

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208398Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208398

SUPPL #

HFD #

Trade Name Vermox Chewable Tablets, 500 mg

Generic Name mebendazole chewable

Applicant Name Janssen Pharmaceuticals, Inc.

Approval Date, If Known October 19, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

n/a

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17481

Vermox (mebendazole) Chewable Tablets, 100 mg

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

n/a

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

n/a

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

n/a

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

n/a

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support

the effectiveness of a previously approved drug product?

Investigation #1 YES NO X
Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

n/a

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 115959 YES X ! NO
! Explain:

Investigation #2 !
!

Date: September 29, 2016

Name of Division Director signing form: Sumathi Nambiar, MD, MPH

Title: Director, Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ALISON K RODGERS
10/19/2016

SUMATHI NAMBIAR
10/19/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208398	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: VERMOX™ Chewable Established/Proper Name: mebendazole chewable tablets Dosage Form: Tablet		Applicant: Janssen Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 19, 2016</u> 		AP
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 5 – New formulation
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: [CST SharePoint](#))

- | | |
|---|--|
| NDAs: Subpart H | BLAs: Subpart E |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510) | <input type="checkbox"/> Accelerated approval (21 CFR 601.41) |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520) | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I | Subpart H |
| <input type="checkbox"/> Approval based on animal studies | <input type="checkbox"/> Approval based on animal studies |

- | | |
|---|---|
| <input type="checkbox"/> Submitted in response to a PMR | REMS: <input type="checkbox"/> MedGuide |
| <input type="checkbox"/> Submitted in response to a PMC | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU |
| | <input type="checkbox"/> MedGuide w/o REMS |
| | <input type="checkbox"/> REMS not required |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	No
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	Verified
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	Included
Documentation of consent/non-consent by officers/employees	Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval: 10-19-16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	X Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	6-2-16 5-31-16
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 5-17-16 DMEPA: 9-19-16; 9-8-16; 6-9-16; 5-31-16 DMPP/PLT (DRISK): None OPDP: 9-6-16 SEALD: None CSS: None Product Quality None Other: Division of Anti-Infective Products Associate Director for Labeling: 10-18-16; PMHS: 10-14-16
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	8-16-16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	10-12-16
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<p>No</p> <p>Not an AP action</p>
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC: N/A If PeRC review not necessary, explain: Product has orphan designation so PREA not triggered. 	
❖ Breakthrough Therapy Designation	X N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	10-23-16; 6-30-16; 6-13-16; 6-2-16; 5-25-16; 4-22-16
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	03-08-16
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	None
❖ Advisory Committee Meeting(s)	No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	None
Division Director Summary Review (<i>indicate date for each review</i>)	10-19-16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10-11-16
PMR/PMC Development Templates (<i>indicate total number</i>)	None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	10-6-16; 5-16-16 (2)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Please see page 70 of clinical review dated 10/6/2016.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	10-3-16
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	10-4-16
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	9-23-16
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	9-29-16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	9-23-16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	9-30-16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	9-30-16 (Please see page 23 of Integrated Quality Assessment)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 9-27-16

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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

/s/

ALISON K RODGERS
10/19/2016



NDA 208398

MEETING MINUTES

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VERMOX Chewable (mebendazole chewable tablets), 500 mg.

We also refer to the teleconference between representatives of your firm and the FDA on September 13, 2016. The purpose of the meeting was to discuss pre-inspection clinical site visit findings.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Category: Guidance

Meeting Date and Time: September 13, 2016

Meeting Location: Teleconference

Application Number: NDA 208398

Product Name: VERMOX Chewable (mebendazole chewable tablets), 500 mg

Indication: Treatment of (b) (4) gastrointestinal (b) (4) by *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), and *Ancylostoma duodenale* (b) (4)

Sponsor/Applicant Name: Janssen Pharmaceuticals, Inc.

Meeting Chair: Sumathi Nambiar, MD, MPH

Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Abimbola Adebowale, PhD, Associate Director for Labeling (via phone)

Shukal Bala, PhD, Clinical Microbiology Reviewer

Lynette Berkeley, PhD, Acting Clinical Microbiology Team Leader

Janelle Charles, PhD, Statistics Reviewer

Philip Colangelo, Pharm D, PhD, Clinical Pharmacology Team Leader

Maureen Dillon-Parker, Chief, Project Management Staff

Karen Higgins, ScD, Statistics Team Leader

Dmitri Iarikov, MD, PhD, Acting Deputy Director

Abhay Joshi, PhD, Clinical Pharmacology Reviewer

Sumathi Nambiar, MD, MPH, Director

Sheral Patel, MD, Medical Officer

Alison Rodgers, Regulatory Project Manager

Hala Shamsuddin, MD, Clinical Team Leader

Joseph Toerner, MD, MPH, Deputy Director for Safety

Janice Pohlman, MD, Medical Officer (Good Clinical Practice Assessment Branch, CDER)

APPLICANT ATTENDEES

Janssen Pharmaceuticals, Inc.

Benny Baeten, PhD, Compound Development Team Lead

Marc Engelen, DVM, PMP, Project Management Lead

Andrew Friedman, MD, Clinical Lead
Joseph Massarella, PhD, Clinical Pharmacology Lead
Kevin Shalayda, Clinical Pharmacology
Peter Hu, PhD, Biostatistics
Veerle Huffkens, Global Clinical Development Operations Lead
Jessica Holthuizen, Global Clinical Development Operations
Arianne Bodard, BioResearch Quality Assurance
Christine Redman, Medical Writing
Melissa Tokosh, Global Regulatory Lead
Andrea Kollath, DVM, North America Regulatory Lead
Jenna Giacchi, Regulatory Scientist

BACKGROUND

The Applicant submitted NDA 208398 on April 19, 2016. The application was granted a priority review with a PDUFA goal date of October 19, 2016. On September 2, 2016, the Applicant notified the Division that during the Applicant's pre-inspection site visits of the clinical study sites in Gondar, Ethiopia and Jimma, Ethiopia, deviations to the Swiss Tropical and Public Health Institute Quality Control Procedures for Kato-Katz thick smear slides from stool samples were identified. The Applicant requested a teleconference with the Division to discuss the impact of the findings on the application. On September 12, 2016, the Applicant submitted written documentation of its preliminary assessment of the quality control (QC) deviations and slides as background for the discussion. The written documentation was submitted to the NDA on September 14, 2016. The slides are appended.

DISCUSSION

The Applicant stated that they conducted pre-inspection visits of the clinical study sites in Ethiopia to ensure that documentation was readily available and organized, and that upon review of source documents at the sites, discrepancies in QC procedures were identified. With regard to the pharmacokinetic (PK) substudy, the Applicant explained that two subjects spit out the tablet and should not have been included in the substudy. The Applicant stated that a detailed preliminary assessment of the findings concluded that the discrepancies did not impact safety or the overall conclusion of efficacy and that the overall PK conclusions were not changed.

Due to the short timeframe remaining for review of the NDA, the Applicant proposed filing an erratum detailing the findings to the clinical study report post-approval.

The Division requested clarification as to how often the QC process for egg counts was done and how a consensus was reached. The Applicant explained that QC was ongoing during the trial and done at regular intervals throughout the study at the sites in Ethiopia and Kigali, Rwanda. Experts from the Swiss Tropical and Public Health Institute visited the sites and randomly collected sample slides to re-read. If a discrepancy was found between the original slide read and the re-read, then a discussion took place to reach a consensus on the final value and staff retraining was provided. In response to the Division's request for clarification, the Applicant explained that a re-reading would be done if there were readings of 0 and 1, and if the consensus is that the final value is 1, then 1 would be entered in the case report form (CRF). The Applicant reported that Table 1 represents all of the QC samples done; the total number of samples is 260.

The Applicant stated that the Rwandan site had the highest number of discrepancies; most of the discrepancies occurred early in the study, and retraining was successful.

The Division asked if the Applicant rechecked sites after corrective actions were taken to be sure that QC issues were not recurring. The Applicant responded that QC was done throughout the entire study. The Division asked if there was a trend as a site became more familiar and comfortable with the study. The Applicant responded that they did not have this information but would check.

The Division noted that almost 100% of samples had errors at the site in Kigali, Rwanda. The Division wants to be sure that corrective actions were taken to reduce errors. The Division had concern regarding possible discrepancies in the samples that were not read. The Division asked for more information regarding this site to help the Division understand how significant the errors were and how many subjects there were whose samples were not checked. The Applicant responded that they will conduct an analysis to determine the information. The Applicant stated that they would check the extent of the discrepancies at the site in Kigali, Rwanda and determine the timing of the QC checks to see if there was improvement over time. The Division asked that the Applicant consider an analysis that would apply the error rate in the QC samples to the overall population as a sensitivity analysis.

The Division asked if all staff were blinded in the QC process. The Applicant explained that staff was blinded to treatment assignment for the first part of the study. The Division asked how many slides were read each time the experts read slides. The Applicant responded that 20-30 slides were read each time the experts read slides.

The Division stated that it would send a request for additional information and decide how to proceed with the review of the NDA after it has reviewed the response.

ACTION ITEMS

- The Division will send an information request (IR) and decide how to proceed with review of the NDA after reviewing the Applicant's response to the IR.

ATTACHMENTS AND HANDOUTS

- Applicant's slides are attached.

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/s/

SUMATHI NAMBIAR
10/19/2016

From: Rodgers, Alison
To: "[Kollath, Andrea \[JRDU51\]](#)"
Subject: NDA 208398 Container Labeling
Date: Friday, September 09, 2016 9:19:00 AM

Hi Andrea,

With regard to the container labeling submitted September 6, 2016, please note:

To minimize the risk of medication errors involving the dispensing or administration of deteriorated drug product, revise the statement "Discard after _/_/_. Discard unused portion XX months after first opening." on the principal display panel of the container label. We recommend changing the font color, surrounding this information with a box, or highlighting the information, to draw attention to this important information and the need to complete/fill-in this information to provide an accurate expiration date after opening.

Please let me know if you have questions. Please resubmit container labeling by September 15, 2016.

Please confirm receipt of this email.

Thank you

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9887

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/s/

ALISON K RODGERS
09/09/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: September 8, 2016
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 208398
Product Name and Strength: Vermox Chewable (mebendazole Chewable Tablets), 500 mg
Submission Date: September 6, 2016
Applicant/Sponsor Name: Janssen Pharmaceuticals, Inc.
OSE RCM #: 2016-997-2
DMEPA Primary Reviewer: Deborah Myers, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label for Vermox Chewable (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to label suggestions that were made by the Office of Pharmaceutical Quality (OPQ).

2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. As presented, there is lack of differentiation of the statement "Discard after / / . Discard unused portion XX months after first opening." from the other text on the principal display panel. We recommend changing the font color, surrounding this information with a box, or highlighting the information, to draw attention to this important information and to minimize the potential of medication errors involving the dispensing or administration of deteriorated drug product.

3 RECOMMENDATIONS FOR JANSSEN PHARMACUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 208398:

To minimize the risk of medication errors involving the dispensing or administration of deteriorated drug product, revise the statement “Discard after / / . Discard unused portion XX months after first opening.” on the principal display panel of the container label. We recommend changing the font color, surrounding this information with a box, or highlighting the information, to draw attention to this important information and the need to complete/fill-in this information to provide an accurate expiration date after opening.

APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 6, 2016

Container label (not to scale)



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/s/

DEBORAH E MYERS
09/08/2016

BRENDA V BORDERS-HEMPHILL
09/08/2016



NDA 208398

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated April 19, 2016, received April 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vermox (mebendazole) Chewable Tablets, 500 mg. We also reference the June 14, 2016, telephone communication between you and Alison Rodgers, of this Division, during which you were notified that this NDA will be reviewed as a 505(b)(2) application.

We also refer to your amendments dated April 29, May 6, and 20, and June 8, 10, 20, and 24, 2016.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by July 22, 2016:

Data regarding qualification of related impurities in the drug substance (impurities A to G) in accordance with ICH Q3 and M7. Please provide these data or revise specification limits to values below qualification thresholds.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *There is no reference following the Adverse Reactions topic.*

2. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *There is a dash between Approval and 1974 instead of a colon.*

3. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: *The revised date is not listed.*

4. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: *Under section 2.3, the first letters of the words years and age are not capitalized.*

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 22, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
06/30/2016



NDA 208398

PRIORITY REVIEW DESIGNATION

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated April 19, 2016, received April 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vermox (mebendazole) Chewable Tablets, 500 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is October 19, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2016.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before July 2, 2016.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
06/13/2016



NDA 208398

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Janssen Pharmaceuticals, Inc.
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

ATTENTION: Andrea F. Kollath, DVM
 Director, Global Regulatory Affairs

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated April 19, 2016, received April 19, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mebendazole Chewable Tablets, 500 mg.

We acknowledge receipt of your April 29, 2016, correspondence, received April 29, 2016, requesting a review of your proposed proprietary name, Vermox Chewable.

If the application is filed, the user fee goal date will be July 28, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet G. Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. For any other information regarding this application, contact Alison Rodgers, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Janet G. Higgins
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

JANET G HIGGINS
05/25/2016



NDA 208398

NDA ACKNOWLEDGMENT

Janssen Pharmaceuticals, Inc.
c/o Janssen Research & Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Global Regulatory Affairs
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Vermox (mebendazole) Chewable Tablets, 500 mg

Date of Application: April 19, 2016

Date of Receipt: April 19, 2016

Our Reference Number: NDA 208398

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 18, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
04/22/2016



IND 115959

MEETING MINUTES

Janssen Pharmaceutical Research & Development, LLC
c/o Janssen Research & Development, LLC
Attention: Andrea F. Kollath, DVM
Director, Global Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Dr. Kollath:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vermox (mebendazole) Chewable Tablets, 500 mg.

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2016. The purpose of the meeting was to discuss the content and format of the New Drug Application for Vermox (mebendazole) Chewable Tablets, 500 mg.

A copy of the official minutes of the Pre-NDA meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: March 8, 2016, 3:00 – 4:00 PM
Meeting Location: 10903 New Hampshire Avenue, Silver Spring, MD 20903
Building 22, Room 1415
Application Number: 115959
Product Name: Vermox (mebendazole) Chewable Tablets, 500 mg
Indication: Treatment of single or mixed gastrointestinal infestations by
Trichuris trichiura (whipworm), *Ascaris lumbricoides* (large
roundworm), (b) (4)

Sponsor/Applicant Name: Janssen Pharmaceutical Research & Development, LLC

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Shukal Bala, PhD, Clinical Microbiology Reviewer
Elsbeth Chikhale, PhD, Biopharmaceutics Team Leader
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Maureen Dillon-Parker, Chief, Project Management Staff
Cheryl Dixon, PhD, Statistical Reviewer (via telecon)
Kerian Grande Roche, PhD, Clinical Microbiology Team Leader (Acting)
Karen Higgins, ScD, Statistical Team Leader
Abhay Joshi, PhD, Clinical Pharmacology Reviewer
Dorota Matecka, PhD, Product Quality Team Leader (Acting)
Sumathi Nambiar, MD, MPH, Director
Amy Nostrandt, PhD, Pharmacology and Toxicology Reviewer
Sheral Patel, MD, Medical Officer
Alison Rodgers, Regulatory Project Manager
Wendelyn Schmidt, PhD, Pharmacology and Toxicology Team Leader
Hala Shamsuddin, MD, Clinical Team Leader
Joseph Toerner, MD, MPH, Deputy Director for Safety

Office of Antimicrobial Products

Sunita Shukla, PhD, Associate Director for Regulatory Science (Acting)

Division of Medication Errors and Prevention

Deborah Myers, RPh, MBA, Safety Evaluator

SPONSOR ATTENDEES

Janssen Research & Development (Janssen)

Benny Baeten, Senior Director, Compound Development Team Lead

Marc Engelen, DVM, PMP, Director, Project Management Lead

Joseph Mrus, MD, MSc, Director, Clinical Lead

Min Wang, MD, PhD, Director, Global Medical Safety Physician

Joseph Masarella, PhD, Director, Clinical Pharmacology Lead

Mark Kao, PhD, Scientific Director, DMPK Lead

Michael Kelley, VMD, PhD, Senior Scientific Director, Toxicology Lead

Daniel Schaufelberger, PhD, Scientific Director, CMC Lead

Peter Hu, PhD, Associate Director, Biostatistics

Melissa Tokosh, Director, Global Regulatory Lead

Jenna Giacchi, Manager, Regulatory Scientist

BACKGROUND

A Pre-IND meeting was held in October 2012. During the meeting, the Division suggested that the Sponsor develop a different, age-appropriate formulation for the pediatric population. Subsequently, the Sponsor developed a rapidly disintegrating chewable tablet. This new 500 mg chewable formulation was utilized in the Phase 3 study. The product was granted Orphan Drug Status on September 3, 2014, for the treatment of single or mixed gastrointestinal infestations by *T. trichiura* (whipworm), *A. lumbricoides* (large roundworm), (b) (4)

The Sponsor submitted a request for a Pre-NDA meeting on December 3, 2015. The meeting was granted and scheduled for February 9, 2016. On December 15, 2015, the Sponsor requested postponement of the meeting to a date in early March. A meeting package was submitted on February 8, 2016. The FDA sent preliminary comments to the Sponsor on March 4, 2016. The Sponsor requested further discussion of questions 3, 5, 6, 13, and 15 (in that order), and sent slides to serve as background for the discussion at the March 7, 2016 meeting. The Sponsor's original questions and the Division's responses, as well as the Sponsor's slides submitted on March 7, 2016, are appended. The format provides for the meeting discussion points in the order requested by the Sponsor.

DISCUSSION

The Sponsor opened the meeting by summarizing that the new chewable tablet formulation of mebendazole will be donated to the World Health Organization to replace the current 500 mg solid tablet. The product is intended to treat a neglected tropical disease and has been granted

orphan designation. The Sponsor does not plan to market the new chewable tablet formulation in the United States or any other country.

The Sponsor stated that they no longer require discussion of question 15.

Sponsor question #3:

Does the Agency agree that the use of literature will support the additional indication of hookworm (ie, mebendazole 500-mg chewable tablets is an anthelmintic indicated for the treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* [whipworm], *Ascaris lumbricoides* [large roundworm], and *Ancylostoma duodenale* and *Necator americanus* [hookworm]) in the proposed product label? We also propose the addition of these data to support the clinical trial and microbiology sections of the USPI. Does the Agency agree?

Meeting Comments:

- The Sponsor clarified that they do not have access to the primary source data cited in the literature references used to support the hookworm indication because many of the studies are 40 years old and were conducted around the world. The Sponsor will provide a literature review and copies of the publications referenced in the literature review in the NDA. The Sponsor explained that the literature review also assessed *A. lumbricoides* and *T. trichiura*, and the cure rates were similar to the cure rates observed in the Phase 3 trial. The Sponsor maintained that this similarity in cure rates provides confidence in the accuracy of the methodology used in the literature review. The Sponsor stated that the hookworm indication is also supported by the pooling of the studies and the sample size; eight of the 23 studies for hookworms were placebo-controlled trials with more than 1000 people receiving 500 mg of mebendazole.
- The Sponsor asked if there was anything else that would support the addition of the hookworm indication. The Division inquired about an internal study that was mentioned in the briefing package. The Sponsor responded that one study conducted in 1985 evaluating two dose strengths in the treatment of hookworm resulted in a 60% cure rate for the 500 mg dose, but was not placebo-controlled. The Division stated that the study results might help to provide additional support for the treatment of hookworm if the data could be provided. The Sponsor agreed to try and obtain the source data for this study. The Division explained that it cannot confirm that the literature review and available data will be sufficient until the data are reviewed. The Sponsor asked for clarification of what the Division would expect for source data. The Division responded that any amount of patient level data as well as protocols should be provided.
- The Sponsor asked what would be required to include information in the Clinical Studies section of the package insert. The Division explained that according to the regulations, this section should include adequate and well-controlled trials used to support the indication(s). The Sponsor asked if it would be possible to include information on

hookworm in the Clinical Studies section of the package insert if the indication was not granted. The Division said that it would be unlikely.

- With regard to microbiologic evaluation, the Sponsor noted that in their literature review and submission of study GAI3003 (3003), the data do not include information on hookworm species and asked for clarification as to how this will be handled in the NDA and labeling. The Division responded that based on epidemiological findings, the hookworm species known to be prevalent in the different geographic region(s) should be listed. The Sponsor agreed to provide this information in the NDA. The Sponsor also agreed to provide details of the parasitological methods that were included in quantitating egg count or determining the presence or absence of eggs in fecal specimens.

Sponsor question #5:

The Sponsor does not plan to submit a separate Integrated Summary of Safety (ISS) in Module 5. Does the Agency agree with this proposal?

Meeting Comments:

- The Sponsor asked if the Division wants only the SAS programs that were used for adverse events or for all safety related parameters. The Division responded that it would prefer that the Sponsor submit SAS programs for all safety related parameters and for the efficacy data for studies GAI3002 (3002) and 3003 if possible. The Division does not need SAS programs for studies GAI1002 (1002) or GAI1003 (1003).

Sponsor question #6:

Does the Agency agree with the Sponsor's proposal for the subgroup analyses in the Summary of Clinical Safety (SCS)?

Meeting Comments:

- The Sponsor proposed to match data from study 3002 to age categories they have already established for study 3003 and not adjust age categories as the Division requested in its response to question #6. The Sponsor addressed the Division's concerns regarding safety in younger age groups by presenting data from the open label phase of study 3003. In the youngest age group, exposure did not appear to correlate with adverse events as no adverse events occurred in children less than three years old. The Division agreed that the Sponsor could match data from study 3002 to age categories already established for study 3003.

Sponsor question #13:

Does the Agency agree with the Sponsor's conservative approach for analyzing pharmacokinetic data in the Phase 3 efficacy study (GAI3003)? Furthermore, does the Agency agree that the PK data obtained are sufficient to characterize the PK profile in pediatric patients?

Meeting Comments:

- The Sponsor explained that they do not have pharmacokinetic (PK) data based on venous whole blood except for 10 children in the 7 to 16 year age group at 3 and 24 hours post-dose, as requested by the Division in November 2014. They do have exposure data for mebendazole and the two primary metabolites that was estimated from whole blood concentrations from fingerstick samples for all 44 children. The Sponsor acknowledged that there is a limited amount of PK data from study 3003 that can be analyzed.
- The Sponsor acknowledged that inconsistent drug concentration values may have resulted from contamination by site personnel, but maintained that the frequency and magnitude of the contamination is not large. The Sponsor believes that the higher exposures in young children are due to the higher dose that these children received on a mg/kg basis.
- The Division explained that it is still concerned about higher exposures in children. The Division does not agree that there is a good correlation between fingerstick blood samples and venous plasma concentrations, given the observed sporadic overestimation of the actual exposure in fingerstick samples obtained in both adults and children.
- The Division clarified that the Sponsor would not have to conduct any new pediatric PK studies. The acceptability of the PK results obtained solely from fingerstick samples will be determined upon review of the NDA.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

- The Sponsor agreed to try and obtain the source data for the study conducted in 1985 evaluating two dose strengths in the treatment of hookworm.
- The Sponsor agreed to provide information on the hookworm species known to be prevalent in different geographic region(s) in the NDA.
- The Sponsor agreed to provide details of the parasitological methods that were included for quantitating egg count or determining the presence or absence of eggs in fecal specimens.
- The Division will issue meeting minutes within 30 days.
- The Sponsor plans to submit the NDA in mid-to-late April.

ATTACHMENTS AND HANDOUTS

Sponsor slides

ADDITIONAL APPLICATION INFORMATION**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy

registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

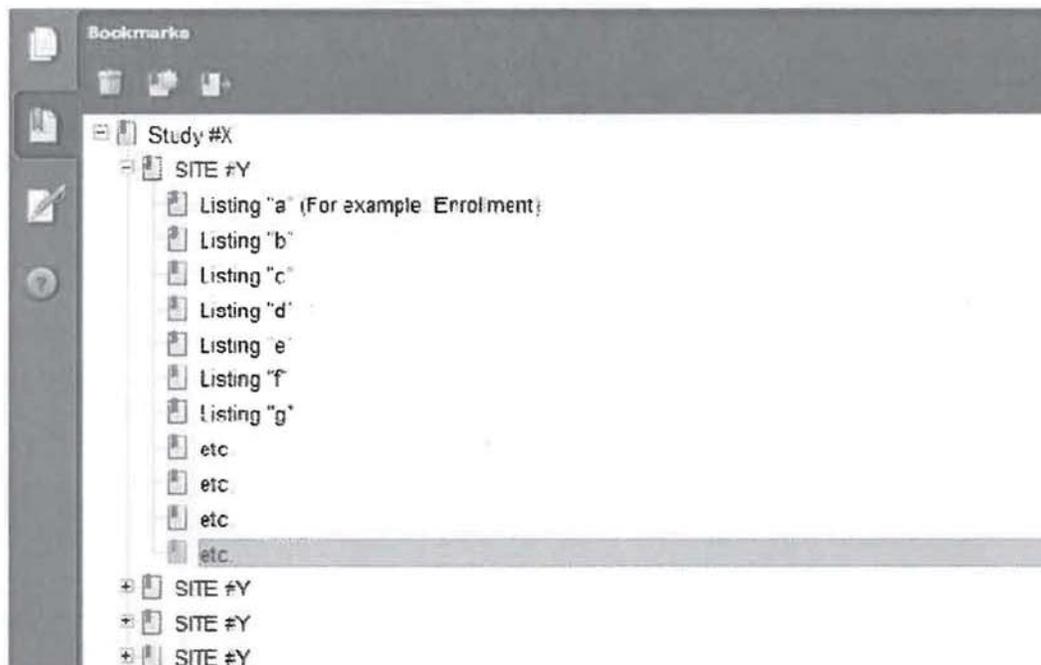
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

- the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

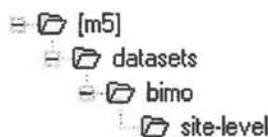
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID

for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

SPONSOR'S ORIGINAL QUESTIONS AND DIVISION'S RESPONSES
(Division's responses were sent to Janssen on March 4, 2016 via email)

Clinical Efficacy Questions

QUESTION 1: The sponsor does not plan to submit a separate Integrated Summary of Efficacy (ISE) in Module 5. Does the Agency agree with this proposal?

FDA Response: *We agree.*

QUESTION 2: Pending a thorough review of the data submitted in the NDA, does the Agency agree that the proposed efficacy package is adequate to support the Indications and Clinical Studies Section of the USPI?

FDA Response: *We agree.*

QUESTION 3: Does the Agency agree that the use of literature will support

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(u) (4)

FDA Response: *Please clarify if you have access to, or intend to submit, primary source data for the individual studies cited in the literature reports. If no primary source data are available, the adequacy of the literature review to support the hookworm indication will be assessed at the time of NDA review. In particular, we would focus on the individual reports of placebo-controlled trials that evaluated the proposed dosing regimen and evaluated cure rather than decrease in egg count. Inclusion of the results of such literature data in the Clinical Studies section of labeling will be made upon review of the data.*

Regarding microbiologic evaluation, please include in your NDA details of the microbiological methods used for identifying helminthic species and performing egg counts. If the methods are not available to identify species,

(b) (4)

(b) (4) then it should be specified that the species listed are based on epidemiological data.

Clinical Safety Questions

QUESTION 4: Does the Agency agree with the planned approach of the NDA submission to assess the overall safety profile of the new 500-mg mebendazole chewable tablets?

FDA Response: *Your approach is acceptable.*

QUESTION 5: The sponsor does not plan to submit a separate Integrated Summary of Safety (ISS) in Module 5. Does the Agency agree with this proposal?

FDA Response: *Your approach is acceptable. However, whenever possible, safety results for each study, including subgroup analyses, should be provided in one table to facilitate interpretation of the data. A sample table is provided for illustrative purposes. You can modify the table according to your specific submission.*

You should submit all SAS programs used for safety analyses.

Sample table illustrating how to display results from both Phase 3 studies.

	Study GAI3002	Study GAI3003	
		Study Drug	Comparator
Deaths			
Adverse events associated with discontinuation of study drug (if any)			
Any serious adverse events			
Any treatment related adverse events			

QUESTION 6: Does the Agency agree with the sponsor's proposal for the subgroup analyses in the Summary of Clinical Safety (SCS)?

FDA Response: *Your approach to include subgroup analyses in the Summary of Clinical Safety is acceptable. However, whenever possible, safety results for each study, including subgroup analyses, should be provided in one table to facilitate interpretation of the data (see Question 5).*

You should provide an analysis of adverse reactions, including tolerability, in patients who received the dose of mebendazole chewable tablets with food (i.e., under fed conditions) versus those patients who received the dose of mebendazole chewable tablets without food (i.e., under fasted conditions)

Furthermore, in order to allow comparability of safety findings from studies GAI3002 and GAI3003, and review adverse events in the preschool population, we suggest a different age stratification scheme:

GAI3003: less than 2 years, 2 to less than 5 years, 5 to less than 11 years, and 11 to 16 years

GAI3002: 2 to less than 5 years, 5 to less than 11 years

QUESTION 7: Does the Agency agree with the proposed approach for listing adverse drug reactions (ADRs) in the USPI?

FDA Response: *We agree.*

QUESTION 8: The sponsor proposes that a Pharmacovigilance Plan will not be submitted to the NDA. Does the Agency agree?

FDA Response: *Please also see our response to question 12. Your approach is acceptable provided that you can provide data demonstrating that systemic exposures in all age cohorts are negligible.*

QUESTION 9: The sponsor requests a waiver of the requirement to submit a 4-month safety update. Does the Agency agree?

FDA Response: *We agree.*

QUESTION 10: The sponsor requests a waiver of the requirements for periodic adverse drug experience reports (PADERS). Does the Agency agree?

FDA Response: *Waiver requests are reviewed by the Office of Surveillance and Epidemiology and a decision will be made at the time of NDA review.*

Clinical Pharmacology Questions

QUESTION 11: Does the Agency agree with the proposal to submit all Clinical Pharmacology information in a single module? Does the Agency agree with the proposed content of the module?

FDA Response: *Yes, we agree. However, in relevant sections of Module 5, please include the complete study reports separately including the datasets (if applicable) that were utilized to deduce the summaries in Module 2.7.*

QUESTION 12: The sponsor believes that further demonstration of the similarity in systemic exposure across mebendazole formulations discussed in the upcoming NDA submission is not warranted. Does the Agency agree?

FDA Response: *Given that the efficacy is believed to be limited locally in the GI tract and mebendazole is poorly absorbed following oral administration of the single 500 mg dose, we agree that further demonstration of the similarity in systemic exposure across mebendazole formulations is not warranted. However, we have the following concerns with regard to potential safety issues of the proposed to-be-marketed new chewable 500 mg tablet formulation, in the context of increased systemic exposure:*

1. *The PK substudy from Study GAI3003 indicated that the systemic exposures (both C_{max} and AUC) to mebendazole in pediatric patients were substantially higher following administration of the new 500 mg chewable tablet as compared to that in adults following administration of VERMOX 500 mg solid oral tablet. This was particularly the case for the youngest age group of pediatric patients (1 to <3 years).*
2. *The systemic exposures to mebendazole were significantly higher when the new chewable tablet formulation was administered with food to healthy adult volunteers. Under fed conditions, mean C_{max} and AUC estimates were 4- and 2.9- fold higher, respectively, as compared to fasted conditions.*

Therefore, the need for any additional relative BA/BE study(ies) may be reconsidered by the Division based on the review of the safety results from the Phase 3 Study GAI3003 in pediatric patients.

QUESTION 13: Does the Agency agree with the sponsor's conservative approach for analyzing pharmacokinetic data in the Phase 3 efficacy study (GAI3003)? Furthermore, does the Agency agree that the PK data obtained are sufficient to characterize the PK profile in pediatric patients?

FDA Response: *Yes, in general, we agree with the "conservative approach" to include all PK data generated in the pediatric substudy of Phase 3 Study GAI3003, with no exclusions. However, we will not accept PK results obtained solely from capillary fingerstick samples because of spurious and/or inconsistent drug concentration values due to potential contamination by site personnel. We recommend that you characterize the PK profile and derive the PK estimates in pediatric patients primarily from venous blood samples, rather than from capillary blood samples.*

Preclinical Questions

QUESTION 14: As a follow-up to the Agency's 11 August 2015 written response, the sponsor proposes that no additional human PK studies or nonclinical studies are needed for the reasons described below. Does the Agency agree?

FDA Response: *As long as the clinical data referenced in the briefing package are found to be supportive of the safety of exposures to mebendazole and its metabolites using the proposed dosing regimen and formulation by the clinical reviewer, then additional nonclinical data should not be needed.*

QUESTION 15: Does the Agency agree with the proposed preclinical content for the NDA?

FDA Response: *Please refer to the ICH M3 guidance and other relevant ICH guidances. Assuming the studies submitted to NDA 17-481 to support the safety of that product, along with the more recently completed nonclinical studies, provide relevant data to support the safety of the proposed dose and dose regimen in accordance with that guidance, the content appears to be acceptable. Please include the comparative data to support the relative safety of and systemic exposure to polymorph C*

(b) (4)

(b) (4) *It is possible that one or more toxicology study reports may be requested if clarification is needed.*

Regarding preclinical microbiology, all nonclinical microbiology studies (published or unpublished) supporting mechanism of action, activity in vitro and/or in animal models of infection as well as a potential for development of drug resistance and mechanism of drug resistance should be included in the NDA submission. The microbiology information should be in Section 12.4 of the package insert.

Regulatory Questions

QUESTION 16: In accordance with 21 CFR 54, the sponsor proposes to provide financial disclosure certification for the pivotal efficacy study, GAI3003, in the NDA. All of the other studies are considered supportive and financial disclosure information will not be provided. Is *this acceptable?*

FDA Response: *We agree.*

QUESTION 17: The sponsor provides the planned Table of Contents for the NDA in the Briefing Book. Does the Agency agree that the inclusion of the covered items will be sufficient for review?

FDA Response: *We agree.*

ADDITIONAL BIOPHARMACEUTICS COMMENTS:

We have the following comments regarding the dissolution information that should be provided in your NDA.

- 1) ***Dissolution method development report:*** *The report should include the following information:*
 - a. *Solubility data for the drug substance over the physiologic pH range.*
 - b. *Detailed description of the dissolution test parameters (i.e., equipment/apparatus, type and volume of media, agitation/rotation speed, pH, temperature, etc.). Include a narrative of why these parameters were selected and how the test conditions were optimized (e.g., sink conditions, stability considerations). If applicable, the type and the amount of surfactant added to the dissolution medium, and/or the use of strength dependent dissolution methods should be justified. The dissolution –time profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached; initial sampling time points typically include 10, 15, 20, 30, 45, 60, 90 and 120 min. At least twelve samples should be used per testing variable.*
 - c. *Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the*

test (variant) products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., \pm 10-20% change to the specification-ranges of these variables). If available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent to the reference (target) product.

- d. *A list of the critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.*
 - e. *Summary figures and tables showing mean and %RSD cumulative amount of drug released at each sampling timepoint, and if applicable, f_2 (profile similarity) values.*
 - f. *Validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*
 - g. *A detailed justification of the proposed dissolution acceptance criterion.*
2. **Dissolution Acceptance Criterion:** *For the selection of the dissolution acceptance criterion for the proposed drug product, the following points should be considered.*

- a. *In setting the dissolution acceptance criterion of the product (i.e., specification- sampling time point and specification value), use the dissolution profile data of the pivotal PK and clinical batches, i.e., based on USP Stage ^(b)₍₄₎ dissolution testing ($n =$ ^(b)₍₄₎ of the batches at the time of manufacture and during long-term storage for the duration of the trial(s). In addition, the dissolution profiles of the primary (registration) and supportive stability batches during long-term storage should be considered.*

b.

(b) (4)

3. **Supporting Data:** *The following detailed experimental data should be submitted to support the dissolution method development and setting of acceptance criterion:*

- a) *As much individual vessel data as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.*
- b) *Analysis datasets in ".xpt" format, and their define files. The dataset should contain individual vessel data for all sampling timepoints.*
- c) *Batch release and stability dissolution data presented graphically. The plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.*

SPONSOR'S SLIDES SUBMITTED ON MARCH 7, 2016

9 Pages have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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

/s/

SUMATHI NAMBIAR

04/04/2016