole is a benzimidazole derivative that was initially approved in 1974 as chewable 100 mg tablets (Vermox, NDA 017841) 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. Marketing in the US was discontinued for commercial reasons in 2006.

Mebendazole is currently marketed in many countries and is available as different formulations, including solid oral tablets, chewable tablets, and oral suspension. The Applicant is currently donating 500 mg mebendazole solid oral tablets to the World Health Organization (WHO) for distribution to countries with moderate-to-high prevalence of STH infections.

In support of this NDA, the Applicant has submitted data from the following four clinical studies:

1. MEBENDAZOLGAI1001: A relative bioavailability study of a new chewable tablet formulation of mebendazole compared to the currently marketed tablet in healthy adult subjects.
2. MEBENDAZOLGAI1002: A study of the bioavailability of a rapidly disintegrating chewable tablet formulation of mebendazole in healthy adult subjects.
3. MEBENDAZOLGAI3002: A single-arm, open-label safety study in children 2-10 years of age living in a high prevalence area, where parasite infection was endemic.
4. MEBENDAZOLGAI3003: A Phase 3 efficacy and safety study in children 1-16 years of age.

In addition, the Applicant submitted a review of the literature to support the efficacy of the single dose of 500-mg mebendazole for treating STH infections.

3. Product Quality

The Application Technical Lead for this NDA is Dorota Matecka, PhD. The mebendazole drug substance is manufactured [redacted] but practically insoluble in water and various organic solvents [redacted] The drug substance can exist as [redacted] The Applicant provided information to confirm that the mebendazole used in the manufacture of the currently proposed mebendazole chewable tablets is polymorph C. The proposed acceptance criteria for impurities were revised during the review and the drug substance specification was found to be adequate. The detailed chemistry, manufacture and control information for the mebendazole drug substance has been provided via a reference to DMF [redacted]. This DMF was reviewed and found to be adequate in support of the NDA.

The drug product, mebendazole chewable tablet, 500 mg, is round, white to yellowish and debossed. The inactive ingredients include crospovidone, magnesium stearate, microcrystalline cellulose [redacted] povidone [redacted], strawberry flavor, sucralose, and water. All the excipients are compendial except for the strawberry flavor. Information for the strawberry flavor is provided via a reference to DMF [redacted] which was reviewed in support of this NDA and found to be adequate. The proposed drug product specification was found to be adequate following the revision of the acceptance criterion for dissolution.

The commercial drug product packaging configuration includes white, [redacted] polyethylene (HDPE) bottle with [redacted] closure, with induction seal liner, containing 200 tablets each. The suitability of the container-closure system was demonstrated by adequate stability data.

Stability data for [redacted] were provided. Additionally, tablets from each batch were tested in a light cabinet exposed on a Petri dish. There are no obvious trends and no out of specification results except for [redacted]. In-use studies were conducted in which tablets were mixed with 2-3 mL water to form a soft mass. This soft mass met the acceptance criteria with respect to assay, degradants, and polymorphic form. As it is possible that during use, the induction seal will be removed and the bottle allowed to stand with only the closure [redacted] the Applicant conducted an additional stability study [redacted] Stability data were provided to support labeling 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 (USP Apparatus II paddle, [redacted] (b) (4) [redacted] 75 rpm) with adequate discriminating power for the proposed drug product was found acceptable by the Biopharmaceutics reviewer. The dissolution data are within the linearity range of [redacted] (b) (4) of mebendazole as established during the method validation. The in vitro dissolution method validation is considered acceptable.

All facilities listed in the NDA were found acceptable and an overall "Approve" recommendation was issued by the Office of Process and Facilities on September 27, 2016.

The OPQ review team recommends approval of this NDA as the Applicant has provided sufficient chemistry, manufacturing and controls information to assure the identity, strength, purity, and quality of mebendazole chewable tablets. I agree with the OPQ review team's assessment.

4. Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology reviewer for this NDA is Amy Nostrandt, DVM PhD. No general toxicology studies were submitted in the NDA. The Applicant's summary indicates that NOAEL doses of mebendazole were 10 mg/kg (HED = 1.7 mg/kg) in a 13-week rat study and approximately 2.5 mg/kg/day (HED = 1.25 mg/kg) in a 13-week dog study. In a HERG assay, at the highest concentration tested (10 μM), mebendazole caused a 5.4% reduction of the membrane K+ current (IKr). In a study in isolated Langendorff-perfused female rabbit hearts, no relevant electrophysiological effects were observed at concentrations up to 10 μM. In a study in anaesthetized guinea pigs, mebendazole (0.16 to 1.25 mg/kg IV) had no statistically significant effects on the cardiovascular parameters examined. No safety pharmacology studies of the respiratory or central nervous systems were performed.

Two Ames assays were conducted and were negative. In the mouse lymphoma assay, mebendazole was considered to be mutagenic in the absence of S9 metabolic activation when tested using continuous (24 hour) incubation. In an in vitro micronucleus assay, mebendazole induced aneuploidy. In one in vivo mouse micronucleus assay, no increase in the number of micronucleated polychromatic erythrocytes (PCEs) was reported. In the second study, mebendazole induced micronuclei in PCEs in the bone marrow of treated mice. Fluorescence in-situ hybridization (FISH) evaluation of two samples demonstrated that it was due to an aneugenic mechanism. The non-disjunction in dividing cells may be related to the proposed mechanism of interference with microtubule function. No carcinogenicity studies were submitted. The Applicant's summary states that 22- and 24-month studies in mice and rats, respectively, were negative for carcinogenicity.

No effects on either male or female fertility were reported in male or female rats. Of the six studies of embryofetal toxicity, in which dams were dosed during the period of organogenesis,

two studies in rabbits and one in hamsters appeared to be negative or had an equivocal finding. In two rat studies and one mouse study, mebendazole was embryotoxic and teratogenic. Embryo-fetal death occurred at doses of 10 mg/kg and above and was as high as 100% at doses with maternal toxicity. At 10 mg/kg/day, an increased incidence of malformations, primarily skeletal was observed. At a dose of 2.5 mg/kg/day (HED = 0.42 mg/kg), administered through the period of organogenesis, no adverse effects were seen. In a peri- and postnatal development study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (0.8-fold the MRHD, based on mg/m^2), a reduction of the number of live pups was observed. Information on the observed embryo-fetal effects and mutagenic effects will be described in Sections 8 and 13 of labeling, respectively.

Dr. Nostrandt recommends approval of this NDA and I agree with her assessment.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Abhay Joshi, PhD. Of the four clinical studies in support of the NDA, pharmacokinetic (PK) assessments were included in three studies. The three studies assessed the PK of two different formulations. One study (GAI1001) evaluated a chewable formulation referred to as "Previous Chewable" formulation and two studies (GAI1002 and GAI3003) used the final to-be-marketed chewable formulation, referred to as "New Chewable" formulation.

The relative bioavailability (BA) of the "New Chewable" tablet was determined by historical comparison to the PK of the "Previous Chewable" tablet and Vermox solid oral tablet. Relative BA comparison between the "New Chewable" and the "Previous Chewable" tablet formulation or between the "New Chewable" and the Vermox solid oral tablet formulation was not conducted. A food effect study was conducted with the "New Chewable" tablet. The relative BA/PK results between Vermox solid oral tablet and the "Previous Chewable" tablet suggests that the BA from the "Previous Chewable" tablet is higher (mean Cmax↑ by 50% and mean AUC↑ by 68%). Since, the reported mebendazole systemic exposure from the "Previous Chewable" tablet (BA study, GAI1001) was similar to that from the "New Chewable" tablet (Food effect study, GAI1002), it can be assumed that the "New Chewable" tablet will also have similar BA.

As the site of action of mebendazole is the gastrointestinal tract, systemic exposure is not expected to relate directly to efficacy. The mean mebendazole systemic exposure from a single 500 mg dose of mebendazole chewable tablet was approximately 4-fold higher in children 1-3 years than children > 3 years and adults. This was thought to be related to the fixed dosing strategy rather than weight-based dosing. The observed higher exposure in children was not associated with a higher incidence of adverse reactions in children 1-3 years of age.

In healthy volunteers, administration of the "New Chewable" tablet with a high fat breakfast resulted in approximately 3- to 4-fold higher systemic exposure compared to when administered under fasted conditions. Labeling will recommend that Vermox Chewable tablets can be administered without regard to meals/food.

(b) (4) Therefore, it is likely that the mebendazole plasma levels will be equal or lower than the levels seen in fingerstick samples. Dr. Joshi agrees with the Applicant's approach of using mebendazole concentrations in the fingerstick samples as the maximum estimates for the systemic exposure to mebendazole.

Dr. Joshi recommends approval of the NDA and I agree with his assessment.

6. Clinical Microbiology

Shukal Bala, PhD is the microbiology reviewer for this NDA. Mebendazole binds to different organs of the worm, reduces the uptake of glucose and other nutrients, interferes with cellular microtubule formation, and causes death of the parasites. As a direct ovicidal effect of the drug, the eggs do not progress to the larval stage. There does not appear to be any effect on the infective larvae of hookworms. In vitro and in vivo studies suggest a potential for development of resistance to mebendazole. (b) (4)

In Study GAI3003, parasitological measurements included identification of helminthic species and egg count in fecal samples, by the Kato-Katz method. On direct microscopic examination, the eggs of *A. lumbricoides* and *T. trichiura* can be identified. However, hookworm species cannot be differentiated by this method. In this study, the hookworm species were not identified.

The numbers of eggs in the thick smear were counted for each of the STHs. On-site quality control (QC) was performed by experts from the (b) (4) 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 Swiss TPHI, and a consensus value was documented on the case report form.

On September 06, 2016, the Applicant informed the Division that during the pre-inspection visit at the two sites in Ethiopia, a deviation in the QC procedure for the Kato-Katz thick smear slides from stool samples was noted. Information about the QC procedures was also obtained for the site in Rwanda where the deviations were most common. Following a teleconference with the Applicant and submission of additional clarification on September 29, 2016, it was determined that the deviations did not impact the overall conclusion of the primary efficacy endpoint for both *A. lumbricoides* and *T. trichiura*. Overall, the consensus value was not updated in the case report forms for 9/295 patients.

In the published studies, the identification of helminth species and egg counts in fecal specimens were based on different methods. The cure rates and egg reduction rates reported in the different published studies varied. The parasitological method used, number and quantity of stool specimens collected and processed for egg count, time of collection of stool specimens post-treatment varied in different studies. Overall, results from the published studies were similar to those of Study GAI3003. Cure rates appear to be higher with *A. lumbricoides* than with *T. trichiura, A. duodenale* and *N. americanus*.

In Dr. Bala recommends approval of this NDA and I agree with her assessment.

7. Clinical/Statistical-Efficacy

Sheral Patel, MD is the clinical reviewer for this NDA and Janelle Charles, PhD is the statistics reviewer for this NDA.

The Applicant conducted one randomized, double-blind, placebo-controlled trial, Study 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,* including patients who were also infected with hookworms. Patients infected only with hookworm were excluded.

The trial was conducted at three sites, two in Ethiopia and one in Rwanda. A total of 295 patients 1 to 16 years of age were randomized to receive either a single 500 mg mebendazole chewable tablet or matching placebo. At day 19, the end of the double-blind period, all patients received a single 500 mg mebendazole chewable tablet after a stool specimen was collected. Randomization was stratified by site and type of STH. A subset of patients enrolled in the trial was selected for participation in a PK sub-study.

The two primary efficacy endpoints were the cure rate for *A. lumbricoides* and *T. trichiura* at the end of the double-blind treatment period. For each type of STH, clinical cure is defined as an average post-treatment egg count of zero in patients who had that STH at baseline. These hypotheses were tested sequentially in order to preserve the overall Type I error rate at 0.05

(two-sided). Superiority for the first primary endpoint (cure for *A. lumbricoides*) had to be established before testing of superiority on the second primary endpoint (cure for *T. trichiura*). The primary analysis population is the intent-to-treat (ITT) population, which includes all randomized patients with an average positive pre-treatment stool sample.

A total of 295 patients were randomized, 149 to mebendazole and 146 to placebo. There was slight female preponderance and ~70% were 5-11 years of age; 27 patients were 1-3 years of age. Approximately 86% of patients were enrolled at the two sites in Ethiopia. A total of 167 patients (86 mebendazole and 81 placebo) had *A. lumbricoides* at baseline and 243 patients (124 mebendazole and 119 placebo) had *T. trichiura* at baseline. Thirteen randomized patients had hookworm at baseline; of the 115 patients with mixed infections with *A. lumbricoides* and *T. trichiura* (61 mebendazole and 54 placebo), 109 patients (59 mebendazole and 50 placebo) had *A. lumbricoides* and *T. trichiura* only. The egg density on stool examination was balanced between arms. Approximately 94% of patients in both study arms completed the double blind period.

In the ITT population, for both *A. lumbricoides* and *T. trichiura*, the clinical cure rate observed at the test of cure visit in the mebendazole arm was superior to that in the placebo arm. The observed cure rates for *T. trichiura* are lower than that observed for *A. lumbricoides*. For the secondary endpoint of egg count reduction, mebendazole was superior to placebo for both *A. lumbricoides* and *T. trichiura*.

Efficacy results are presented in Table 1.

Table 1: Clinical Response at the End of the Double-Blind Period (Day 19), ITT Population

Infection Type	Mebendazole Chewable 500 mg All Patients=149*	Placebo All Patients=146*	Difference[1] (95% CI)
A. lumbricoides	**N= 86 n (%)**	**N=81 n (%)**	
Cure	72 (83.7)	9 (11.1)	**72.6 (62.3, 82.7)**
Failure Missing	9 (10.5) 5 (5.8)	67 (82.7) 5 (6.2)	
T. trichiura	**N=124 n (%)**	**N=119 n (%)**	
Cure	42 (33.9)	9 (7.6)	**26.2 (16.7, 35.6)**
Failure Missing	76 (61.3) 6 (4.8)	103 (86.6) 7 (5.8)	
Hookworms[#]	4/4 (100.0)	2/9 (22.2)	**77.8 (17.1, 99.4)**

[1]Difference in cure rates, expressed in percentages, and based on Mantel Haenzel methods to account for stratification by site, for large roundworm and whipworm; and based on exact methods for hookworm.
Failures include patients who tested positive at the test-of-cure (day 19)
*****Some patients had mixed infection
[#] Species not identified

Source: Statistics review, Tables 1 and 4

Of the 109 patients with both *A. lumbricoides* and *T. trichiura* infection, 37.2% of patients in the mebendazole arm had zero egg count for both helminths compared to 6% in the placebo arm, treatment difference of 31.3%; 95% CI (12.7%, 48.2%).

In Study GAI3003, only four patients in the mebendazole arm had hookworm identified; all had mixed infections as patients with hookworm infection alone were excluded. Cure rate for hookworm infection was not one of the primary efficacy endpoints; the two primary efficacy endpoints were cure rate for *A. lumbricoides* and *T. trichiura* at the end of the double-blind treatment period. (b) (4) (b) (4)

Dr. Charles evaluated six placebo-controlled trials from the published literature submitted by the Applicant that assessed the efficacy of a single dose of mebendazole 500 mg for treatment of single or mixed infection with hookworm. In these trials, there were a total of 571 mebendazole recipients and 557 placebo recipients. Two other studies submitted by the Applicant were not reviewed; one was uncontrolled and the second evaluated low birth weight in pregnant women. Additional information provided by the Applicant clarified that there was an additional placebo-controlled study (Albonico et al. 2002) that could be supportive.

In these six published studies, the age of patients ranged from 2 -71 years, follow up period ranged from 2 weeks-up to 4 weeks, and techniques used to summarize the mean egg counts varied. The reported cure rates were also highly variable and ranged from 2.9% to 91.1% for mebendazole and from 0% to 33% for placebo.

Two studies (Sacko et al. and Abadi K) had the highest treatment difference between mebendazole and placebo-treated patients. In the study by Sacko et al. conducted in Africa, the reported cure rate for mebendazole was 51.4% compared to 16.7% for placebo.[1] In the study by K. Abadi conducted in Asia, the cure rate for mebendazole was 91.1% compared to 0% for placebo.[2] Three studies (Charoenlarp P et al., Albonico M et al., and Flohr C et al.) that were conducted in Asia, had the largest sample sizes and included only pediatric patients, reported treatment differences in cure rates of less than 5% between mebendazole and placebo.[3,4,5] The sixth study conducted in Africa reported lack of efficacy of mebendazole in treatment of hookworm infections with essentially no difference in cure rates between mebendazole (22.9%) and placebo (22.6%).[6] In the additional publication referred to by the Applicant (Albonico M et al. 2002), the cure rates in the mebendazole arm were 13.2% compared to 6.2% in the placebo arm. [7] The confidence intervals around these treatment effects were not calculated as in some publications the reported cure rates excluded randomized patients who were positive for hookworm and did not provide stool samples at test of cure time points.

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[1] Sacko M1, 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. J.Trans R Soc Trop Med Hyg. 1999 Mar-Apr;93(2):195-203.

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

[3] Charoenlarp P, Waikagul J, Muennoo C, et al. Efficacy of single-dose mebendazole, polymorphic forms A and C, in the treatment of hookworm and Trichuris infections. Southeast Asian J Trop Med Public Health. 1993 Dec;24(4):712-6.

[4] Albonico M, Bickle Q, Ramsan M, et al. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. Bull World Health Organ. 2003;81(5):343-52. Epub 2003 Jul 7.

(b) (4)

Dr. Charles notes that the heterogeneity in the publications (e.g., differences in designs, patient populations, geographic locations, intensity of infection, and endpoint ascertainment) limited the ability to perform a meta-analysis to obtain an overall treatment effect estimate for mebendazole in the treatment of hookworm.

Dr. Charles concluded that the superiority findings in Study GAI3003 provide evidence to support the efficacy of mebendazole for the treatment of single or mixed infection with *A. lumbricoides* and *T. trichiura*. For hookworm, the observed cure rates for mebendazole were higher than placebo in the published placebo-controlled studies reviewed and in Study GAI3003. However, given the variability in the clinical cure rates, Dr. Charles noted that it is difficult to adequately assess the strength of the findings from a statistical perspective, and deferred to clinical expertise regarding the ability to rely on the efficacy of mebendazole in *A. lumbricoides* and *T. trichiura* to support efficacy in hookworm infection.

I agree with the assessment by Drs. Charles, Patel and Shamsuddin that the Applicant has provided adequate evidence to support the effectiveness of mebendazole chewable 500 mg tablet for the treatment of gastrointestinal infections due to *A. lumbricoides* and *T. trichiura*. I also agree with the assessment provided by Drs. Patel and Shamsuddin that the labeled indication should include pediatric and adult patients. For the indication of hookworm, Dr. Shamsuddin the CDTL notes in her review that despite the very high variability of cure rates reported in the literature, mebendazole resulted in higher cure rates and greater reduction in egg burden compared to placebo across studies and that despite weakness in each piece of supportive evidence, (b) (4) I agree with the assessment by Dr. Charles that the cure rates in the published literature are very variable and it is difficult to estimate the treatment effect of mebendazole. (b) (4)

(b) (4)

8. Safety

The safety review for this NDA was performed by Sheral Patel, MD.

A total of 712 patients received at least one dose of 500 mg mebendazole (solid tablet or either chewable tablet formulations); 536 children received a single 500 mg dose and 141 children and 35 adults received two 500 mg doses. Only safety data in children are included in this review.

No deaths or serious adverse events were reported in any of the trials.

In Study GAI3002, 6 subjects (1.5%) withdrew due to failure to take the study medication. At least one treatment emergent adverse event (TEAE) was reported by 44/396 (11%) patients. The most common TEAEs were pyrexia, diarrhea, lymphadenopathy and cough.

In Study GAI3003, 17 patients (5.8%) withdrew during the double-blind phase. Reasons for discontinuation included subject choice, lost to follow-up, protocol violation, and physician decision. In the double-blind phase, TEAEs were reported by 9/144, (6.3%) patients in the mebendazole arm and 8/140 (5.7%) in the placebo arm. The most common TEAEs were reported in the Infections and Infestations SOC. In the open-label phase, TEAEs were reported in 6/141 (4.3%) mebendazole recipients and 1/170 (0.7%) placebo recipients. The most common TEAEs were reported in the Gastrointestinal Disorders SOC.

No laboratory assessments were done in studies GAI30002 and GAI3003.

The frequency of TEAEs was similar across the various age subgroups in Studies GAI3002 and GAI3003; however, the number of patients in the 1-3 year cohort was very small. Dr. Patel concluded that the higher systemic exposure noted in younger children did not correlate with a higher incidence of AEs. Dr. Patel notes that data from the published literature also support the safety in children 1 to 3 years of age.

In addition to the safety data from the clinical trials, the Applicant submitted an analysis of adverse drug reactions from in-house unpublished clinical trial reports from subjects treated with any dose of mebendazole for intestinal helminthic infections. The Applicant also submitted a Periodic Benefit Risk Evaluation Report/ Periodic Safety Update Report for the period May 2015-May 2016 for mebendazole and mebendazole/quinfamide. Safety data for adults from published studies and from postmarketing reports are consistent with the safety findings in the pediatric population. In general, the reported AEs were similar to the known safety profile of mebendazole. The Applicant identified potential risks of choking with the solid oral formulation, and two reports of convulsions in infants, 4 and 8 weeks of age.

Labeling will include warnings about the risk of seizures, risk of agranulocytosis and neutropenia when mebendazole is used at higher doses and for more prolonged durations, and risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) with the concomitant use of mebendazole and metronidazole. The Adverse Reactions section will describe the adverse reactions reported postmarketing with mebendazole (includes formulations, dosages and treatment durations other than mebendazole chewable 500 mg tablet).

In Dr. Patel's assessment, the safety of the proposed mebendazole chewable tablet 500 mg has been well characterized. I agree with her assessment.

9. Advisory Committee Meeting

No advisory committee meeting was held to discuss this NDA.

10. Pediatrics

Mebendazole 500-mg chewable tablets received Orphan Drug Designation on September 03, 2014 for the treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), and (b) (4) Due to the orphan drug designation, the product is exempt from requirements of the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

- *Office of Scientific Investigations (OSI) Audits*

The OSI reviewer for this NDA is John Lee, MD. An inspection of the largest (of three) participating clinical investigator (CI) sites (Site 251002, Jimma) for Study GAI3003 was conducted. This site enrolled 156/295 patients (53%) in this trial. No significant Good Clinical Practice (GCP) deficiencies were observed. Study conduct appeared GCP compliant, including sponsor oversight of study conduct. All audited data were adequately verifiable against source records and Case Report Forms. Dr. Lee notes that the data from this site appear reliable as reported in the NDA.

12. Labeling

The indication [redacted] (b) (4) include *A. lumbricoides* and *T. trichuria* and the indicated population was revised to patients 1 year of age and older. The Clinical Studies section will include information from the placebo-controlled trial conducted by the Applicant to demonstrate efficacy and safety of the proposed mebendazole 500 mg chewable tablet (Study GAI3003). A new subsection (8.6) has been added to describe the adult population. A review of the key labeling changes and recommendations provided by the Labeling Development Team (LDT) has been provided by Abimbola Adebowale, PhD, Associate Director for Labeling. Several additional revisions were made to the labeling proposed by the Applicant primarily to provide clarity around the information included in labeling. Carton and container labeling was reviewed by Deborah Myers, RPh, MBA from DMEPA and found to be acceptable. Recommendations provided by Adam George, PharmD from OPDP have been incorporated in labeling.

13. Postmarketing

There are no postmarketing commitments or requirements.

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/s/

SUMATHI NAMBIAR
10/19/2016