

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204684Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204684

SUPPL # Not Applicable

HFD # 520

Trade Name IMPAVIDO Capsule 50 mg

Generic Name miltefosine

Applicant Name Paladin Therapeutics, Inc.

Approval Date, If Known March 19, 2014

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)(1)

c) 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.

Not Applicable

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:

Not Applicable

d) Did the applicant request exclusivity?

YES NO

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

7 years

e) 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?

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#

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:

(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:

(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:

- (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:

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:

- 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

interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

Investigation #2
!
! YES NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Gregory F. DiBernardo
Title: Regulatory Project Manager
Date: March 18, 2014

Name of Office/Division Director signing form: Sumathi Nambiar, M.D., M.P.H.
Title: Director Division of Anti-Infective Products

APPEARS THIS WAY ON ORIGINAL

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

/s/

GREGORY F DIBERNARDO
03/18/2014

SUMATHI NAMBIAR
03/19/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204684	NDA Supplement # Not Applicable	If NDA, Efficacy Supplement Type: Not Applicable <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: IMPAVIDO Established/Proper Name: miltefosine Dosage Form: Capsule, 50 mg		Applicant: Paladin Therapeutics, Inc. Agent for Applicant: Jonathan Berman, M.D., Fast Track Drugs and Biologics, LLC
RPM: Gregory F. DiBernardo		Division: Anti-Infective Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input 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)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: _____ <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>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>March 19, 2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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, (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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1 - NME
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input checked="" 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 | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" 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)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: Approval 3/19/14
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>) 	<input checked="" type="checkbox"/> Included 3/18/14 Division 2/ 27/14 Applicant
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input 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>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ 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 	<input checked="" type="checkbox"/> 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>) 	Letter: Conditionally Acceptable 9/6/13 Review: 9/6/13
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> Communicated in Filing Letter 6/18/13 DMEPA: <input checked="" type="checkbox"/> 9/13/3 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 11/19/13 OPDP: <input checked="" type="checkbox"/> 11/18/13 SEALD: <input checked="" type="checkbox"/> 2/4/14 CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> MHT 11/25/13
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	11/26/12 & 3/19/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ 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 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>n/a</u> If PeRC review not necessary, explain: <u>Orphan Designation Granted</u> 	
<ul style="list-style-type: none"> Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	2012: 7/27, 10/12, 10/23, 11/26, 12/17; 2013: 1/24, 5/24, 5/31, 6/5, 6/18, 6/20, 7/9, 7/31, 8/2, 8/13, 9/23, 10/1, 10/15, 10/24, 11/8 (2), 12/17; 2014: 1/14, 1/21, 2/14 (3), 2/21, 2/28 (2)
<ul style="list-style-type: none"> 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) 	2/14/14, 3/5/14
<ul style="list-style-type: 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>) Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) EOP2 meeting (<i>indicate date of mtg</i>) Mid-cycle Communication (<i>indicate date of mtg</i>) Late-cycle Meeting (<i>indicate date of mtg</i>) Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 1/13/12 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A 7/31/13 <input type="checkbox"/> N/A 10/8/13 Type A Meeting 1/8/13
<ul style="list-style-type: none"> Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 	<input type="checkbox"/> No AC meeting 10/18/13
Decisional and Summary Memos	
<ul style="list-style-type: none"> Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 3/19/14
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 3/19/14
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 2/18/14
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None [6 Total]
Clinical	
<ul style="list-style-type: none"> Clinical Reviews <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) Clinical review(s) (<i>indicate date for each review</i>) Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 12/04/13 <input checked="" type="checkbox"/> None
<ul style="list-style-type: 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>) 	3/4/14
<ul style="list-style-type: none"> Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input type="checkbox"/> None QT-IRT 8/12/13 & 12/24/13; DBRUP: 9/5/13, 9/10/13, 10/17/13, 1/16/14, & 2/6/14

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> 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>) 	n/a n/a <input type="checkbox"/> None 9/16/13 & 12/4/13 Clinical Review
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 10/15/13
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/26/13
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/30/13 & 2/19/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/24/13
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 10/4/13
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/4/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page n/a
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/12/13, 9/6/13, 11/21/13, & 1/23/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 6/5/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	n/a
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	CMC Review 9/6/13
<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 checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 1/17/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: n/a <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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 type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<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 checked="" 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 checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done n/a
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" 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/

MAUREEN P DILLON PARKER
03/20/2014

From: [Winiarski, Aleksander](#)
To: [DiBernardo, Gregory](#)
Cc: [Neshiewat, Julie](#)
Subject: RE: New Submission: NDA 204684-IMPAVIDO (miltefosine)-Paladin-Revised FINAL Carton/Container labels & Revised Debarment Certification
Date: Tuesday, February 25, 2014 12:50:31 PM

Hi Greg,

The resubmitted container labels and carton labeling are acceptable to DMEPA.

Thank you,

Alek

Aleksander Winiarski, PharmD

Safety Evaluator

FDA/CDER/OSE/OMEPRM/DMEPA

10903 New Hampshire Avenue

Building 22 Room 4426

Silver Spring, MD 20993

301-796-5295

aleksander.winiarski@fda.hhs.gov

From: DiBernardo, Gregory
Sent: Tuesday, February 25, 2014 12:35 PM
To: Winiarski, Aleksander
Subject: RE: New Submission: NDA 204684-IMPAVIDO (miltefosine)-Paladin-Revised FINAL Carton/Container labels & Revised Debarment Certification

Hi Alek,

In your 2/21/14, email you stated that the revised "unofficial" carton and container labels were acceptable from a DMEPA perspective. I was hoping you could respond to my 2/24 email that included the "official" submission of the revised carton and container labels.

I will DARRT your email response if that is okay.

Thanks,

Greg

From: DiBernardo, Gregory

Sent: Monday, February 24, 2014 2:27 PM

To: Smith, Thomas; Shamsuddin, Hala; Bala, Shukal; Wild, James S.; Zeng, Lan; Jang, Seong H; Zhou, Maotang; Banerjee, Anamitro; Seggel, Mark R; Winiarski, Aleksander

Cc: Nambiar, Sumathi; Laessig, Katherine A; Snow, Kerry; Schmidt, Wendelyn J; Higgins, Karen M; Colangelo, Philip M; Matecka, Dorota M; Dorantes, Angelica; Dillon Parker, Maureen P; Neshiewat, Julie; Neshiewat, Julie; Neshiewat, Julie

Subject: New Submission: NDA 204684-IMPAVIDO (miltefosine)-Paladin-Revised FINAL Carton/Container labels & Revised Debarment Certification

New Submission

NDA 204684

Impavido (miltefosine)

Paladin

Indication: Treatment of VL, CL, and ML

Revised Carton and Container Labels and Debarment Certification

Letter Date: 2/24/14

Stamp Date: 2/24/14

DARRTS Supporting Document #: 31

eCTD Sequence Number: 0030

PDUFA Goal Date: 3/19/14

Hello Team,

The Applicant has submitted revised/updated carton and container/blister labels per Information Request from DMEPA. The Applicant has also submitted an updated Debarment Certification in this submission per RPM request. I have copied DMEPA on this submission to see if they are in agreement with these **Final revisions**.

You can access this submission via the EDR Link below:

\\CDSESUB1\evsprod\NDA204684\0030

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager

FDA/CDER/OND/OAP/Division of Anti-Infective Products

10903 New Hampshire Avenue

Building 22, Room 6223

Silver Spring, MD 20993

Telephone: (301) 796-4063

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/s/

GREGORY F DIBERNARDO

03/05/2014

Memo to File: DMEPA agreement to final Carton and Container Labels

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Cc: ["jbe9320457@aol.com"](mailto:jbe9320457@aol.com)
Subject: FDA Communication: NDA 204684-IMPAVIDO (miltefosine)-Paladin-PMR Agreement-2/28/14
Date: Friday, February 28, 2014 5:39:00 PM
Attachments: [02.28.14 FINAL PMR Request.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an information request that includes the final Postmarketing Requirements (PMRs) for NDA 204684 IMPAVDIO (miltefosine). Please submit your agreement and concurrence as outlined in the attached document no later than **March 5, 2014**.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 28, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 3

Comments:

NDA 204684-Postmarketing Requirements for NDA 204684 to Paladin for Final Agreement

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL). In order to assist with of the review of NDA 204684, please submit your final agreement and concurrence information listed below.

We request that you submit to the NDA, an official submission, your stated agreement to each of the Postmarketing Requirements identified below. We further request that your agreement identify each Postmarketing Requirement specifically and completely.

Please be aware due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than **March 5, 2014**.

2127-1 Collect and analyze data regarding pregnancy outcomes for 10 years after approval of Impavido (miltefosine) in women who become pregnant while taking Impavido (miltefosine) or during 5 months after end of Impavido (miltefosine) therapy.

Final Protocol Submission:	March 2015
Interim Report Submission:	March 2016
Interim Report Submission,	March 2017
Interim Report Submission:	March 2018
Interim Report Submission:	March 2019
Interim Report Submission:	March 2020
Interim Report Submission:	March 2021
Interim Report Submission:	March 2022
Interim Report Submission:	March 2023
Interim Report Submission:	March 2024
Study Completion:	March 2025
Final Study Report Submission:	March 2026

2127-2 Conduct a study to evaluate the effects of Impavido (miltefosine) on spermatogenesis and male hormones in patients with leishmaniasis receiving Impavido (miltefosine) treatment. Evaluations will include semen volume, sperm count, sperm concentration and motility as well as evaluation of total testosterone and FSH.

Final Protocol Submission:	March 2015
Study Completion:	March 2018
Final Study Report Submission:	March 2019

2127-3 **Conduct a dedicated QT study in leishmaniasis patients receiving Impavido (miltefosine) treatment to evaluate the effects of Impavido (miltefosine) on the QT interval. ECGs and PK samples will be obtained to identify potential effects of Impavido (miltefosine) on the QT interval or other ECG parameters.**

Final Protocol Submission:	March 2015
Study Completion:	March 2018
Final Study Report Submission:	March 2019

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

APPEARS THIS WAY ON ORIGINAL

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/s/

GREGORY F DIBERNARDO
02/28/2014

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Cc: ["jbe9320457@aol.com"](mailto:jbe9320457@aol.com)
Subject: FDA Communication: NDA 204684-IMPAVIDO (miltefosine)-Paladin-PMC Agreement-2/28/14
Date: Friday, February 28, 2014 5:37:00 PM
Attachments: [02.28.14 FINAL PMC Request.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an information request that includes the final Postmarketing Commitments (PMCs) for NDA 204684 IMPAVDIO (miltefosine). Please submit your agreement and concurrence as outlined in the attached document no later than **March 5, 2014**.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 28, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

NDA 204684-Postmarketing Commitments for NDA 204684 to Paladin for Final Agreement
Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL). In order to assist with completion of the review of NDA 204684, please provide your final agreement and concurrence to the information listed below.

We request that you submit to the NDA, an official submission, your stated agreement to each of the Postmarketing Commitments identified below. We further request that your agreement identify each Postmarketing Commitment specifically and completely.

Please be aware due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than **March 5, 2014**.

2127-4 Conduct a descriptive study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75kg.

Final Protocol Submission:	March 2015
Interim Report Submission:	March 2016
Interim Report Submission:	March 2017
Interim Report Submission:	March 2018
Interim Report Submission:	March 2019
Study Completion:	March 2020
Final Study Report Submission:	March 2021

2127-5 Develop an appropriate method (such as HPLC) to be used for release and stability testing of the drug substance (assay and impurities) and the drug product (assay, impurities, and dissolution).

Final Protocol Submission:	April 2014
Study Completion:	March 2015
Final Report Submission:	June 2015

2127-6 In conjunction with the development and implementation of the HPLC methodology, perform (b) (4) testing in accordance with the 2003 FDA draft guidance for stratified testing.

Final Protocol Submission:	June 2014
Study Completion:	June 2017
Final Report Submission:	November 2017

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
02/28/2014

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Cc: ["jbe9320457@aol.com"](mailto:jbe9320457@aol.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Information Request to submit Revised Package Insert and Medication Guide
Date: Friday, February 21, 2014 5:22:00 PM
Attachments: [February 21 2014 Request to submit Revised PI and MG.pdf](#)
[02.21.14 draft-labeling-text-track-changes-JW and HS-2-5-2014.docx](#)
[2.10.14 Medication Guide.docx](#)
Importance: High

Hello Dr. Berman,

As a follow up to the ongoing labeling negotiations for NDA 204684, I am providing an Information Request to submit a revised Package Insert and Medication Guide to NDA 204684. As requested I have included both documents in the MS Word format with all changes accepted, please see the attached PDF document for the FDA proposed revisions.

Please be aware we have requested your official submission by **February 28, 2014**.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 21, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 23

Comments:

Information Request to submit a revised Package Insert and Medication Guide to NDA 204684

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for treatment of visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

As a follow up to the ongoing labeling negotiations, between Paladin and the FDA we would like to share the following information:

1. We are requesting you submit a revised Package Insert (PI) and Medication (MG) for NDA 204684 at this time. Please see the attached PI and MG for the FDA proposed revisions.
2. We request you use the format ~~strikeout~~ = deleted information and underline = added information as appropriate in your submission. Please include a clean MS Word version, a marked up MS Word version, a clean PDF version, and an annotated PDF version of the PI and MG in your submission.

Please submit your response to this information request to the NDA no later than **February 28, 2014**. If you anticipate any delay please contact the FDA.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GREGORY F DIBERNARDO

02/21/2014

Request to submit a revised Package Insert and Medication Guide

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684-IMPAVIDO (miltefosine)-Paladin-PMC Agreement
Date: Friday, February 14, 2014 5:05:00 PM
Attachments: [02.14.14 FINAL PMC Communication.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an information request that includes the final Postmarketing Commitments (PMCs) for NDA 204684 IMPAVDIO (miltefosine). Please submit your agreement and concurrence as outlined in the attached document no later than **February 21, 2014**.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 14, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 2

Comments:

NDA 204684-Postmarketing Commitments for NDA 204684 to Paladin for Final Agreement

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Information Request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL). In order to assist with completion of the review of NDA 204684, please provide your final agreement and concurrence to the information listed below.

We request that you submit to the NDA, an official submission, your stated agreement to each of the Postmarketing Commitments identified below. We further request that your agreement identify each Postmarketing Commitment specifically and completely.

Please be aware due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than **February 21, 2014**.

2127-005 Develop an appropriate method (such as HPLC) to be used for release and stability testing of the drug substance (assay and impurities) and the drug product (assay, impurities, and dissolution).

Final Protocol Submission:	April 2014
Study Completion:	March 2015
Final Report Submission:	June 2015

2127-006 In conjunction with the development and implementation of the HPLC methodology, perform (b) (4) testing in accordance with the 2003 FDA draft guidance for stratified testing.

Final Protocol Submission:	June 2014
Study Completion:	June 2017
Final Report Submission:	November 2017

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO

02/14/2014

Information Request to submit Agreement on PMC

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684-IMPAVIDO (miltefosine)-Paladin-PMR Agreement
Date: Friday, February 14, 2014 5:05:00 PM
Attachments: [02.14.14 FINAL PMR Communication.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an information request that includes the final Postmarketing Requirements (PMRs) for NDA 204684 IMPAVDIO (miltefosine). Please submit your agreement and concurrence as outlined in the attached document no later than **February 21, 2014**.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 14, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 2

Comments:

NDA 204684-Postmarketing Requirements for NDA 204684 to Paladin for Final Agreement

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1400. Thank you.

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL). In order to assist with of the review of NDA 204684, please submit your final agreement and concurrence information listed below.

We request that you submit to the NDA, an official submission, your stated agreement to each of the Postmarketing Requirements identified below. We further request that your agreement identify each Postmarketing Requirement specifically and completely.

Please be aware due to time constraints involved in this NDA review, we ask you submit a complete, official response to this request no later than **February 21, 2014**.

2127-001 Conduct a dedicated QT study to evaluate the effects of Impavido on the QT interval.

Final Protocol Submission:	March 2015
Study Completion:	March 2018
Final Study Report Submission:	March 2019

2127-002 Conduct a study to evaluate the effects of Impavido on spermatogenesis and male hormones.

Final Protocol Submission:	March 2015
Study Completion:	March 2018
Final Study Report Submission:	March 2019

2127-003 Collect data regarding pregnancy outcomes for 10 years after approval of Impavido in women who become pregnant while taking Impavido or during 5 months after end of Impavido therapy.

Final Protocol Submission:	March 2015
Interim Report Submission:	March 2016, then Annually
Trial/Study Completion:	March 2025
Final Study Report Submission:	March 2026

2127-004 Conduct a descriptive study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75kg.

Final Protocol Submission:	March 2015
Interim Report Submission:	March 2016, then Annually
Trial/Study Completion:	March 2020
Final Study Report Submission:	March 2021

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO

02/14/2014

Information Request to Submit PMR Agreement

From: [Winiarski, Aleksander](#)
To: [DiBernardo, Gregory](#); [Smith, Thomas](#); [Shamsuddin, Hala](#); [Bala, Shukal](#); [Wild, James S.](#); [Zeng, Lan](#); [Jang, Seong H](#); [Zhou, Maotang](#); [Banerjee, Anamitro](#); [Seggel, Mark R](#)
Cc: [Nambiar, Sumathi](#); [Laessig, Katherine A](#); [Snow, Kerry](#); [Schmidt, Wendelyn J](#); [Higgins, Karen M](#); [Colangelo, Philip M](#); [Matecka, Dorota M](#); [Dorantes, Angelica](#); [Dillon Parker, Maureen P](#); [Neshiewat, Julie](#)
Subject: RE: New Submission: NDA 204684-IMPAVIDO (miltefosine)-Paladin-Revised Carton/Container labels
Date: Tuesday, February 11, 2014 1:31:01 PM

Hi Greg,

The firm revised the blister labels and carton labeling as per our recommendations, except for one omission on the blister labels.

In our review we asked for each blister label to include an expiration date. I recognize that there is an expiration date on the blister card, but an expiration date on each blister label is necessary in case these individual blisters are separated.

Please instruct the firm to add an expiration date to each one of the blister labels, as per our original review. Otherwise the resubmitted labels and labeling are acceptable from DMEPA's perspective.

Feel free to upload this email to DARRTS as documentation.

Thank you,

Alek

Aleksander Winiarski, PharmD

Safety Evaluator

FDA/CDER/OSE/OMEPRM/DMEPA

10903 New Hampshire Avenue

Building 22 Room 4426

Silver Spring, MD 20993

301-796-5295

aleksander.winiarski@fda.hhs.gov

From: DiBernardo, Gregory
Sent: Friday, February 07, 2014 3:27 PM
To: Smith, Thomas; Shamsuddin, Hala; Bala, Shukal; Wild, James S.; Zeng, Lan; Jang, Seong H; Zhou, Maotang; Banerjee, Anamitro; Seggel, Mark R; Winiarski, Aleksander
Cc: Nambiar, Sumathi; Laessig, Katherine A; Snow, Kerry; Schmidt, Wendelyn J; Higgins, Karen M;

Colangelo, Philip M; Matecka, Dorota M; Dorantes, Angelica; Dillon Parker, Maureen P; Neshiewat, Julie; Neshiewat, Julie; Neshiewat, Julie
Subject: New Submission: NDA 204684-IMPAVIDO (miltefosine)-Paladin-Revised Carton/Container labels

New Submission

NDA 204684

Impavido (miltefosine)

Paladin

Indication: Treatment of VL, CL, and ML

Revised P

Letter Date: 2/7/14

Stamp Date: 2/7/14

DARRTS Supporting Document #: 28

eCTD Sequence Number: 0027

PDUFA Goal Date: 3/19/14

Hello Team,

The Applicant has submitted revised/updated carton and container/blister labels. This included the addition of their NDC number, keep out of reach of children statement, capsule ingredients, and barcodes . I have copied DMEPA on this submission to see if they are in agreement with these revisions.

You can access this submission via the EDR Link below:

<\\CDSESUB1\evsprod\NDA204684\0027>

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager

FDA/CDER/OND/OAP/Division of Anti-Infective Products

10903 New Hampshire Avenue

Building 22, Room 6223

Silver Spring, MD 20993

Telephone: (301) 796-4063

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/s/

GREGORY F DIBERNARDO

02/14/2014

Memo to Request Revised Carton and Container Labels Per DMEPA 2/11/14 Email Communication

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Request for revised carton and container labels
Date: Friday, February 14, 2014 2:39:00 PM
Attachments: [DMEPA Information Request to submit revised carton and container labels.pdf](#)
Importance: High

Hello Dr. Berman,

I have attached and information request to submit revised carton and container labels to NDA 204684. Please be aware that there will be no paper/hardcopy communication to follow this email communication.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: February 14, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

NDA 204684-Information Request to submit revised carton and container labels

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Information Request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL). We also refer to your February 7, 2014, submission that included revised carton and container labels for Impavido (miltefonine).

In order to assist with of the review of NDA 204684 we requested the Division of Medication Error, Prevention, and Analysis (DMEPA) review your February 7, 2014, submission. We request that you please submit revised carton and container labels that address the following:

We recognize that there is an expiration date on the blister card, but an expiration date on each blister label is necessary in the event that these individual blisters are separated. We also note that this information was provided to Paladin in our September 23, 2013, letter.

- Please add an expiration date to each one of the blister labels.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO

02/14/2014

DMEPA Information Request for Revised Carton and Container Labels

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684-Impavido (miltefosine)-Paladin-Request to Submit Revised Package Insert and Medication Guide
Date: Tuesday, January 21, 2014 4:45:00 PM
Attachments: [01.21.14 FDA impavido MG.docx](#)
[01.21.14 draft-labeling miltefosine.docx](#)
[01.21.14 Request to submit revised PI and MG.pdf](#)
Importance: High

Hello Dr. Berman,

As a follow up to the January 17, 2014, labeling teleconference I am providing an Information Request to submit a revised Package Insert and Medication Guide to NDA 204684. As requested I have included both documents in the MS Word format with all changes accepted, please see the attached PDF document for the FDA proposed revisions.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: January 21, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 22

Comments:

Information Request to submit a revised Package Insert and Medication Guide to NDA 204684
Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

As a follow up to the labeling teleconference held on January 17, 2014, between Paladin and the FDA we would like to share the following information:

1. We are requesting you submit a revised Package Insert (PI) and Medication (MG) for NDA 204684 at this time. Please see the attached PI and MG for the FDA proposed revisions.
2. We request you use the format ~~strikeout~~ = deleted information and underline = added information as appropriate in your submission. Please include a clean MS Word version and a marked up MS Word version of the PI and MG in your submission.

Please submit your response to this information request to the NDA no later than **February 4, 2014**.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GREGORY F DIBERNARDO

01/21/2014

Request to submit revised PI and MG to NDA

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Revised Labeling for 1/17/14 Teleconference
Date: Tuesday, January 14, 2014 5:20:00 PM
Attachments: [FDA Revised labeling for 01.17.17 Labeling Teleconference.pdf](#)
Importance: High

Hello Dr. Berman,

I would like to provide the revised labeling and supportive materials for the scheduled labeling teleconference on January 17, 2014, regarding NDA 204684. Please be aware that there will be no hardcopy/paper communication to follow this email communication.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: January 14, 2014

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 26

Comments:

FDA revisions to Package Insert and Medication Guide for NDA 204684

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

In preparation for the scheduled labeling teleconference on January 17, 2014, at 3:00 P.M., we would like to share the following information:

1. A revised/marked up version of the Package Insert (PI) and Medication Guide (MG) for Impavido (miltefosine).
2. FDA pharmacology/toxicology responses to labeling revisions proposed by Paladin in your January 3, 2014 submission.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GREGORY F DIBERNARDO
01/14/2014
FDA Revised Labeling for Labeling Teleconference

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684-Impavido (miltefosine)-Paladin-Request for Revised Package Insert and Medication Guide
Date: Tuesday, December 17, 2013 5:21:00 PM
Attachments: [12.17.13 Revised PI and MG IR.pdf](#)
[12.17.13 draft-labeling clean.doc](#)
[12.17.13 Copy of Medication Guide clean copy.docx](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request to submit a revised Package Insert and Medication Guide to NDA 204684. As requested I have included both documents in the MS Word format, please see the attached PDF for the FDA proposed revisions.

Please let me know if you have questions.

Thank you,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: December 17, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 22

Comments:

Information request to submit a revised Package Insert and Medication Guide to NDA 204684

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We would like to share the following information:

1. We are requesting you submit a revised Package Insert (PI) and Medication (MG) for NDA 204684 at this time. Please see the attached PI and MG for the FDA proposed revisions.
2. Since the **HIGHLIGHTS OF PRESCRIBING INFORMATION** is greater than a ½ page, you will need to include a request for a waiver from this requirement in your submission.
3. We request you use the format ~~strikeout~~ = deleted information and underline = added information as appropriate in your submission. Please include a clean MS Word version and a marked up MS Word version of the PI and MG in your submission.

FDA may have additional PI and MG revisions, if they are needed this information will be provided at a later date.

Please submit your response to this information request to the NDA no later than **January 7, 2014**.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GREGORY F DIBERNARDO
12/17/2013
Revised Labeling Request for NDA 204684



NDA 204684

MID-CYCLE COMMUNICATION

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) Capsule, 50 mg.

We also refer to the teleconference between representatives of your firm and the FDA on July 31, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Thomas Smith, M.D.
Clinical Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 31, 2013 at 2:00 P.M. to 3:00 P.M.

Application Number: NDA 204684

Product Name: Impavido (miltefosine)

Indication: Treatment for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

Applicant Name: Paladin Therapeutics, Inc.

Meeting Chair: Thomas Smith, M.D.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H. Acting Director
Thomas Smith, M.D. Clinical Team Leader
Hala H. Shamsuddin, M.D. Medical Officer
Shukal Bala, Ph.D. Clinical Microbiology Reviewer
James S. Wild, Ph.D. Pharmacology/Toxicology Reviewer
Frances V. LeSane Chief, Project Management Staff
Susmita Samanta, M.D. Safety Regulatory Project Manager
Gregory F. DiBernardo Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Seong H. Jang, Ph.D. Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Lan Zeng, M.S. Biostatistics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Dorota M. Matecka, Ph.D. Chemistry, Manufacturing, and Controls (CMC) Lead
Moatang Zhou, Ph.D. CMC Reviewer-Drug Substance

Anamitro Banerjee, Ph.D.

CMC Reviewer-Drug Product

Division of Risk Management (DRISK)

Cynthia LaCivita

Risk Management Team Leader

Office of Strategic Programs (OSP)

Kimberly Taylor

Operations Research Analyst



APPLICANT ATTENDEES

Paladin Therapeutics, Inc.

Robert K. Vinson, Ph.D.

Director, Product Development

Fast Track Drugs and Biologics, LLC



Jonathan Berman, M.D., Ph.D.

Vice President Clinical Affairs



1.0 INTRODUCTION

FDA read the following information to start the meeting: We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

FDA informed Paladin that two review disciplines had identified significant review issues. The following information was provided to Paladin:

Chemistry, Manufacturing, and Controls (CMC) Comments:

Reference is made to our June 20, 2013 communication. We note that deficiencies #1, #7, #8 and #9 concerning drug substance characterization by  analytical method validation, polymorphicity, and identity testing, respectively, are currently outstanding. You

stated on July 10, 2013, that responses to these questions would be submitted within 90 days. Our reviews are now being finalized in accordance with our internal review milestones.

Pharmacology/Toxicology Comments:

In the June 20, 2013, communication from the FDA, you were notified that the HPTLC method of measuring the two degradants, (b) (4) was considered deficient and corrective actions were recommended. In order to verify that levels of (b) (4) and (b) (4) in the drug substance remain within the qualification threshold amounts recommended in the ICH Q3A(R2) guidance, the HPTLC method deficiencies must be corrected.

Meeting Discussion:

Paladin informed FDA that some of the requested CMC information could not be responded to in the time period FDA had requested, but Paladin informed FDA that this information would be submitted to the NDA in early October, 2013. Paladin stated the delay in providing the information was due to the fact that the information simply was not available, that time was needed to develop the information, and that the vacation period in Europe affected their contractors who were working on this request. Paladin stated they could address all requests within 90 days. Paladin asked FDA if they would like the requested information as a single submission or multiple submissions as the information became available. FDA stated that the original response due date was July 10, 2013. Paladin stated that it was physically impossible for them to respond completely to FDA's requests by that date. FDA stated that if Paladin wanted to submit the information in multiple submissions that would be acceptable. FDA stated that since the 90 day date falls outside of the time period the primary review team would be examining information for this NDA review cycle, FDA would need to determine if the final submission along with the other submissions constituted a Major Amendment to the NDA. FDA stated that the implication of a Major Amendment to an NDA was an extension of the PDUFA NDA due date. FDA also stated that they planned to move forward with the Advisory Committee meeting for this NDA review cycle.

Paladin inquired if the validation data for HPTLC method could be submitted as a Postmarketing Requirement (PMR). Paladin stated that the request for HPTLC method would take the most time and if it could not be completed, could they present the option of completing this requirement as a PMR to the CMC team. FDA stated that the validation data for the current HPTLC methodology is needed in this review cycle. It is understood that in the future the HPTLC method will be replaced with a suitable HPLC method via a PMR.

The Pharmacology/Toxicology Team indicated that their comments would be addressed if all of the CMC issues were resolved. FDA stated that once that happened the Pharmacology/Toxicology Team's comments would not be a significant issue.

3.0 INFORMATION REQUESTS

FDA stated the following regarding current and outstanding Information Requests:

A Clinical Information Request will issue within a week.

Meeting Discussion:

FDA informed Paladin they would be issuing a Clinical Information Request within the week and wanted Paladin to be aware of this request. Paladin stated the sooner they received the information request the better it would be for them. FDA stated they would get the Information Request out as soon as possible.

FDA stated they would like to briefly discuss their expectation on Paladin's responses to FDA Information Requests.

Meeting Discussion:

FDA stated that they were concerned about the turnaround time for FDA Information Requests. FDA stated that they thought it was reasonable to expect Paladin to submit a response to an Information Request to the NDA within two weeks. Paladin stated that if no due date was presented in an Information Request, then the request would not be acted upon immediately. Therefore, Paladin requested that a due date be included in future Information Requests. Paladin also agreed that they would be able to turnaround future FDA Information Requests within two weeks.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

FDA stated that there were no major safety concerns identified at this time; however, the need for a REMS would be a review issue.

FDA stated they would like to have a brief discussion on the July 29, 2013, response to DRISK Information Request.

Meeting Discussion:

Paladin inquired if FDA thought there would be a reason to require a REMS, since Paladin did not think one would be needed. FDA stated that they were interested in Paladin's plan to mitigate teratogenicity; for instance, would Paladin propose labeling and/or a Medication Guide to mitigate this risk. Paladin stated that they proposed a Medication Guide and appropriate language in the US Package Insert (USPI) in their response. Paladin stated that they could draft a Medication Guide and submit it to the NDA, but wanted to hear input from the FDA before it was finalized and submitted. Paladin stated they understood that a REMS had many elements. Paladin stated a REMS was not one item but many to select from and this lack of clarity had

created a problem for them. FDA suggested that Paladin draft and submit a Medication Guide to the NDA for FDA to review. FDA stated that a Medication Guide alone was not a REMS, but it could be a part of a REMS plan. Again, FDA wanted to make Paladin aware that the inclusion of a REMS for this NDA, as stated earlier, was still a review issue. Paladin agreed that a Medication Guide was needed for their product and stated they would submit one to the NDA. FDA inquired on the expected date of submission and Paladin stated it would be submitted by August 10, 2013.

5.0 ADVISORY COMMITTEE MEETING

FDA confirmed that the date of the Advisory Committee was October 18, 2013.

Meeting Discussion:

FDA again stated that they planned on moving forward with the October 18, 2013, Advisory Committee meeting in light of the significant review issues identified earlier and that the FDA Advisors and Consultants staff would contact Paladin to assist them in the process, especially in notifying Paladin of the required due dates. FDA stated they had no further updates.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

FDA provided Paladin with the following information on the projected NDA Milestone dates:

Issue Labeling to Paladin: September 23, 2013

If needed, Issue Discipline Review Letters: September 28, 2013

Issue Late Cycle Meeting Package to Paladin: October 1, 2013

Late Cycle Meeting date: October 8, 2013

Meeting Discussion:

FDA stated the purpose of this meeting was to discuss substantive review issues. FDA also informed Paladin that they would receive the FDA Advisory Committee background package in preparation for this meeting. FDA stated Paladin would see overlap in what FDA presented to the Advisory Committee and what Paladin would most likely present, and Paladin would see the issues FDA planned to discuss. FDA stated that under PDUFA V the primary FDA reviewers would need to have their reviews completed before the Advisory Committee meeting; however, PDUFA V offers upper level reviewers more time to access primary reviews and the input of the

NDA 204684
Mid-Cycle Communication

Advisory Committee before they need to finalize their decisions. This meeting would not include a discussion of the final outcome of FDA's review of Paladin's NDA.

PDUFA Goal Date: December 19, 2013

FDA thanked Paladin for their time and looked forward to receiving the materials discussed during the teleconference.

APPEARS THIS WAY ON ORIGINAL

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/s/

THOMAS D SMITH
11/22/2013



NDA 204684

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your April 19, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Impavido (miltefosine) Capsules, 50 mg.

On October 15, 2013, we received your October 14, 2013, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 19, 2014.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
11/08/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-CMC Information Request
Date: Friday, November 08, 2013 11:39:00 AM
Attachments: [CMC Request for revised Carton Label.pdf](#)

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: November 8, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-4063
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

Information request to NDA 204684 to submit revised carton label

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Information Request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL).

We also refer to your October 17, 2013, submission and we would like to request the following information be officially submitted to the NDA.

Please make the following change on the carton label:

Change from [REDACTED] [REDACTED] ^{(b) (4)} **to** "Store at 20-25 °C (68–77 °F); excursions permitted to 15-30 °C (59 – 86 F). [See USP Controlled Room Temperature]."

Please submit the revised carton label to the NDA no later than **November 22, 2013**.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO

11/08/2013

Request to submit revised carton label



NDA 204684

**METHODS VALIDATION
MATERIALS RECEIVED**

Paladin Therapeutics, Inc.
Attention: Jonathan Berman, MD, PhD, VP for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898
FAX: (301) 230-0427

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Impavido® (miltefosine) capsules, 50 mg and to our June 28, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 23, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/24/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Clinical/Clinical Pharmacology Information Request
Date: Tuesday, October 15, 2013 2:35:00 PM
Attachments: [Clinical and Clinical Pharmacology Information Request.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: October 15, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

Information request to NDA 204684

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Information Request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis (VL), mucosal leishmaniasis (ML), and cutaneous leishmaniasis (CL).

We would like to request the following information be officially submitted to the NDA:

Miltefosine labeling recommends a dose of 150 mg daily for patients weighing more than 45 kg. Clinical studies evaluating the efficacy and safety of miltefosine in the treatment of VL and CL indicate that cure is numerically lower in patients who received less than 2 mg/kg/day. In the United States, the anticipated use of miltefosine to treat VL or CL will be in deployed personnel or travelers to endemic areas, in whom the proposed 150 mg daily dose may be equivalent to < 2 mg/kg/day dose.

Please submit a rationale for proposing a fixed total daily dose rather than a mg/kg/day dose, including any safety or tolerability data pertaining to doses greater than 150 mg daily in patients weighing more than 75 kg.

Please submit your response to the NDA no later than October 29, 2013.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
10/15/2013
NDA Information Request

From: [Josh Berman](#)
To: [DiBernardo, Gregory](#)
Subject: RE: FDA Communication: IND 105430-Impavido (miltefosine)-Paladin-"The Program" under PDUFA V
Date: Friday, July 27, 2012 3:44:31 PM

Dear Gregory,

Thank you for this notice, and for our telephone conversation.

We intend to submit the NDA for Impavido (miltefosine) in Sep 2012 prior to 1 Oct 2012.

We will keep in mind

- 1) The Agency-Sponsor understanding on pivotal trials as finalized in the minutes of the 13 Jan 2012 pre-NDA meeting
- 2) issues about final CMC stability reports. All Study Reports are complete.
- 3) The need for a complete NDA according to 212 CFR 314.50, including listing of clinical sites and manufacturing facilities.

If we submit on or after 1 Oct 2012, we will of course accord with PDUFA V.

Regards,

Jonathan Berman MD PhD
Vice President for Clinical Affairs
Fast Track Drugs and Biologics
North Bethesda MD 20852
301-922-2097

From: DiBernardo, Gregory [mailto:Gregory.DiBernardo@fda.hhs.gov]
Sent: Friday, July 27, 2012 2:55 PM
To: jberman@fasttrackresearch.com
Cc: Dillon Parker, Maureen P; LeSane, Frances V
Subject: FDA Communication: IND 105430-Impavido (miltefosine)-Paladin-"The Program" under PDUFA V
Importance: High

Hello Dr. Berman,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine). We also refer to the pre-NDA meeting between representatives of your firm and the FDA on January 13, 2012, and to our February 9, 2012, official meeting minutes.

Please be advised that if your application is submitted to FDA on or after October 1, 2012, it will be subject to "The Program" under PDUFA V (see: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

Under the Program, applicants are strongly encouraged to discuss the planned content of their application with the appropriate FDA review division at a pre-submission (pre-NDA or pre-BLA) meeting to 1) reach agreement on the content of a complete application, including preliminary discussions on the need for risk evaluations and mitigation strategies (REMS) or other risk management actions, and 2) reach agreement on submission of a limited number of minor application components (components of the type that would not be expected to materially impact the ability of the review team to begin its review) not later than 30 calendar

days after submission of the original application.

As previously noted, the pre-submission meeting for your proposed application has already been held. We encourage you to request a follow-up teleconference with the review division to discuss the elements of the Program outlined above. If you wish to have such a discussion, please contact me at (301) 796-4063 and I will schedule the teleconference.

If you elect not to schedule such a teleconference, we strongly encourage you to review the *PDUFA Reauthorization Performance Goals and Procedures, Fiscal Years 2013 through 2017* and, in particular, the elements of the Program that can be found at the link provided above.

If you have questions please let me know.

Thank you,

Gregory F. DiBernardo
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063

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/s/

GREGORY F DIBERNARDO

10/03/2013

Communication offering Applicant Follow Up Teleconference prior to NDA submission



NDA 204684

LABELING PMR/PMC DISCUSSION COMMENTS

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your April 19, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavdio (miltefosine) Capsules, 50 mg.

We also refer to our June 18, 2013, letter in which we notified you of our target date of September 23, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017."

We received your June 27, and August 9, 2013, submissions to this application and have proposed labeling revisions that are included as an enclosure. Although these revisions have been reviewed and cleared to the level of Cross Discipline Team Leader, we anticipate additional labeling discussions/communications pertaining to these revisions and to the other sections of the product labeling.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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

ENCLOSURE: Labeling Revisions and Postmarketing Requirements/Commitments

I. FULL PRESCRIBING INFORMATION REVISIONS:

2 DOSAGE AND ADMINISTRATION

The (b) (4) for 28 consecutive days. Administer with food to ameliorate gastrointestinal adverse reactions.

Table xxx. Miltefosine Dosage

Weight	Dosage and Administration
30 kg to 44 kg	One 50 mg capsule twice daily with food (breakfast and dinner)
45 kg or greater	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)

10 OVERDOSAGE

(b) (4)
Please propose a revised **OVERDOSAGE** Section. If known, please include a description of signs, symptoms, and laboratory findings of overdose, complications that can occur, whether the drug is dialyzable, and any specific measures for support of vital functions (e.g., antidotes, gastric lavage, and forced diuresis).

12.4 MICROBIOLOGY

Mechanism of Action

The specific mode of action of miltefosine against *Leishmania* species is unknown. The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death.

Activity *In Vitro* and *In Vivo*

Miltefosine has anti-leishmanial activity *in vitro* and in clinical infections [see *Clinical Studies (14)*]. Sensitivity of different *Leishmania* species as well as different strains of a *Leishmania* species to miltefosine may vary in different geographic regions.

Drug Resistance

In vitro studies show a potential for development of resistance to miltefosine. Some strains of *L. braziliensis* with intrinsic resistance to miltefosine have been identified.

Drug resistance could be due to a decrease in miltefosine accumulation in *Leishmania*, which is thought to be due to either an increase in drug efflux mediated by the overexpression of the ABC transporter P-glycoprotein, and/or a decrease in drug uptake by the inactivation of the miltefosine transport machinery that consists of the miltefosine transporter and its beta subunit. (b) (4) mutation in the transporter gene was reported in the isolates from a relapsed patient in one study.

II. CARTON AND CONTAINER REVISIONS:

Blister Labels

1. The current blister card configuration does not provide labeling on each individual blister; therefore if individual blisters are cut or separated from the blister card, they would be unidentifiable. Revise the blister label so that each individual capsule blister contains at least all of the elements required by the small label rules, including the proprietary name, the established name, strength statement, lot number, expiration date, and manufacturer name, as per 21CFR 201.10(i).
2. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Your product has not been provided an exception, therefore we request you add the product barcode to each individual capsule blister as required per 21CFR 201.25(b)(1)(ii).
3. Relocate the dosage form “capsule” from next to the proprietary name to after the active ingredient, which creates the full established name (miltefosine) capsules.
4. Remove the (b) (4) statement as it contributes to clutter and its removal will allow room for the addition of other required elements to the labels.
5. Replace the (b) (4) statement with the “Lot:” statement, as that is the customary statement on US labels.

Carton Labeling

1. The company logo competes for prominence with the product names and strength statement. Decrease the prominence of the company logo by significantly decreasing its size.
2. Decrease the prominence of checkered graphic and net quantity statement by decreasing their size, as it is as prominent as the strength statement, and thus could be confused for the strength.
3. Revise the net quantity statement to: 2 blister cards, 14 blisters per card, 1 capsule per blister.
4. To clarify that each capsule contains 50 mg of miltefosine, revise the strength statement from 50 mg Capsules to 50 mg per Capsule.
5. Include the dosage form after the active ingredient, which creates the full established name, for example (miltefosine) capsules.

III. PROPOSED POSTMARKETING REQUIREMENTS/COMMITMENTS:

Following are some preliminary thoughts on potential PMRs/PMCs. We may have additional requests as the review progresses.

Clinical Postmarketing Requirement:

Please complete a dedicated QT study to evaluate the effects of Impavido (miltefosine) on cardiac repolarization.

CMC (Quality) Postmarketing Commitment:

Develop an appropriate method (such as HPLC) for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules.

APPEARS THIS WAY ON ORIGINAL

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/s/

MAUREEN P DILLON PARKER
09/23/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204684

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
5 Paramus Court
North Potomac, MD 20898

ATTENTION: Jonathan Berman, M.D., Ph.D.
Vice President for Clinical Affairs

Dear Dr. Berman:

Please refer to your New Drug Application (NDA), dated and received, April 19, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Miltefosine Capsules, 50 mg.

We also refer to your correspondence, dated and received June 10, 2013, requesting review of your proposed proprietary name, Impavido. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Impavido, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If **any** of the proposed product characteristics as stated in your April 19, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Gregory DiBernardo, at (301) 796-4063.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/06/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Cc: ["jbe9320457@aol.com"](mailto:jbe9320457@aol.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-DBRUP IR
Date: Tuesday, August 13, 2013 3:44:00 PM
Attachments: [DBRUP_IR_08.13.13.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: August 13, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	
Cc: jbe9320457@aol.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

Information request

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NDA 204684
Information Request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We would like to request the following information be officially submitted to the NDA:

Please clarify whether any of the women enrolled in the clinical trials had any follow up regarding reproductive function. Specifically, did they have any pregnancies (incidence and outcome) or problems conceiving? If such follow up information was collected, please tabulate the following information by study:

- Number of Women of Childbearing Age Enrolled
- Subject ID
- Form of Birth Control During Treatment
- Treatment Period
- Pregnancy During the Year Following Treatment
- Attempted Pregnancy During the Year Following Treatment
- Estimated Date of Conception
- Pregnancy Outcome

We would like to request your response to this request by August 16, 2013, if possible. If this timeline is not feasible, please submit your response no later than August 27, 2013.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
08/13/2013
NDA Information Request



NDA 204684

INFORMATION REQUEST

Paladin Therapeutics Inc.
Attention: Jonathan Berman
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted September 26, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido, (miltefosine) capsules.

We also refer to your June 26, 2013 submission, containing a response to our June 20, 2013 information request.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by August 8, 2013, in order to complete our evaluation of your NDA.

1. In response to the deficiency 5 in the IR letter dated June 20, 2013, you indicated that the specifications for [REDACTED] ^{(b) (4)} will be removed upon generation of acceptable data for the first three commercial drug substance batches. Although we agree the above specification may be removed if a representative number of commercial batches demonstrate process capability for removal of these impurities, data from three batches alone is not sufficient. The supplement for removal of the specifications for these impurities should also include data from several historical batches (manufactured by the proposed commercial process) or data from additional commercial batches.
2. Reference is made to the statement, "Other batch sizes within validated ranges may be used with proportional scaling of ingredients," in Section 3.2.P.3.2 of the NDA submission. Please clarify what batch size ranges are currently validated and/or proposed for commercial manufacture in the NDA.
3. Table 3.2.P.3.4-1 in Section 3.2.P.3.4 of the NDA submission lists [REDACTED] ^{(b) (4)} values ranging from [REDACTED] ^{(b) (4)} for top, middle, and bottom samples of Batch 2639 and Batch 3150.. Clarify what these values represent and how they were determined. Indicate if the [REDACTED] ^{(b) (4)} criteria in FDA's draft Guidance for Industry, [REDACTED] ^{(b) (4)} [REDACTED] are met and provide the RSD and mean values for the above data.

4. Based on the totality of the information submitted in the NDA, we have determined a shelf life of 24 months when stored under USP controlled room temperature, i.e. 20 - 25 °C (68 - 77 °F), with excursions permitted for 15 – 30 °C (59 – 86 °F) is appropriate for Impavido® (miltefosine) Capsules, 50 mg. Provide revised labeling at the time the division initiates labeling discussion.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWA
08/02/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Clinical Information Request
Date: Wednesday, July 31, 2013 3:18:00 PM
Attachments: [07.31.13 Clinical.pdf](#)
Importance: High

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA by August 14, 2013.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 31, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 4

Comments:

Information Request

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We also refer to your September 26, 2012, and April 19, 2013, submissions and would like to request the following information be officially submitted to the NDA:

Upon review of the study report and datasets submitted we note the following:

Visceral Leishmaniasis – Study 3154

1. The study report for Study 3154 states that 97 subjects who received miltefosine and 16 subjects who received amphotericin B had symptoms compatible with visceral leishmaniasis (VL) at the 6 months follow-up visit.

A listing of the 113 subjects was provided in Table 12.1 of the study report. Of the 16 amphotericin subjects listed, 6 months data were not available for 4 subjects (subjects 1/137, 2/021, 3/052 and 3/024). Of the 97 miltefosine subjects listed, 6 months data were not available for 9 subjects (subjects 1/086, 2/009, 2/043, 2/048, 2/092, 3/030, 3/038, 3/069, 3/092). The remaining 88 subjects in the miltefosine arm and the remaining 12 subjects in the amphotericin arm could be identified from the VS, OM and LB datasets using the protocol definition of residual VL signs and symptoms (fever, spleen that had not regressed by at least 30% of baseline, hemoglobin < 10 if female and < 11.5 if male, platelets < 100,000 and WBC < 3500).

The DC dataset also identifies 88 miltefosine subjects and 12 amphotericin subjects with residual signs and symptoms of VL at the 6 month follow period in the domain DCTERM = "Cause of abnormality". However, 4 of the identified miltefosine subjects (3154-2/025, 3154-2/046, 3154-2/069, 3154-2/129) do not fit the protocol specified criteria and also do not appear in Table 12.1 of the study report, while another 4 subjects (3154-1/061, 3154-2/111, 3154-2/128, 3154-3/106) who are identified as having signs and symptoms (lack of spleen regression in one and anemia in 3) using the protocol specified criteria and who are included in Table 12.1 are not identified in the DC dataset.

2. The study report states that 27 subjects were further assessed with bone marrow or spleen aspirates, and alternative diagnoses explained the residual symptoms at 6 months in the remaining subjects with residual signs of symptoms compatible with VL.

We note that the clinical response dataset ADCRP indicates that 29 subjects underwent a follow up aspirate at the 6 month follow up visit, not 27. These two additional subjects included one amphotericin subject (subject 1/104) and one miltefosine subject (subject 1/003).

3. Of the 100 subjects with any abnormality in Table 12.1 that may be related to VL at the 6 months follow up, 27 were at study site 1, 35 were at site study 2, and 38 were at study site 3. However, more than 90% the aspirates were performed at site 1 (23 aspirates out of 27 if the study report is accurate, or 25 out of 29 if the datasets are accurate) compared to 2 aspirates at each of sites 2 and 3. This substantial variation in performing a follow up aspirate versus attributing the abnormalities to an alternative diagnosis between the study sites may alter the final cure rate.

We identified 14 additional subjects in whom a follow up aspirate may have been informative because of persistent severe anemia and/or persistent thrombocytopenia or leukopenia, 2 in the amphotericin arm and 12 in the miltefosine arm. These subjects are 2/101 and 3/019 in the amphotericin arm and 2/002, 2/012, 3/003, 3/012, 3/025, 3/035, 3/077, 3/078, 3/095, 3/102, 3/103 and 3/109. Considering these subjects failures, the final cure rate is calculated as 270/299 (90.3%) in the miltefosine arm and 94/99 (94.9%) in the amphotericin arm. The difference is -4.6% (95% CI -.82%, 10.1%) in the ITT population. The cure rates are 93.0% vs. 97.9% in the PP population (difference -4.9%, 95% CI 0.70%, 8.99%).

Although the amended cure rates indicate that miltefosine still meets the 10% NI margin, we would be interested in discussing the above noted discrepancies and our approach to determining the final cure rate.

Cutaneous Leishmaniasis

Review of the submitted studies indicates that the cure rate of lesions in Guatemalan subjects enrolled in Study 3168 is lower compared to subjects enrolled in Studies Soto and Z020b where *L. braziliensis* is the predominant pathogen. An earlier timepoint to evaluate apparent or partial cure was used in Study 3168, and failures at 2 weeks post therapy were carried forward to 6 months. Adjusting for this difference in definition of endpoints does not alter the placebo and miltefosine cure rates in Colombia and increases the placebo cure rate in Guatemala to 25.0%. The miltefosine cure rate in Guatemala increases to 57.5%, a rate that is still lower compared to the approximately 80% rate in the other two studies.

We are unable to identify differences in drug exposure, host factors or disease characteristics to explain the lower response in Guatemala. If available, please provide any data that may exist regarding possible geographic differences in susceptibility of *L. braziliensis* to miltefosine.

Safety

Please clarify the definitions used to identify subjects who experienced elevations of Cr or liver enzymes. Using version 4.03 of CTCAE definitions, our results for the number of subjects who experienced elevations in these laboratory parameters are widely different than the numbers reported in the study report of each submitted study. For example, in Study 3168, you report that 33% of miltefosine subjects and 9% of placebo

NDA 204684
Information Request

subjects had Cr elevation at EOT. Our results indicate that the number of subjects who had elevation of Cr 1-<1.5x above baseline was 51/89 (57.3%) in the miltefosine arm and 24/44 (54.5%) in the placebo arm. 11/89 (12.4%) miltefosine subjects and 2/44 (4.5%) placebo subjects had elevations ≥ 1.5 -3x baseline and one miltefosine subject had elevation ≥ 3 x baseline. In the same study, the study report indicates that 18 and 29% of miltefosine and placebo recipients respectively experienced an elevation of AST or ALT at the EOT. Our results indicate that 5/89 (5.6%) and 2/44 (4.5%) of miltefosine and placebo recipients had any elevation of ALT or AST above ULN, and no subject experienced an elevation of ALT or AST ≥ 3 x ULN at EOT.

Please submit your response to this information request by August 14, 2013.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 31, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 4

Comments:

Information Request

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We also refer to your September 26, 2012, and April 19, 2013, submissions and would like to request the following information be officially submitted to the NDA:

Upon review of the study report and datasets submitted we note the following:

Visceral Leishmaniasis – Study 3154

1. The study report for Study 3154 states that 97 subjects who received miltefosine and 16 subjects who received amphotericin B had symptoms compatible with visceral leishmaniasis (VL) at the 6 months follow-up visit.

A listing of the 113 subjects was provided in Table 12.1 of the study report. Of the 16 amphotericin subjects listed, 6 months data were not available for 4 subjects (subjects 1/137, 2/021, 3/052 and 3/024). Of the 97 miltefosine subjects listed, 6 months data were not available for 9 subjects (subjects 1/086, 2/009, 2/043, 2/048, 2/092, 3/030, 3/038, 3/069, 3/092). The remaining 88 subjects in the miltefosine arm and the remaining 12 subjects in the amphotericin arm could be identified from the VS, OM and LB datasets using the protocol definition of residual VL signs and symptoms (fever, spleen that had not regressed by at least 30% of baseline, hemoglobin < 10 if female and < 11.5 if male, platelets < 100,000 and WBC < 3500).

The DC dataset also identifies 88 miltefosine subjects and 12 amphotericin subjects with residual signs and symptoms of VL at the 6 month follow period in the domain DCTERM = "Cause of abnormality". However, 4 of the identified miltefosine subjects (3154-2/025, 3154-2/046, 3154-2/069, 3154-2/129) do not fit the protocol specified criteria and also do not appear in Table 12.1 of the study report, while another 4 subjects (3154-1/061, 3154-2/111, 3154-2/128, 3154-3/106) who are identified as having signs and symptoms (lack of spleen regression in one and anemia in 3) using the protocol specified criteria and who are included in Table 12.1 are not identified in the DC dataset.

2. The study report states that 27 subjects were further assessed with bone marrow or spleen aspirates, and alternative diagnoses explained the residual symptoms at 6 months in the remaining subjects with residual signs of symptoms compatible with VL.

We note that the clinical response dataset ADCRP indicates that 29 subjects underwent a follow up aspirate at the 6 month follow up visit, not 27. These two additional subjects included one amphotericin subject (subject 1/104) and one miltefosine subject (subject 1/003).

3. Of the 100 subjects with any abnormality in Table 12.1 that may be related to VL at the 6 months follow up, 27 were at study site 1, 35 were at site study 2, and 38 were at study site 3. However, more than 90% the aspirates were performed at site 1 (23 aspirates out of 27 if the study report is accurate, or 25 out of 29 if the datasets are accurate) compared to 2 aspirates at each of sites 2 and 3. This substantial variation in performing a follow up aspirate versus attributing the abnormalities to an alternative diagnosis between the study sites may alter the final cure rate.

We identified 14 additional subjects in whom a follow up aspirate may have been informative because of persistent severe anemia and/or persistent thrombocytopenia or leukopenia, 2 in the amphotericin arm and 12 in the miltefosine arm. These subjects are 2/101 and 3/019 in the amphotericin arm and 2/002, 2/012, 3/003, 3/012, 3/025, 3/035, 3/077, 3/078, 3/095, 3/102, 3/103 and 3/109. Considering these subjects failures, the final cure rate is calculated as 270/299 (90.3%) in the miltefosine arm and 94/99 (94.9%) in the amphotericin arm. The difference is -4.6% (95% CI -.82%, 10.1%) in the ITT population. The cure rates are 93.0% vs. 97.9% in the PP population (difference -4.9%, 95% CI 0.70%, 8.99%).

Although the amended cure rates indicate that miltefosine still meets the 10% NI margin, we would be interested in discussing the above noted discrepancies and our approach to determining the final cure rate.

Cutaneous Leishmaniasis

Review of the submitted studies indicates that the cure rate of lesions in Guatemalan subjects enrolled in Study 3168 is lower compared to subjects enrolled in Studies Soto and Z020b where *L. braziliensis* is the predominant pathogen. An earlier timepoint to evaluate apparent or partial cure was used in Study 3168, and failures at 2 weeks post therapy were carried forward to 6 months. Adjusting for this difference in definition of endpoints does not alter the placebo and miltefosine cure rates in Colombia and increases the placebo cure rate in Guatemala to 25.0%. The miltefosine cure rate in Guatemala increases to 57.5%, a rate that is still lower compared to the approximately 80% rate in the other two studies.

We are unable to identify differences in drug exposure, host factors or disease characteristics to explain the lower response in Guatemala. If available, please provide any data that may exist regarding possible geographic differences in susceptibility of *L. braziliensis* to miltefosine.

Safety

Please clarify the definitions used to identify subjects who experienced elevations of Cr or liver enzymes. Using version 4.03 of CTCAE definitions, our results for the number of subjects who experienced elevations in these laboratory parameters are widely different than the numbers reported in the study report of each submitted study. For example, in Study 3168, you report that 33% of miltefosine subjects and 9% of placebo

NDA 204684
Information Request

subjects had Cr elevation at EOT. Our results indicate that the number of subjects who had elevation of Cr 1-<1.5x above baseline was 51/89 (57.3%) in the miltefosine arm and 24/44 (54.5%) in the placebo arm. 11/89 (12.4%) miltefosine subjects and 2/44 (4.5%) placebo subjects had elevations ≥ 1.5 -3x baseline and one miltefosine subject had elevation ≥ 3 x baseline. In the same study, the study report indicates that 18 and 29% of miltefosine and placebo recipients respectively experienced an elevation of AST or ALT at the EOT. Our results indicate that 5/89 (5.6%) and 2/44 (4.5%) of miltefosine and placebo recipients had any elevation of ALT or AST above ULN, and no subject experienced an elevation of ALT or AST ≥ 3 x ULN at EOT.

Please submit your response to this information request by August 14, 2013.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
07/31/2013
Clinical Information Request

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-DRISK IR
Date: Tuesday, July 09, 2013 10:53:00 AM
Attachments: [DRISK Information Request.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: July 9, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 2

Comments:

Information request

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Information request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We also refer to your September 26, 2012, and April 19, 2013, submissions and would like to request the following information be officially submitted to the NDA:

1. All worldwide post marketing reports of pregnancy exposure, including the treatment period, the estimated time of conception, and pregnancy outcome, whether known or unknown
2. The estimated U.S. future use of miltefosine
3. The estimated U.S. military use of miltefosine, including within the U.S. for military personnel, and use outside the U.S. for U.S. military personnel
4. The estimated U.S. use of miltefosine among women of childbearing potential, including military use and non-military use
5. Your rationale for why miltefosine does not need a risk evaluation and mitigation strategy (REMS) to mitigate the risk of teratogenicity

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
07/09/2013
DRISK Information Request



NDA 204684

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Paladin Therapeutics, Inc.
Attention: Jonathan Berman, MD, PhD
VP for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898
FAX: (301) 230-0427

Dear Dr. Jonathan Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Impavido® (miltefosine) capsules, 50 mg.

We will be performing methods validation studies on Impavido® (miltefosine) capsules, 50 mg, as described in NDA 204684.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Miltefosine assay, identification and impurities by HPLC (b) (4)

Miltefosine identification and assay by HPTLC (b) (4)

Unknown degradants by HPTLC

Dissolution of Miltefosine capsules by HPTLC

Samples and Reference Standards

3 g of Miltefosine drug substance

3 g of Miltefosine drug reference standard (b) (4)

100 mg of C18 analog of Miltefosine

100 mg of C14 analog of Miltefosine if available (b) (4)

100 IMPAVIDO (miltefosine) 50 mg capsules

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
06/28/2013



NDA 204684

INFORMATION REQUEST

Paladin Therapeutics Inc.
Attention: Jonathan Berman
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, Md 20898

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted September 26, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido, (miltefosine) capsules.

We also refer to your June 11, 2013 submission, containing a response to our June 5, 2013 information request.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 10, 2013, in order to continue our evaluation of your NDA.

Drug Substance

1. We were unable to verify from the spectral data if the (b) (4) group is linear. Provide (b) (4) spectra of miltefosine to verify the structure of the (b) (4)
2. The permissible Value/Range for the critical process parameters provided in the Table 3.2.S.2.4-2 are not adequately justified and do not match the corresponding values included in the description of the manufacturing process (Section 3.2.S.2.2). Update the manufacturing process description to accurately reflect the ranges for these parameters. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.
3. Provide robustness and stability of solutions data for the (b) (4) method for Residual Solvents.

4. Include ^{(b) (4)} in the drug substance specification as they are Class ^{(b) (4)} solvents ^{(b) (4)}
5. Include acceptance criteria for the ^{(b) (4)} impurities in the drug substance specifications. The tests for these impurities may be removed when ample data is available to show that the risk of its formation in the drug substance manufacturing is minimal.

HPTLC Methods

6. You have proposed to use HPTLC methods for release and stability testing of the drug product and for two impurities ^{(b) (4)} in the drug substance. Based on the information contained in your application, FDA does not recommend the use of the HPTLC methods for this product given the significant advantages of the HPLC method. HPLC is the preferred method for analysis of this product (rather than HPTLC) due to significant advantages in sensitivity and precision. In addition, FDA encourages the use of "green chemistry" methods, noting that the reagents used in the HPTLC method are more hazardous than those used in the HPLC method. FDA recommends that another method (such as LC/IR) be used, as the HPTLC methods proposed are not appropriate for life-cycle management of the NDA for miltefosine capsules. To facilitate first-cycle approval of the NDA, FDA would consider a proposal to develop the new method under a Post-Marketing Requirement (PMR) within a defined time period (assuming the NDA is approved this cycle). If necessary, you may request a teleconference to further discuss a PMR approach and details.
7. HPTLC Method Deficiencies are listed below.
 - a) With regards to the HPTLC method for ^{(b) (4)} impurities in the drug substance,
 - i. As ^{(b) (4)} are potential degradants, validate the analytical method for quantitative testing rather than limit testing.
 - ii. Provide data from spiking studies to show that the HPTLC method can reliably detect OOS data for the impurities ^{(b) (4)}
 - b) With regards to the drug product analytical procedures in Section 3.2.P.5.2 of the NDA submission, we note the system suitability tests for all HPTLC methods use only a single system suitability test (i.e. RSD for repeatability). Both resolution and reproducibility should be evaluated as part of the system suitability test. Therefore,
 - i. Revise the acceptance criteria for repeatability tests (i.e., RSD) so that they are comparable to those required by USP <621>
 - ii. Include at least one additional parameter to verify the system's resolution capability.

- c) As per ICH Q3, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products using samples subjected to relevant stress conditions (i.e., light, heat, humidity, acid/base hydrolysis, and oxidation), as appropriate. We note that you only performed a limited validation on the HPTLC method for degradant test by using miltefosine as a model due to lack of impurities samples. We also note that no degradant products were observed in your forced degradation study. However, it seems to us that you used relatively mild conditions (b) (4). In order to confirm that the appropriate analytical procedures are truly stability-indicating,
- i. Conduct a forced degradation study using more forceful conditions targeting approximately (b) (4) total degradation of the drug substance in order to determine the stability-indicating nature of the HPTLC method. The forced degradation study should be conducted under the following conditions, as appropriate: (b) (4)
 - ii. Validate the HPTLC methods using appropriately stressed samples as described above.
 - a. Use appropriately stressed drug product samples to demonstrate that the proposed HPTLC methods are able to discriminate between compounds (i.e., impurities/degradants) of closely related structures which are likely to be present.
 - b. Compare the HPTLC test results to those from a second well-characterized procedure, i.e., pharmacopoeial method or other validated analytical procedure (e.g., independent procedure such as LC/MS, GC/MS, etc).

Drug Product

8. Please provide data to show the drug substance (b) (4) state form remains unchanged over the proposed shelf life of the drug product. In Section 3.2.S.3.1 of the NDA submission, you state that the drug substance is hygroscopic (b) (4).
9. In reference to Section 3.2.P.5.1 of the NDA submission concerning the drug product specification:
 - a. As per ICH Q6A, identity tests should be specific for the new drug substance in the drug product. An R_f by HPTLC alone is not considered to be specific. We recommend that you use either one specific test for identity (such as IR) or if using non-specific tests, you add at least one additional analytical procedures where the separation is based on different principles, or use a combination of tests into a single procedure (e.g. HPLC/MS, HPLC/UV diode array, GC/MS) to achieve the necessary level of discrimination.

- b. Given the hygroscopic nature of the drug substance and based the limited available batch data and stability data, we recommend that the acceptance criterion for water content be tightened to NMT (b) (4)
10. For each drug product batch used in pivotal clinical trials listed in Table 3.2.P.5.4-2, provide the batch size, manufacturing date, and the specific manufacturing process used (i.e., indicate if it is the commercial process or the original process).

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

DOROTA M MATECKA
06/20/2013



NDA 204684

FILING COMMUNICATION

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) dated April 19, 2013, received April 19, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Impavido (miltefosine) Capsule, 50 mg.

We also refer to your amendments dated June 7, 10, and 11, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is December 19, 2013.

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 23, 2013. In addition, the planned date for our internal mid-cycle review meeting is July 19, 2013. We are currently planning to hold an advisory committee meeting to discuss this application.

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:

Information on the *in vitro* protein binding of miltefosine. This information may come from the literature, if available.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. A Highlights (HL) limitation statement must appear at the beginning of HL in **bold** type and be placed on the line immediately beneath the heading “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” and state: “**These highlights do not include all the information needed to use IMPAVIDO capsules safely and effectively. See full prescribing information for IMPAVIDO capsules.**”
2. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION**, the drug name must be followed by the drug’s dosage form (unless the dosage form is part of the drug name) and route of administration. Please revise as follows: **IMPAVIDO (miltefosine) capsules, for oral use.**
3. A horizontal line must be located between the Table of Contents and the Full Prescribing Information.
4. Manufacturer information [e.g., name and location of business (street address, city, state and zip code)] is required in labeling (see 21 CFR 201.1 and 201.100(e) for drugs) and should be located after the **PATIENT COUNSELING INFORMATION** section, at the end of the Package Insert.

We request that you resubmit labeling that addresses these issues by July 2, 2013. The resubmitted labeling will be used for further labeling discussions.

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:

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

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
06/18/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Microbiology Information Request
Date: Wednesday, June 05, 2013 5:36:00 PM
Attachments: [06.05.13 Microbiology IR.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: June 5, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

Advice/Information request

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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NDA 204684
Advice/Information request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We refer to your September 26, 2012, November 12, 2012, and April 19, 2013, submissions and would like to provide you with the following information request.

Microbiology:

- In response to the Division of Anti-Infective Products information request dated October 23, 2012, you provided us with the clinical microbiology information on November 12, 2012; this information included summary Tables for Studies 3154, 3168, Z020a, and Z020b as well as analysis data sets for Studies 3154 and 3168. However, the summary Tables for studies Z022 and Z025 and analysis data sets for studies Z020a, Z020b, Z022 and Z025 were not included in your response. Please submit the following information for our review:
 - Please specify if there are any changes to the summary Tables and analysis datasets submitted in response to clinical microbiology requests on November 12, 2012.
 - Summary Tables for studies Z022 and Z025 (similar to those prepared for Studies Z022a and Z022b; see Table 1 for template).
 - Analysis datasets for studies Z020a, Z020b, Z022, and Z025 (see Table 2 for template) that will aid clinical microbiology review.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
06/05/2013
Microbiology Information Request

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684- Impavido (miltefosine)-Paladin-Information Request
Date: Friday, May 31, 2013 1:53:00 PM
Attachments: [05.31.13 CMC and Stats IR.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing an Information Request for NDA 204684. Please be aware there will be no paper/hardcopy communication to follow this email communication. Please submit your response officially to the NDA.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: May 31, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 3

Comments:

Advice/Information request

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We also refer to your September 26, 2012, and April 19, 2013, submissions and would like to provide you with the following comments.

Biostatistics:

1. There exists discrepancy in treatment identification between study report and datasets provided for Study Z025. For instance, Subjects 494, 381, 395, 409, 027, 430, 509 and 569 received miltefosine according to the study report (Table 37) but SSG according to their datasets. The study report (Table 37) shows that Subjects 092, 272, 390, 398, 423, 460, 504, 205 and 536 received SSG but the datasets indicates their group assignment were miltefosine. Please clarify.
2. Some important variables are not clearly labeled. For instance, according to the study 3154 report (Section 6.1), Subject 3/060 was randomized to the miltefosine group but received AmpB. However, planned treatment for this patient is recorded as AmpB in “dm.xpt” (ARM and ARMCD labeled as “Description of Planned treatment”). According to the Soto study report (Section 10.2), Subject 10 was randomized to Glucantime but received miltefosine. However, the planned treatment for this subject was recorded as miltefosine in “adsl.xpt” (TRTA labeled as “Planned Treatment”). Please clarify.
3. The length of some variables is not consistently defined. For example, the length of USUBJID (unique subject ID) variable in the analysis datasets is different from that in the tabulation datasets in Studies 3154, 3168 and Soto. In Study 3154, USUBJID length=10 in analysis datasets but length=11 in tabulation datasets. In Study Soto, USUBJID length=7 in analysis datasets but length=10 in tabulation datasets. In Study 3168, USUBJID length=10 in analysis datasets but length=9 in tabulation datasets. Please clarify. Additionally for Study 3168, please confirm if, for example, Subject 3168-1/067 in the analysis datasets is the same as Subject 3168-1/67 in the tabulation datasets.
4. For Studies Z020a and Z020b, the length and width of ulcerated or induration lesion are provided in the datasets while the study report summarizes the lesion area. There is no specification on how ulcerated or induration lesion area is computed. Please clarify.
5. Some variables are not available in the datasets. For instance, while Study 3168 report Table 5.2.1 shows summary statistics for Performance status (Karnofsky), this parameter is not provided in Study 3168 datasets (‘vs.xpt’ has BMI instead).

Chemistry, Manufacturing, and Controls (CMC):

6. Please provide a sample of the drug product, miltefosine capsules, packaged in the proposed (b) (4) packaging configuration. Also, for comparison purposes, include a sample of a blister without the (b) (4) feature.
7. As the NDA was resubmitted seven months after the first NDA submission on September 26, 2012, please provide updated stability data for the batches listed in the drug product section 3.2.P.8, particularly for batches 1F2639, 1M3150, and batch 2C3816 (b) (4)
(b) (4)
8. Based on the available dissolution data, a mean of (b) (4) miltefosine dissolved occurs at (b) (4) 15 minutes. The proposed acceptance criterion of NLT (b) (4) is not justified. Accordingly, revise the acceptance criterion for miltefosine capsules to NLT (b) (4) (Q) at 15 minutes (see USP <711> Dissolution, Acceptance Table 1).

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
05/31/2013
Biostatistics and CMC Information Request



NDA 204684

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President, Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

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: Impavido (miltefosine) Capsule, 50 mg

Date of Application: April 19, 2013

Date of Receipt: April 19, 2013

Our Reference Number: NDA 204684

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, 2013, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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
05/24/2013



NDA 204684

MEETING MINUTES

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine).

We also refer to the meeting between representatives of your firm and the FDA on January 8, 2013. The purpose of the meeting was to discuss your December 3, 2012, submission that included your responses to the Refuse-to-File concerns identified in our November 26, 2012 letter.

A copy of the official minutes of the 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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Acting Director
Division of Ant-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: A

Meeting Category: Guidance

Meeting Date and Time: January 8, 2013 at 3:00 P.M.

Meeting Location: White Oak Campus, Building 22, Room 1415

Application Number: 204684

Product Name: Impavido (miltefosine)

Indication: Treatment of visceral, cutaneous, and mucosal leishmaniasis

Applicant Name: Paladin Therapeutics, Inc.

Meeting Chair: John J. Farley, M.D., M.P.H.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Division of Anti-Infective Products (DAIP)

John J. Farley, M.D., M.P.H.	Acting Director
Sumathi Nambiar, M.D., M.P.H.	Deputy Director for Safety
Thomas Smith, M.D.	Clinical Team Leader
Hala H. Shamsuddin, M.D.	Medical Officer
Lynette Y. Berkeley, Ph.D.	Acting Clinical Microbiology Team Leader
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
James S. Wild, Ph.D.	Pharmacology/Toxicology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Reviewer
Maureen P. Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Seong H. Jang, Ph.D.	Clinical Pharmacology Reviewer
----------------------	--------------------------------

Division of Biometrics IV (DBIV)

Karen Higgins, Sc.D.
Lan Zeng, M.S.

Biostatistics Team Leader
Biostatistics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Mark Seggel, Ph.D.

Chemistry, Manufacturing, and Controls
(CMC) Reviewer-Drug Product

Anamitro Banerjee, Ph.D.

CMC Reviewer-Drug Substance

Office of Business Informatics (OBI)/Division of Data Management Services & Solutions (DDMSS)

Douglas Warfield

Operations Research

SPONSOR ATTENDEES

Paladin Therapeutics, Inc.

Robert K. Vinson, Ph.D.

Director, Product Development

Fast Track Drugs and Biologics, LLC

Jonathan Berman, M.D., Ph.D.

Vice President Clinical Affairs

(b) (4)

(b) (4)

(b) (4)

1.0 BACKGROUND

Paladin Therapeutics, Inc., c/o Fast Track Drugs and Biologics, LLC (Paladin) submitted NDA 204684 for Impavido (miltefosine) for the treatment of visceral, cutaneous, and mucosal leishmaniasis on September 26, 2012. FDA received this NDA on September 27, 2012, and following the FDA NDA Filing issued a Refuse-to-File (RTF) letter to Paladin on November 26, 2012. In the November 26, 2012 letter, FDA offered Paladin the opportunity to discuss the RTF deficiencies in a meeting. On December 3, 2012, Paladin submitted a type A meeting request. The meeting was granted for a January 8, 2013. In the December 3, 2012, submission Paladin informed FDA that the submission included their (Paladin's) responses the RTF deficiencies and that no additional materials will be submitted for the meeting.

2. DISCUSSION

Following introductions, FDA thanked Paladin for their submission of NDA 204684 and their efforts to develop a new drug for the treatment of visceral, cutaneous, and mucosal leishmaniasis. FDA also confirmed it had received Paladin's preliminary responses to the November 26, 2012, RTF letter via the December 3, 2012, submission. Paladin thanked the FDA for their effort to schedule this meeting quickly and expressed that they were disappointed to receive the RTF letter, but believed they were on the right track to resolving all of the identified deficiencies. Paladin provided FDA with a handout, that was used as the basis for the meeting discussion.

FDA's RTF deficiencies are identified in normal font below and Paladin's December 3, 2012, Preliminary Responses are identified in *italics*. Additionally, Paladin's January 8, 2013, talking point comments/questions are identified in normal font and the meeting comments identified in *italics*.

I. December 3, 2012 Paladin Comments Responses to the FDA's November 26, 2012, RTF Letter:

CLINICAL and STATISTICAL

- Efficacy was not investigated for important subgroups such as gender in any of the 6 studies conducted for VL and CL. Please perform and submit efficacy analyses based on gender.

Preliminary Response: We were not aware that evaluation of efficacy by gender was an NDA requirement. The evaluation can be performed.

Question to the Agency: For omnibus issues such as this, should the data be presented in a stand-alone document, or should each study's data be integrated into an amendment to the Study Report for that study?

- The submitted datasets do not allow a meaningful review of the efficacy and safety data. Specifically:

1. Some important datasets are not submitted. For example, according to the cover letter dated November 12, 2012, “the ADaM dataset for study 3154 contains two xpt files, one for clinical response data (study 3154 adcr.xpt) and one for the parasitological methods, clinical response, and parasitological response (study 3154 adcrp.xpt).” However, the two datasets submitted on November 12, 2012, namely “adcr.xpt” and “adcrp.xpt”, appear to be identical. If the cover letter is correct, then one dataset has not been submitted.

Preliminary Response: The adcrp.xpt file was posted as both the adcr.xpt file and the adcrp.xpt file. This correct adcr.xpt will be posted. This was a result of some last minute name changes to the datasets and remapping with the xml backbone.

2. Some key parameters are missing or erroneous in the datasets. For example,
 - a. There is no variable in the datasets indicating if the actual treatment a subject received is the same as planned. Treatment assignment for some subjects is not consistent across datasets. For example, in Study 3154, Subject 3154-3060 had TRT=1 (miltefosine) in “rando.xpt”, TRT=2 (amphotericin B) in “rando-c.xpt”, TRT=2 (amphotericin B) in “response.xpt”, and TRTA=’amphotericin B’ in “adcr.xpt”. All of these variables are labeled as “Actual Treatment”.

Preliminary Response: The planned treatment and actual treatment variables will be clearly identified in the posting of the revised datasets for this study.

- b. Start and stop date of study treatment are not provided for most studies. Treatment duration is not available for Study Soto.

Preliminary Response: In the tabulation dataset for the study Soto, the EX.xpt table contains fields for the study day EXSEQ (with day 1 being the start of treatment and each subsequent days’ treatment numbered by day with the highest day being the last day of treatment, typically day 28), the date of each treatment, the treatment group, and the dose administered on each day. Therefore the start, stop, and duration data were provided within this table for the study Soto. With the exception of the Z020a and Z020b studies, for which a stop date will need to be imputed to add to the datasets as the total daily dose was only provided thru study day 21, and separately a notation of whether the subject completed the full 28 days treatment, the other studies did have start and stop dates, although admittedly, in the 3154 and 3168 studies these dates are contained in 2 different database tables and are difficult to find. This will be fixed when revised datasets are provided.

- c. Treatment durations are not consistent for several subjects in Study Z020a, Z020b and 3168. For example, in Study Z020a, treatment duration is report as both 10 and 28 for Subject 048.

Preliminary Response: This discrepancy will be resolved.

- d. There is no information about apparent cure (secondary efficacy endpoint) in the datasets for Studies Z020a and Z020b. The study reports defined apparent cure as complete re-epithelialization of all ulcers at the 2 month follow-up. However, the submitted datasets only contain response information at the 6 month follow-up.

Preliminary Response: Information on this secondary endpoint will be added to the study report addendum and the ADaM datasets will have this variable added.

- e. Subject IDs in the datasets do not correlate with those in the study report. For example, in Study 3154 report, subjects are referred as Pat 1/137, Pat 1/116, Pat 3/38, and Pat 2/92, etc. However, in the datasets USUBJID is denoted as 3154-1001, 3154-1100, etc.

Preliminary Response: When complying with FDA's request to provide a unique subject identifier field for the 3154 study, we prepared a separate field in each of the tabulation dataset names in USUBJID, which joined the study id with the site id and the unique subject number to make a single unique id field. Thus, patient 1/137 in the study report, which was subject 137 at site 1, became 3154-1137 in the USUBJID field. Also included in this study were separate fields for the site and subject number, so traceability was retained with the original data.

3. Visit days in your datasets need to be clarified. For example, in Study 3168, visits are designated 55 and 70 in "response.xpt", 37 and 40 in "ae.xpt", 50 and 60 in "final.xpt". Not all of them correlate with the timing of assessments as per the protocol or with the days as designated in the "tv.xpt" dataset or in the "define.pdf".

Preliminary Response: When creating the ADaM datasets, the decodes for the study visits in the 3168 and 3154 studies were provided; however, we did not decode these visit designations in all of the tabulation datasets. This will be incorporated into the revised tabulation datasets.

4. The "define.pdf" file does not provide clear documentation about your datasets.
- a. There are no definitions for many key fields. For example, In Study Z025, CURETEST has entries of ln neg, na, neg, spleen neg but no meanings are provided. Likewise, no meanings are provided for PRE_RX (values: 1, 2), DAT (values: 7, 8, 9, 10, and 11), and ASPIR (values: 1, 2, 3, 4, 5, and 6).

Preliminary Response: We will review all define.pdf files and provide decodes for all coded or abbreviated data for clarity and provide these in the updated tabulation datasets.

- b. For the analysis datasets in Study 3154, the "define.pdf" does not correlate with the dataset "adcr.xpt". The following variables are specified in the "define.pdf" but don't appear in the dataset "adcr.xpt": TRT, EXAM, RESPONSE, and EXDAYS. Dataset

“adcr.xpt” contains the following variables which are not included in the “define.pdf”: CLINRESP, PARARESP, SEQ, TRTA, and TRTDUR.

Preliminary Response: The adcrp.xpt file was posted as both the adcr.xpt file and the adcrp.xpt file. This correct adcr.xpt will be posted. This was a result of some last minute name changes to the datasets and remapping with the xml backbone.

- c. For the tabulation datasets in Study 3168, the “define.pdf” has the following explanation about RESP_FIN in “response.xpt”: “At 3 months, 1=apparent cure, 2=partial cure, 3=clinical failure, 4=not assessable; at six month follow up, 1=definite cure, 2=clinical failure, 3=other”. However, there is no variable indicating 3 month time point in dataset “response.xpt”.

Preliminary Response: The variables will be clearly defined in the revised 3168 dataset that will be posted.

- d. For the tabulation datasets in Study 3154, the “define.pdf” indicates “One record per subject” for datasets “ecg.xpt” and “final-t.xpt”. However, there are multiple records per subject in these datasets (a total of 1967 records in “ecg.xpt” and 935 records in “final-t.xpt”).

Preliminary Response: “One record per subject” should have read “One record per subject per visit” and will be corrected in the revised submission.

ADDITIONAL COMMENTS AND REQUESTS

1. Datasets for Study Z020a and Study Z020b are combined. Please submit data for different studies under separate directories.

Preliminary Response: These datasets will be separated and provided in the revised submission.

2. Coded variables are used in SAS datasets but no formats are provided. Please submit a format.xpt file for the ease of reading your data.

Preliminary Response: A format.xpt file will be provided.

3. Some key parameters are defined as character variables in one dataset and numeric variables in another. For example, in Study Soto, SITEID is defined as numeric in “adsl.xpt” but character in “dm.xpt”.

Preliminary Response: The data formats between tables will be checked for consistency and corrected when necessary.

4. Some variables are not clearly labeled. For example, in Study Soto, DOMAIN in “dc.xpt” is labeled as “then delete”.

Preliminary Response: Data labels will be checked and clearly labeled where needed and provided in the revised submission.

5. You state in your letter dated November 12, 2012, that a summary of the parasitological methods used in different laboratories will be provided. In addition to the details of the methods, please include the performance characteristics of the assays in the laboratory where testing was performed. The name and address of the laboratories should be specified.

Preliminary Response: The sentence stating that a summary will be provided originally preceded the summary. When the summary was moved up to its present position on pages 3-5, we omitted to remove the introductory sentence to which the reviewer refers, which now follows the summary. Since the summary is on pages 3-5, the sentence to which the reviewer refers should be deleted.

The November 12, 2012, letter states that since academics performed the non-FDA-cleared assays, the performance characteristics of the assays are unfortunately not available.

We will ask the academics for full addresses of the laboratories.

6. Please provide a description and a validation report for the HPLC analytical procedure used for the detection of [REDACTED] (b) (4) in miltefosine drug substance described in section 3.2.S.3.2: Impurities.

Preliminary Response: Will be provided.

7. Add tests for [REDACTED] (b) (4) residual solvents in the drug substance specifications or provide justification for exclusion of these tests from the specification.

Preliminary Response: Will be provided.

8. For the drug substance, include the Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) in section 3.2.S.7.2: Postapproval Stability Protocol and Stability Commitment.

Preliminary Response: Will be provided.

Question to the Agency from December 3, 2012 Submission:

As the NDA is electronic, we do not plan to resubmit a revised complete NDA. We plan to submit only the revised and new data as indicated above in response to the Agency's issues raised in the RTF.

Please confirm that this is acceptable to the Agency.

II. January 8, 2013, Talking Points and Meeting Discussion between Paladin and FDA:

1. We plan to resubmit the revised section of the NDA application as a new serial submission to the previous NDA. Is the acceptable?

Discussion:

Paladin informed FDA that the cover letter they planned to submit will outline all of the changes and identify how these changes have been addressed. The staff from FDA's Office of Business Informatics (OBI)/Division of Data Management Services & Solutions (DDMSS) informed Paladin this plan was acceptable.

2. Below we describe the major changes to the submission. In addition, there will be some minor corrections to some of the documents. For example, the sponsor recently received an update on one of the species of *Leishmania* identified in the Z020b study. For reports that are amended, each amended report would have a revised cover page, followed by a Summary of Changes, then the Synopsis, Table of Contents, then the report contents itself, with new content included. There are some minor corrections to the Quality section as well. In these cases, the revised module will be submitted. Is this acceptable?

Discussion:

FDA stated that they would appreciate it if all datasets were submitted in M5, stating that it is not efficient use of time to search through other submissions for the datasets. Therefore FDA requested to include all datasets as mentioned. Paladin stated that would be done and all datasets would be submitted. Paladin also stated that they plan to replace two legacy studies, these datasets would be reformatted to CDISC and all codes would be provided in MS Word, so that smaller changes to the study reports and major changes will be conveyed in one topic.

3. The following lists the changes to the original modules to address the FDA's requests:
 - a. **Clinical Microbiology: Module 2.7.2 Summary of Clinical Pharmacology Studies.** Will be revised to include the Clinical and Parasitological Response Tables requested by FDA and included in the 12NOV2012 response to the 23OCT2012 request for information along with the available information on the methodology for diagnosis and speciation of *Leishmania*. Further discussion of methodology will occur at the end of this meeting if time permits.
 - b. **Efficacy by Gender: Modules 2.7.3. A Summary of Clinical Efficacy (Visceral Leishmaniasis) and 2.7.3. B Summary of Clinical Efficacy (Cutaneous/Mucosal Leishmaniasis)** will be updated to include the requested analysis of efficacy by gender. The planned analysis of efficacy by gender will be performed for the pivotal studies which include the 4 CL studies (study -Z020a, study-Z020b, study-3168, study-soto), the single ML study (study-Z022), and of the two VL studies (study-3154). The other VL study (Z025) included only males. The analysis will present the primary efficacy endpoint by gender and overall for these studies. Is this acceptable?

- c. Module 5-Datasets: Clinical datasets for the following studies have been previously provided:

Protocol Number	Study Brief Title
study-3154	India VL
study-Z025	Ethiopia VL
study-Z020a	Brazil CL-Dietze/Talahari
study-Z020b	Brazil CL-Machado
study-Soto	Bolivia CL
study-3168	Guatemala CL
study-Z022	Bolivia ML
study-dutch-pk-report	PK in Dutch Military with CL Returning from Afghanistan

Modifications to the above datasets, as appropriate to the study are being prepared per FDA's requests. Details are provided below.

d. **Module 3.Quality**

Module 3.2.S.3.2: Impurities: A description and a validation report for the HPLC analytical procedure used for the detection of (b) (4) in miltefosine drug will be provided.

Module 3.2.S.4.5. A justification to exclude (b) (4) testing from the API specs will be provided.

Module 3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment. A Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) will be provided.

Module 2 sections will be updated in accordance with the above requests. **Module 2.3.S.3 Characterization, Module 2.3.S.4 Control of Drug Substance and Module 2.3.S.7 Stability**

Discussion:

FDA stated that they planned to issue Paladin a comment on the dissolution profiles over a number of time points for the drug product at release and on stability. Then based on the results, FDA would request Paladin propose a sampling time point at which a mean of Not Less than (b) (4) (Q) is dissolved. Paladin asked if this would be required upon resubmission of the NDA or at what time point did FDA expect this information. FDA stated they would like to see this information as soon as possible and it was for this reason they decided to mention it at today's meeting. (Meeting Follow-Up Note: FDA issued an information request for this point on January 24, 2013 to Paladin).

4. FDA notified Paladin of two manufacturing facility audits for January. One was cancelled after the Refusal to File letter was given to Paladin, but the other was not as of

this date. The visit to the (b) (4) facility is still scheduled for 28 January 2013. Paladin assumed when the refusal to file letter was given, that both audits would be cancelled and this date is no longer a viable option for a visit to the (b) (4) facility. Can we officially close this request?

Discussion:

FDA stated they will issue a comment to the FDA Office of Compliance for closure of the (b) (4) facility inspection/audit after today's meeting.

5. Can FDA provide any comments on plans for clinical site audits after submission of revised NDA?

Discussion:

Paladin asked if FDA could provide its perspective on the clinical site audits for this NDA, since the sites in the studies were not in continual operation. Paladin noted that it has collected as much information as possible from the Indian and Brazilian pivotal study sites. FDA stated in response to this question, that the inspection of the actual clinical sites may not be informative, however the Office of Compliance, Division of Scientific Investigation (DSI) will make the decision. However, at this time the recommendation from DAIP is that they may not be necessary. FDA did state they will need to know the location of the source documentation and that Paladin should be prepared to provide this information.

6. Summary of dataset revisions by Study.

Below is the planned XML backbone for the datasets:

(see page #3 and # 4 of Palladin Handout attached)

Studies 3154 and 3168 contained legacy data obtained from Zentaris. These data are being remapped as much as possible to CDISC SDTM terminology. Also, almost all data were originally given a numeric code. Instead of numeric codes, we are providing the coded term for ease in reviewing the data.

Study Z025: We were just provided the CRF for the subjects who had serious adverse events in this study. Just a single table containing all of the available information on these CRFs is being provided.

Discussion:

FDA asked if Study Z025 would have analysis data sets. Paladin stated this study included a small dataset therefore, to break up these data into pieces it would not work and they did not plan on an analysis dataset for this study. Paladin stated they would reformat this dataset, this would help with the review of these data and that they would identify parasitologic data, again stating they did not think it made sense to break up data because it was a small dataset. FDA stated that this was acceptable.

Study-dutch-pk-report: These data are the population PK analysis that we performed using the raw data provided by Zenataris. No clinical data are provided with these data.

Discussion:

Paladin stated that the Study-dutch-pk-report will not have separate analysis datasets as well. FDA asked if Paladin would provide a population PK model and other key data. Paladin stated yes, they thought this would be included.

Analysis datasets will contain 3 xpt files:

DATASET NAME	DATASET DESCRIPTION
ADSL	Subject disposition, demographic, and baseline characteristics
ADCR	Efficacy endpoints: Final and initial cure rates
ADCRP	Parasitological methods, clinical response and parasitological response

Example of ADSL Define File for Study Z020a

(includes name of planned treatment, name of actual treatment, and duration of treatment and other demographic variables)

Dataset Name	Variable Name	Variable Label	Controlled Terms, Code list or Format
ADSL	STUDYID	Study Identifier	
ADSL	USUBJID	Unique Subject Identifier	
ADSL	SUBJID	Subject Identifier for the Study	
ADSL	SITEID	Study Site Identifier	
ADSL	AGE	Age	
ADSL	AGEU	Age Units	“YEARS”
ADSL	SEX	Sex	M=male; F=female
ADSL	RACE	Race	
ADSL	ITTFL	Intent-To-Treat Population Flag	Y
ADSL	ARM	Description of Planned Arm	
ADSL	TRTP	Planned Treatment	
ADSL	EXTRT	Name of Actual Treatment	
ADSL	TRTSDT	Date of First Exposure of Treatment	
ADSL	TRTEDT	Date of Last Exposure to Treatment	

ADSL	EXDUR	Treatment duration	Days
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Example of ADCR Define File for Study Z020a

(includes names of planned treatment, name of actual treatment, and duration of treatment; primary and secondary efficacy endpoints; and population flags)

Dataset name	Variable name	Variable Label	Controlled Terms, Code lists or Format
ADCR	STUDYID	Study Identifier	
ADCR	USUBJID	Unique Subject Identifier	
ADCR	ARM	Planned Treatment	
ADCR	EXTRT	Name of Actual Treatment	
ADCR	EXDUR	Treatment duration	Days
ADCR	PARAM		“FINAL CLINICAL RESPONSE” (primary efficacy endpoint); “INITIAL CLINICAL RESPONSE” (secondary endpoint)
ADCR	PARAMCD		FINLCURE (primary endpoint); INICURE (secondary endpoint)
ADCR	PARAMCAT		“PRIMARY EFFICACY ENDPOINT”; “SECONDARY EFFICACY ENDPOINT”
ADCR	AVALC		“DEFINITIVE CURE”; “FAILURE”; “APPARENTCURE”; “MISSING VISIT” (only valid at 2 month visit)
ADCR	ITT		Y=yes: N=no
ADCR	PP		Y=yes: N=no

Example of ADCRP Define File for Study Z020a

(includes name of planned treatment, name of actual treatment, and duration of treatment; primary efficacy endpoint; parasitological response, parasitological methods, and population flags)

Dataset Name	Variable Name	Variable Label	Controlled Terms, Code list or Format
ADCRP	STUDY	Study Identifier	
ADCRP	USUBJID	Unique Study Identifier	
ADCRP	EXTRT	Actual Treatment	Miltefosine; Guacantime
ADCRP	EXDUR	Duration of Treatment	Duration of treatment in days
ADCRP	ITT	Full analysis set population flag-ITT	Y=yes: N=no
ADCRP	PP	Per protocol population flag	Y=yes: N=no
ADCRP	VISIT	Visit Identifier	0, Screening, 6 months after treatment
ADCRP	SPECIMEN	Specimen Type	Scraping, Aspiration, Smear, Biopsy
ADCRP	STAIN	Result of Staining	Positive; Negative; ND=not done; NA=not applicable
ADCRP	CULTURE	Result of Culture	Positive; Negative; ND=not done; NA=not applicable
ADCRP	PCR	Result of PCR	Positive; Negative; ND=not done; NA=not applicable
ADCRP	IFA	Result of Immunofluorescence	All are blank-method was not done
ADCRP	SPECMETH	Method for Determining Species	PCR=polymerase chain reaction
ADCRP	SPECIES	Leishmania Species	
ADCRP	CLINRESP	Final Clinical Response	“DEFINITIVE CURE”; “FAILURE”
ADCRP	PARARESP	Parasitological Response	All are blank, no follow-up parasitology was performed
ADCRP	LESNO	Lesion Number	
ADCRP	LESSIZE	Lesion Size	Area in mm ²
ADCRP	STATUS	Leishmania History for Current Disease	New
ADCRP	AGE	Subject Age	Age in years

Drug Exposure Notes

An EX table will be provided in the tabulation datasets that contains the start date (EXSTDTC), end date (EXENDTC) and total days of exposure for each (EXDUR). The EXDURE field will also be included in each of the analysis datasets.

Protocol Number	Study Brief Title	Data Available in Database
study-3154	India VL	Yes
study-Z025	Ethiopia VL	Just for exposure days
study-Z020a	Brazil CL-Dietze/Talahari	Needs to be imputed
study-Z020b	Brazil CL-Machado	Needs to be imputed
study-Soto	Bolivia CL	Yes
study-3168	Guatemala CL	Yes
study-Z022	Bolivia ML	Yes
study-dutch-pk-report	PK in Dutch Military with CL Returning from Afghanistan	Not applicable

Discussion:

Paladin provided FDA with an overview of the following tables that are listed above:

*Analysis datasets will contain 3 xpt files
Example of ADSL Define File for Study Z020a
Example of ADCR Define File for Study Z020a
Example of ADCRP Define File for Study Z020a
Drug Exposure Notes*

Paladin informed FDA that in the Brazilian study duration of drug exposure was a derived value or imputed value. The CRF was structured to allow inclusion of 3 weeks of exposure, and did not allow documentation of the fourth week. Paladin stated that the exposure data were accurate up to 3 weeks, if the date was beyond this time then at 4 weeks the dates needed to be imputed. FDA stated that it appeared that Paladin knew the start date, but did not know the end date, and could determine if the patient completed the study. FDA stated that it appears that 1 arm would be considered incomplete at 28 days and another arm would be complete at 3 weeks (meglumine arm). FDA stated that for a test of efficacy this works against miltefosine, but for a test of safety this could benefit miltefosine. Paladin asked if an indicator variable would be okay to use to designate for this concern. FDA stated that an indicator variable would be okay.

Study Z025 (only SAE data):

Exposure Dose (EXDOSE) and exposure days (EXDAYS). No actual start date and end date.

Studies Z020a and Z020b:

START DATE: CRF page #1 RFSTDTC

END DATE: There was a drug accountability CRF with the number of capsules prescribed and a number of capsules returned each week from Week 1 to 3. However, this data was not included for Week 4. There was also a subject disposition form that indicated if the subject completed treatment or not. The sites also provided a separate

listing (not on the CRF) from the monitoring notes of protocol deviations. When a subject was listed as not having completed treatment, there was a protocol deviation indicating the last day of the study that the subject completed treatment. Using this data, the end date will be imputed as Study Day 28 for those subjects who completed treatment and for those subjects who did not, the end date will be calculated for the last reported study day treatment.

Discussion:

Paladin provided FDA with the information above regarding imputation of the end date. Paladin provided FDA with this explanation for Study Z025, Studies Z020a, and Z020b regarding FDA’s concern on the missing data for start and end dates FDA identified in the RTF letter. Paladin also clarified when dates would be imputed and those times when the dates would be calculated.

Parasitology Endpoints and Methodology Notes:

Clinical endpoints in leishmaniasis therapy trials typically do not include an evaluation of parasitological responses; however, in the miltefosine pivotal trials, the parasitological response was evaluated in the VL study in India (study-3154), in the patients who did not die during treatment in the VL study in Ethiopia (study-Z025), in the CL study in Columbia and Guatemala (study-3168). Entry criteria into the trials mostly relies on diagnosis of leishmaniasis by microscopic identification of amastigotes in stained lesion tissue or positive culture for promastigotes. Both methods are considered as gold standard for diagnosis of leishmaniasis. Clinical cure is presumed to be accompanied by parasitological cure when cure is followed for 6 or more months after treatment.

Summary of Methods, Used and Species Identified in Pivotal Efficacy Studies of Miltefosine for VL, CL, and ML for Diagnosis and Parasitological Response

Study	Indication	Method Used for Diagnosis	Method Used for Parasitological Response	Method Used to Identify Species	Species
study-3154 (India)	VL	Microscopy of Giemsa-stained smears (“FDA cleared”) ^a	Microscopy of Giemsa-stained smears	Epidemiology	<i>L. donovani</i> (100%)
study-3154 (Ethiopia)	VL	Microscopy of Giemsa-stained smears (“FDA cleared”) ^a	Microscopy of Giemsa-stained smears	Epidemiology	<i>L. donovani</i> (100%)
study-2168 (Columbia)	CL	Microscopy of Giemsa-	Microscopy of Giemsa-stained	Epidemiology Also: <i>L. v</i>	<i>L. v panamensis</i>

and Guatemala)		stained smears (“FDA cleared”) ^a	smears	<i>panamensis</i> by isoenzymes ^e <i>L. v braziliensis</i> <i>L. mexicana</i> by PCR ^e	(Colombia 100%) <i>L. v braziliensis</i> (Guatemala-67%) <i>L. mexicana</i> (Guatemala-33%)
study-Z020a (Brazil)	CL	Microscopy of Giemsa-stained smears (“FDA cleared”) ^a	Not done	Epidemiology Also: PCR ^d	<i>L. guyanensis</i> (96%)
study-Z020b (Brazil)	CL	Culture only (62-65%) (“FDA-cleared”) ^b Montenegro Skin Test ^c only (20-23%) PCR ^d only (15%)	Not done	Epidemiology Also: PCR ^d	<i>L. braziliensis</i> (100%)
study-soto (Bolivia)	CL	Microscopy of Giemsa-stained smears (“FDA cleared”) ^a	Not done	Epidemiology	<i>L. braziliensis</i> (85%)
Study-Z022 (Bolivia)	ML	Microscopy of Giemsa-stained smears (“FDA cleared”) ^a , culture (“FDA-cleared”) ^b and Montenegro Skin Test ^c	Not done	Epidemiology Also: Isoenzymes ^e	<i>L. braziliensis</i> (85%)

^aTest Brochure = WHO 2010 Annex 4

^bTest Brochure =WHO 2010 Annex 2 and FCSR sect 9.5.1.9

^cMethods = WHO 2010 page 61

^dMethods = FCSR section 9.5.1.9 (Z020b) and FCSR 9.5.1.8 (Z020a)

^eMethods = statement by PI

Discussion:

Paladin asked FDA regarding the CL study that did not have parasitological data did FDA want blanks in analysis. FDA stated they would want to see parasitological data with separate data fields added on top of what is in clinical dataset. FDA stated it did not make much sense to have empty columns, since 2 are the same except for columns for parasitological response. FDA stated Paladin could make it clear that no parasitological data was collected and therefore state the column was left blank. Paladin stated they would like to add something to clarify this issue when they make the NDA submission. FDA stated Paladin could add a summary report and make a table that states there was no parasitological data. FDA OBI staff commented that they have seen a summary data reviewer guide, along side of the define file that is linked to the dataset and this guide could explain how variables are defined. Paladin asked if there should be one per dataset. OBI staff commented that it should be set up by study and that the summary data reviewer guide should be as well.

Paladin stated that they have multiple records for a single subject for a single outcome, and wanted to know how FDA would like them to present this information, taking into consideration the October 23, 2012, FDA Information request. FDA inquired how many patients and how many lesions Paladin had identified. Paladin stated that there could be variable numbers, by a variety of methods, so if any lesion is positive should this not be considered a parasitological response. Paladin stated they are concerned that the CL data FDA wants would show up as not as clean as FDA would like it to be. FDA stated they understood the concern, but wanted to understand the methods that have been used. FDA asked Paladin if the samples from their other trials were sent to the same laboratory in the U.K. or if they used different laboratories in separate countries. FDA stated if you could help clarify this information it would be a helpful.

Diagnosis of Genus (*Leishmania*) by Giemsa staining, an FDA-cleared method was used in all but 1 study. The Test Brochure (requested in the 23OCT2012 Information Request) is the WHO manual which will be provided in the revised NDA.

Diagnosis by culture, an FDA-cleared method was performed in two thirds of the subjects in the Z020b study and 8 patients in the Z022 study. The Test Brochure is the WHO manual which will be provided.

Diagnosis was performed using the Montenegro Skin Test in one third of the patients in the Z020b study and a few patients in the Z022 study.

Speciation: Giemsa-staining and culture identify the genus but not the species, thus speciation was based on epidemiological data for all studies and for the two studies in Brazil with additional confirmatory data obtained by PCR. PCR was considered confirmatory in the Z020a study because the literature states that 94% of speciated parasites in Manaus, Brazil are *L. v guyanensis*. PCR data in this study confirmed that 96% of the parasites in this study were *L. v guyanensis*. PCR was considered confirmatory in the Z020b study because the literature states that 100% of speciated

parasites in Corte de Petra, Bahia are *L. v braziliensis*. PCR data confirmed that 100% of the parasites in Z020b study conducted in Corte de Petra were *L. v braziliensis*.

Data on performance characteristics of these methods by these researches are not available.

Discussion:

Paladin informed FDA that 2 sites used PCR and they would provide FDA species information or use the results as an academic exercise since no performance characteristics are available. Paladin stated that for study Z022 in Bolivia, L. braziliensis is epidemiologically expected and use of PCR would be unlikely to identify another species. FDA stated that this was helpful information and trying to make sure the extent of information that will be available for review. FDA asked Paladin why in Study 3168 there were no speciation datasets, but species were listed in the publication. Paladin stated that species were not specified in the CRFs, but were listed in PI's information however, they do not have this information. Paladin stated that they do not have subject data from PI, all they have is the information from Zantarus.

Paladin stated they did not anticipate a RTF on the miltefosine NDA and inquired if there was more they should consider as they move forward. FDA stated if there were additional/current publications on miltefosine activity and its use with several compounds that could be helpful. Paladin stated they could look in to this and inquired if there was a specific question FDA was considering. FDA stated a more global use of the product would be helpful to understand as the NDA is being reviewed.

FDA emphasized that all datasets need to be complete and the issues identified in the RTF letter did not encompass all of the concerns that can arise during a full NDA review. FDA stated that while Paladin had been focusing on addressing the RTF issues the FDA review team has moved on to other projects, so when the NDA is resubmitted while the team will have prior knowledge, the quality of the resubmission would need to be there so they can pick up where they left off.

FDA informed Paladin that the resubmitted NDA would not be in the "Program" as defined by PDUFA V.

Post Meeting Note: upon further discussion at the FDA, it was determined that the NDA would be considered a "Program" application under PDUFA V. This was communicated to Paladin via telephone call to Dr. Berman by the Regulatory Project Manager on February 7, 2013.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues that require further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue meeting minutes.	FDA	February 7, 2013
Resubmission of NDA	Paladin	Potentially Mid to Late February 2013

6.0 ATTACHMENTS AND HANDOUTS

Paladin's handout.

NDA 204684: Miltefosine for Visceral, Cutaneous and Mucosal Leishmaniasis

Talking points for meeting with FDA on 8 January 2013.

1. We plan to resubmit the revised section of the NDA application as a new serial submission to the previous NDA. Is this acceptable?
2. Below we describe the major changes to the submission. In addition, there will be some minor corrections to some of the documents. For example, the sponsor recently received an update on one of the species of *Leishmania* identified in the Z020b study. For study reports that are amended, each amended report would have a revised cover page, followed by a Summary of Changes, then the Synopsis, Table of Contents, then the report contents itself, with new content included. There are some minor corrections to the Quality section as well. In these cases, the revised module will be submitted. Is this acceptable?
3. The following lists the changes to the original modules to address FDA's requests:
 - a. **Clinical Microbiology: Module 2.7.2 Summary of Clinical Pharmacology Studies** will be revised to include the Clinical and Parasitological Response Tables requested by FDA and included in the 12Nov2012 response to the 23Oct2012 request for information along with the available information on the methodology for diagnosis and speciation of *Leishmania* further discussion of methodology will occur at the end of this meeting if time permits.
 - b. **Efficacy by Gender: Modules 2.7.3.A Summary of Clinical Efficacy (Visceral Leishmaniasis) and 2.7.3.B Summary of Clinical Efficacy (Cutaneous/Mucosal Leishmaniasis)** will be updated to include the requested analysis of efficacy by gender. The planned analysis of efficacy by gender will be performed for the pivotal studies which include the 4 CL studies (study-Z020a, study-Z020b, study-3168, study-soto), the single ML study (study-Z022), and one of the two VL studies (study-3154). The other VL study (Z025) included only males. The analysis will present the primary efficacy endpoint by gender and overall for these studies. Is this acceptable?

- c. **Module 5 – Datasets:** Clinical datasets for the following studies have been previously provided:

Protocol Number	Study Brief Title
study-3154	India VL
study-Z025	Ethiopia VL
study-Z020a	Brazil CL -Dietze/Talahari
study-Z020b	Brazil CL - Machado
study-Soto	Bolivia CL
study-3168	Guatemala CL
study-Z022	Bolivia ML
study-dutch-pk-report	PK in Dutch Military with CL Returning from Afghanistan

Modifications to the above datasets, as appropriate to the study are being prepared per FDA's requests. Details are provided below.

d. Module 3. Quality

Module 3.2.S.3.2: Impurities: A description and a validation report for the HPLC analytical procedure used for the detection of (b) (4) in miltefosine drug substance will be provided.

Module 3.2.S.4.5. A justification to exclude (b) (4) testing from the API specs will be provided.

Module 3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment. A Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) will be provided.

Module 2 sections will be updated in accordance with the above requests. **Module 2.3.S.3 Characterization, Module 2.3.S.4 Control of Drug Substance and Module 2.3.S.7 Stability**

- FDA notified Paladin of two manufacturing facility audits for January. One was cancelled after the Refusal to File letter was given to Paladin, but the other was not as of this date. The visit to the (b) (4) facility is still scheduled for 28 January 2013. Paladin assumed when the refusal to file letter was given, that both audits would be cancelled and this date is no longer a viable option for a visit to the (b) (4) facility. Can we officially close this request?
- Can FDA provide any comments on plans for clinical site audits after submission of revised NDA?

6. Summary of dataset revisions by Study.

Below is the planned XML backbone for the datasets:

Study/Protocol	Description
study-3154	(India VL)
(legacy data from Zentaris)	Analysis Datasets
	Datasets
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-z025	(Ethiopia VL)
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-z020a	(Brazil CL -Dietze/Talahari)
	Analysis Datasets
	Datasets
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-z020b	(Brazil CL -Machado)
	Analysis Datasets
	Datasets
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-3168	(Guatemala and Colombia CL)
(legacy data from Zentaris)	Analysis Datasets
	Datasets
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-Soto	(Bolivia CL)
	Analysis Datasets
	Datasets

Study/Protocol	Description
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-z022	(Bolivia ML)
	Analysis Datasets
	Datasets
	Data Definition Table
	Tabulations Datasets
	Datasets
	Data Definition Table
	Annotated CRF
study-dutch-pk-report	(PK in Dutch Military with CL Returning from Afghanistan)
	Tabulations Datasets
	Datasets
	Data Definition Table

Studies 3154 and 3168 contained legacy data obtained from Zentaris. These data are being remapped as much as possible to CDISC SDTM terminology. Also, almost all data were originally given a numeric code. Instead of numeric codes, we are providing the coded term for ease in reviewing the data.

Study Z025: We were just provided with the CRF for the subjects who had serious adverse events in this study. Just a single table containing all of the available information on these CRFs is being provided.

study-dutch-pk-report: These data are the population PK analysis that we performed using the raw data provided by Zentaris. No clinical data are provided with these data.

Analysis datasets will contain 3 xpt files:

DATASET NAME	DATASET DESCRIPTION
ADSL	Subject disposition, demographic, and baseline characteristics
ADCR	Efficacy endpoints: Final and initial cure rates
ADCRP	Parasitological methods, clinical response and parasitological response

Example ADSL Define File for Study Z020a

(includes name of planned treatment, name of actual treatment, and duration of treatment and other demographic variables)

Dataset Name	Variable Name	Variable Label	Controlled Terms, Code list or Format
ADSL	STUDYID	Study Identifier	
ADSL	USUBJID	Unique Subject Identifier	
ADSL	SUBJID	Subject Identifier for the Study	
ADSL	SITEID	Study Site Identifier	
ADSL	AGE	Age	
ADSL	AGEU	Age Units	"YEARS"
ADSL	SEX	Sex	M=male; F=female
ADSL	RACE	Race	
ADSL	ITTFI	Intent-To-Treat Population Flag	Y
ADSL	ARM	Description of Planned Arm	
ADSL	TRTP	Planned Treatment	
ADSL	EXTRT	Name of Actual Treatment	
ADSL	TRTSDT	Date of First Exposure to Treatment	
ADSL	TRTEDT	Date of Last Exposure to Treatment	
ADSL	EXDUR	Treatment duration	Days

Example ADCR Define File for Study Z020a

(includes name of planned treatment, name of actual treatment, and duration of treatment; primary and secondary efficacy endpoints; and population flags)

Dataset Name	Variable Name	Variable Label	Controlled Terms, Code list or Format
ADCR	STUDYID	Study Identifier	
ADCR	USUBJID	Unique Subject Identifier	
ADCR	ARM	Planned Treatment	
ADCR	EXTRT	Name of Actual Treatment	
ADSL	EXDUR	Treatment duration	Days
ADCR	PARAM	Parameter	"FINAL CLINICAL RESPONSE" (primary efficacy endpoint); "INITIAL CLINICAL RESPONSE" (secondary efficacy endpoint)
ADCR	PARAMCD	Parameter Code	FINLCURE (primary endpoint); INICURE (secondary endpoint)
ADCR	PARAMCAT	Parameter Category	PRIMARY EFFICACY ENDPOINT"; "SECONDARY EFFICACY ENDPOINT"
ADCR	AVALC	Analysis Value (C)	"DEFINITIVE CURE"; "FAILURE"; "APPARENT CURE"; "MISSING VISIT" (only valid at 2 month visit)
ADCR	ITT	Full analysis set population flag-ITT	Y=yes; N=no
ADCR	PP	Per protocol population flag	Y=yes; N=no

Example ADCRP Define File for Study Z020a

(includes name of planned treatment, name of actual treatment, and duration of treatment; primary efficacy endpoint; parasitological response, parasitological methods, and population flags)

Dataset Name	Variable Name	Variable Label	Controlled Terms, Code list or Format
ADCRP	STUDY	Study Identifier	
ADCRP	USUBJID	Unique Subject Identifier	
ADCRP	EXTRT	Actual Treatment	Miltefosine; Glucantime
ADCRP	EXDUR	Duration of Treatment	Duration of treatment in days
ADCRP	ITT	Full analysis set population flag-ITT	Y=yes; N=no
ADCRP	PP	Per protocol population flag	Y=yes; N=no
ADCRP	VISIT	Visit Identifier	0, Screening; 6 months after treatment
ADCRP	SPECIMEN	Specimen Type	Scraping, Aspiration, Smear, Biopsy
ADCRP	STAIN	Result of Staining	Positive; Negative; ND=not done; NA=not applicable
ADCRP	CULTURE	Result of Culture	Positive; Negative; ND=not done; NA=not applicable
ADCRP	PCR	Result of PCR	Positive; Negative; ND=not done; NA=not applicable
ADCRP	IFA	Result of Immunofluorescence	All are blank - method was not done
ADCRP	SPECMETH	Method for Determining Species	PCR=polymerase chain reaction
ADCRP	SPECIES	Leishmania Species	
ADCRP	CLINRESP	Final Clinical Response	"DEFINITIVE CURE"; "FAILURE"
ADCRP	PARARESP	Parasitological Response	All are blank, no follow-up parasitology was performed.
ADCRP	LESNO	Lesion Number	
ADCRP	LESSIZE	Lesion Size	Area in mm ²
ADCRP	STATUS	Leishmania History for Current Disease	New
ADCRP	AGE	Subject Age	Age in years

Drug Exposure Notes

An EX table will be provided in the tabulation datasets that contains the start date (EXSTDTC), end date (EXENDTC) and total days of exposure for each subject (EXDUR). The EXDUR field will also be included in each of the analysis datasets.

Protocol Number	Study Brief Title	Data Available in Database
study-3154	India VL	Yes
study-Z025	Ethiopia VL	Just exposure days
study-Z020a	Brazil CL -Dietze/Talahari	Needs to be imputed
study-Z020b	Brazil CL - Machado	Needs to be imputed
study-Soto	Bolivia CL	Yes
study-3168	Guatemala CL	Yes
study-Z022	Bolivia ML	Yes
study-dutch-pk-report	PK in Dutch Military with CL Returning from Afghanistan	Not applicable

Study Z025 (only SAE data):

Exposure Dose (EXDOSE) and exposure days (EXDAYS). No actual start date and end date.

Studies Z020a and Z020b:

START DATE: CRF page #1 RFSTDTC

END DATE: There was a drug accountability CRF with the number of capsules prescribed and a number of capsules returned for each week from Week 1 to 3. However, this data was not included for Week 4. There also was a subject disposition form that indicated if the subject completed treatment or not. The sites also provided a separate listing (not on the CRF) from the monitoring notes of protocol deviations. When a subject was listed as not having completed treatment, there was a protocol deviation indicating the last day of the study that the subject completed treatment. Using this data, the end date will be imputed as Study Day 28 for those subjects who completed treatment and for those subjects who did not, the end date will be calculated for the last reported study day of treatment.

Parasitology Endpoints and Methodology Notes

Clinical endpoints in leishmaniasis therapy trials typically do not include an evaluation of parasitological responses; however, in the miltefosine pivotal trials, the parasitological response was evaluated in the VL study in India (study-3154), in the patients who did not die during treatment in the VL study in Ethiopia (study-Z025), and in the CL study in Columbia and Guatemala (study-3168). Entry criteria into the trials mostly relies on diagnosis of leishmaniasis by microscopic identification of amastigotes in stained lesion tissue or a positive culture for promastigotes. Both methods are considered the gold standard for diagnosis of leishmaniasis. Clinical cure is presumed to be accompanied by parasitological cure when cure is followed for 6 or more months after treatment.

Summary of Methods Used and Species Identified in Pivotal Efficacy Studies of Miltefosine for VL, CL, and ML for Diagnosis and Parasitological Response

Study	Indication	Method Used for Diagnosis	Method Used for Parasitological Response	Methods Used to Identify Species	Species
study-3154 (India)	VL	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a	Microscopy of Giemsa-stained smears	Epidemiology	<i>L. donovani</i> (100%)
Study-Z025 (Ethiopia)	VL	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a	Microscopy of Giemsa-stained smears	Epidemiology	<i>L. donovani</i> (100%)
study-3168 (Colombia and Guatemala)	CL	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a	Microscopy of Giemsa-stained smears	Epidemiology Also: <i>L. v panamensis</i> by isoenzymes ^e <i>L. v braziliensis</i> <i>L. mexicana</i> by PCR ^e	<i>L. v panamensis</i> (Colombia 100%) <i>L. v braziliensis</i> (Guatemala - 67%) <i>L. mexicana</i> (Guatemala - 33%)

Study	Indication	Method Used for Diagnosis	Method Used for Parasitological Response	Methods Used to Identify Species	Species
study-Z020a (Brazil)	CL	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a	Not done	Epidemiology Also: PCR ^d	<i>L. guyanensis</i> (96%)
study-Z020b (Brazil)	CL	Culture only (62-65%) ("FDA-cleared") ^b Montenegro Skin Test ^c only (20 – 23%) PCR ^d only (15%)	Not done	Epidemiology Also: PCR ^d	<i>L. v braziliensis</i> (100%)
study-soto (Bolivia)	CL	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a	Not done	Epidemiology	<i>L. braziliensis</i> (85%)
study-Z022 (Bolivia)	ML	Microscopy of Giemsa-stained smears ("FDA-cleared") ^a , culture ("FDA-cleared") ^b and Montenegro Skin Test ^c	Not done	Epidemiology Also: Isoenzymes ^e	<i>L. braziliensis</i> (85%)

^aTest Brochure = WHO 2010 Annex 4

^bTest Brochure = WHO 2010 Annex 2 and FCSR sect 9.5.1.9

^cMethods = WHO 2010 page 61

^dMethods = FCSR section 9.5.1.9 (Z020b) and FCSR 9.5.1.8 (Z020a)

^eMethods = statement by PI

Diagnosis of Genus (*Leishmania*) by Giemsa staining, an FDA-cleared method was used in all but 1 study. The Test Brochure (requested in the 23Oct2012 Information Request) is the WHO manual which will be provided in the revised NDA.

Diagnosis by culture, an FDA-cleared method was performed in two thirds of the subjects in the Z020b study and 8 patients in the Z022 study. The Test Brochure is the WHO manual which will be provided

Diagnosis was performed using the Montenegro Skin Test in one third of the patients in the Z020b study and a few patients in the Z022 study.

Speciation: Giemsa-staining and culture identify the genus but not the species, thus speciation was based on epidemiological data for all studies and for the two studies in Brazil with additional confirmatory data obtained by PCR. PCR was considered confirmatory in the Z020a study because the literature states that 94% of speciated parasites in Manaus, Brazil are *L. v guyanensis*. PCR data in this study confirmed that 96% of the parasites in this study were *L. v guyanensis*. PCR was considered confirmatory in the Z020b study because the literature states that 100% of speciated parasites in Corte de Petra, Bahia are *L. (v) braziliensis*. PCR data confirmed that 100% of the parasites in Z020b study conducted in Corte de Petra were *L v braziliensis*.

Data on performance characteristics of these methods by these researchers are not available.

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/s/

JOHN J FARLEY
04/25/2013

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204684-Impavido-Paladin-CMC Advice/IR
Date: Thursday, January 24, 2013 12:54:00 PM
Attachments: [01.24.12 CMC Comment Dissolution.pdf](#)
Importance: High

Hello Dr. Berman,

I would like to provide the attached FDA Advice/Information Request regarding NDA 204684. Please be aware there will be no hardcopy/paper communication to follow this email communication.

Please let me know if you have questions.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: January 24, 2013

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	
Subject: NDA 204684	

Total no. of pages including cover: 2

Comments:

Advice/Information request

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

NDA 204684
Advice/Information request

Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We also refer to your September 26, 2012, NDA submission and would like to provide you with the following comments as you prepare to re-file the NDA.

Chemistry, Manufacturing, and Controls (CMC) Comments:

The proposed regulatory dissolution test for miltefosine capsules, 50 mg, is conducted with USP Apparatus Type II (paddle) at 50 rpm in a medium consisting of 750 mL of 0.1 N HCl at 37°C. An acceptance criterion of Not Less Than (b)(4) dissolved in (b)(4) is proposed. However, the observed mean amount dissolved at (b)(4) is typically at least (b)(4)

For immediate release product the selection of the test sampling time point should be where $Q = (b)(4)$ dissolution occurs. Therefore, please provide dissolution profiles (including 15, 20, 30, and 45 minutes sampling time points, n=12) for your drug product at release and on stability. Based on the results, propose a sampling time point at which a mean of Not Less Than (b)(4) (Q) is dissolved (see USP <711> Acceptance Table 1).

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

GREGORY F DIBERNARDO
01/24/2013
ONDQA Advice/Information Request



NDA 204684

MEETING REQUEST GRANTED

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) Capsules.

We also refer to your December 3, 2012, correspondence requesting a meeting to discuss the Refuse-to-File (RTF) issues identified in the November 26, 2012, letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: January 8, 2013

Time: 3:00 P.M. TO 4:00 P.M. EST

Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants:

Division of Anti-Infective Products (DAIP)

John J. Farley, M.D., M.P.H.	Acting Director
Katherine A. Laessig, M.D.	Deputy Director
Sumathi Nambiar, M.D., M.P.H.	Deputy Director for Safety
Thomas Smith, M.D.	Clinical Team Leader
Hala H. Shamsuddin, M.D.	Medical Officer
Lynette Y. Berkeley, Ph.D.	Acting Clinical Microbiology Team Leader
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
Wendelyn Schmidt, Ph.D.	Pharmacology/Toxicology Team Leader
James S. Wild, Ph.D.	Pharmacology/Toxicology Reviewer

Maureen P. Dillon-Parker
Gregory F. DiBernardo

Chief, Project Management Staff
Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Kimberly L. Bergman, PharmD.
Seong H. Jang, Ph.D.

Clinical Pharmacology Team Leader
Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Karen Higgins, Sc.D.
Lan Zeng, Ph.D.

Biostatistics Team Leader
Biostatistics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Dorota M. Matecka, Ph.D.
Angelica Dorantes, Ph.D.
Mark Seggel, Ph.D.
Anamitro Banerjee, Ph.D.

Chemistry, Manufacturing, and Controls (CMC) Lead
Biopharmaceutics Team Leader
CMC Reviewer-Drug Substance
CMC Reviewer-Drug Product

Office of Business Informatics (OBI)/Division of Data Management Services & Solutions (DDMSS)

Virginia Hussong
Douglas Warfield

Data Management Solutions Team Leader
Operations Research

Please e-mail Mr. Gregory DiBernardo any updates to your attendees at gregory.dibernardo@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email Mr. DiBernardo the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Mr. DiBernardo (301) 796-4063.

Submit background information for the meeting (three paper copies or one electronic copy to the application via the FDA Central Document Room and 20 desk copies to Mr. DiBernardo) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by December 24, 2012, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

Gregory DiBernardo
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6189
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Paladin Therapeutics, Inc. and Fast Track Drugs and Biologics, LLC
MEETING START DATE AND TIME	January 8, 2013, 3:00 P.M. EST
MEETING ENDING DATE AND TIME	January 8, 2013, 4:00 P.M. EST
PURPOSE OF MEETING	Guidance
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Conference Room: 1415
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Gregory DiBernardo Regulatory Project Manager Division of Anti-Infective Products White Oak Building 22, Room: 6189 Telephone Number: (301) 796-4063
ESCORT INFORMATION (If different from Hosting Official)	Same

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/s/

MAUREEN P DILLON PARKER
12/17/2012



NDA 204684

REFUSAL TO FILE

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President, Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

Please refer to your September 26, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) Capsule, 50 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

CLINICAL and STATISTICAL

- Efficacy was not investigated for important subgroups such as gender in any of the 6 studies conducted for VL and CL. Please perform and submit efficacy analyses based on gender.
- The submitted datasets do not allow a meaningful review of the efficacy and safety data. Specifically:
 1. Some important datasets are not submitted. For example, according to the cover letter dated November 12, 2012, “*the ADaM dataset for study 3154 contains two xpt files, one for clinical response data (study 3154 adcr.xpt) and one for the parasitological methods, clinical response, and parasitological response (study 3154 adcrp.xpt).*” However, the two datasets submitted on 11/12/2012, namely “adcr.xpt” and “adcrp.xpt”, appear to be identical. If the cover letter is correct, then one dataset has not been submitted.

2. Some key parameters are missing or erroneous in the datasets. For example,
 - a. There is no variable in the datasets indicating if the actual treatment a subject received is the same as planned. Treatment assignment for some subjects is not consistent across datasets. For example, in Study 3154, Subject 3154-3060 had TRT=1 (miltefosine) in “rando.xpt”, TRT=2 (amphotericin B) in “rando-c.xpt”, TRT=2 (amphotericin B) in “response.xpt”, and TRTA='amphotericin B' in “adcr.xpt”. All of these variables are labeled as “Actual Treatment”.
 - b. Start and stop date of study treatment are not provided for most studies. Treatment duration is not available for Study Soto.
 - c. Treatment durations are not consistent for several subjects in Study Z020a, Z020b and 3168. For example, in Study Z020a, treatment duration is report as both 10 and 28 for Subject 048.
 - d. There is no information about apparent cure (secondary efficacy endpoint) in the datasets for Studies Z020a and Z020b. The study reports defined apparent cure as complete re-epithelialization of all ulcers at the 2 month follow-up. However, the submitted datasets only contain response information at the 6 month follow-up.
 - e. Subject IDs in the datasets do not correlate with those in the study report. For example, in Study 3154 report, subjects are referred as Pat 1/137, Pat 1/116, Pat 3/38, and Pat 2/92, etc. However, in the datasets USUBJID is denoted as 3154-1001, 3154-1100, etc.
3. Visit days in your datasets need to be clarified. For example, in Study 3168, visits are designated 55 and 70 in “response.xpt”, 37 and 40 in “ae.xpt”, 50 and 60 in “final.xpt”. Not all of them correlate with the timing of assessments as per the protocol or with the days as designated in the “tv.xpt” dataset or in the “define.pdf”.
4. The “define.pdf” file does not provide clear documentation about your datasets.
 - a. There are no definitions for many key fields. For example, In Study Z025, CURETEST has entries of ln neg, na, neg, spleen neg but no meanings are provided. Likewise, no meanings are provided for PRE_RX (values: 1, 2), DAT (values: 7, 8, 9, 10, and 11), and ASPIR (values: 1, 2, 3, 4, 5, and 6).
 - b. For the analysis datasets in Study 3154, the “define.pdf” does not correlate with the dataset “adcr.xpt”. The following variables are specified in the “define.pdf” but don't appear in the dataset “adcr.xpt”: TRT, EXAM, RESPONSE, and EXDAYS. Dataset “adcr.xpt” contains the following variables which are not included in the “define.pdf”: CLINRESP, PARARESP, SEQ, TRTA, and TRTDUR.

- c. For the tabulation datasets in Study 3168, the “define.pdf” has the following explanation about RESP_FIN in “response.xpt”: “At 3 months, 1=*apparent cure*, 2=*partial cure*, 3=*clinical failure*, 4=*not assessable*; at six month follow up, 1=*definite cure*, 2=*clinical failure*, 3=*other*”. However, there is no variable indicating 3 month time point in dataset “response.xpt”.
- d. For the tabulation datasets in Study 3154, the “define.pdf” indicates “*One record per subject*” for datasets “ecg.xpt” and “final-t.xpt”. However, there are multiple records per subject in these datasets (a total of 1967 records in “ecg.xpt” and 935 records in “final-t.xpt”).

ADDITIONAL COMMENTS AND REQUESTS

The following comments, while not refuse to file issues, should be addressed in your response to this letter, otherwise they may cause difficulties in navigating your datasets:

1. Datasets for Study Z020a and Study Z020b are combined. Please submit data for different studies under separate directories.
2. Coded variables are used in SAS datasets but no formats are provided. Please submit a format.xpt file for the ease of reading your data.
3. Some key parameters are defined as character variables in one dataset and numeric variables in another. For example, in Study Soto, SITEID is defined as numeric in “adsl.xpt” but character in “dm.xpt”.
4. Some variables are not clearly labeled. For example, in Study Soto, DOMAIN in “dc.xpt” is labeled as “then delete”.
5. You state in your letter dated November 12, 2012, that a summary of the parasitological methods used in different laboratories will be provided. In addition to the details of the methods, please include the performance characteristics of the assays in the laboratory where testing was performed. The name and address of the laboratories should be specified.
6. Please provide a description and a validation report for the HPLC analytical procedure used for the detection of (b) (4) in miltefosine drug substance described in section 3.2.S.3.2: Impurities.
7. Add tests for (b) (4) residual solvents in the drug substance specifications or provide justification for exclusion of these tests from the specification.
8. For the drug substance, include the Postapproval Stability Protocol (with the testing intervals, storage conditions and tests) in section 3.2.S.7.2: Postapproval Stability Protocol and Stability Commitment.

PROCEDURAL

Within 30 days of the date of this letter, you may request, in writing, a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee or exclusion documentation as appropriate.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely yours,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
11/26/2012

From: DiBernardo, Gregory
To: ["jberman@fasttrackresearch.com"](mailto:jberman@fasttrackresearch.com)
Subject: FDA Communication: NDA 204864- Impavido (miltefosine)-Paladin-Information Request
Date: Tuesday, October 23, 2012 5:26:00 PM
Attachments: [Clinical and Micro IRdoc.pdf](#)
Importance: High

Hello Dr. Berman,

I am providing a FDA information request on your September 26, 2012, submission to NDA 204684. Please be aware there will be no paper/hard copy communication to follow this e-mail communication.

Please let me know if you have questions. If you could please inform me as soon as possible the date you expect to submit your response to this information request it would be appreciated.

Regards,

Gregory F. DiBernardo

Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6189
Silver Spring, MD 20993
Telephone: (301) 796-4063



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: October 23, 2012

To: Jonathan D. Berman, M.D., Ph.D. Vice President, Clinical Affairs	From: Gregory F. DiBernardo Regulatory Project Manager
Company: Fast Track Drugs and Biologics, LLC	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	Fax number: (301) 796-9882
Phone number: (301) 922-2097	Phone number: (301) 796-1400
E-mail: jberman@fasttrackresearch.com	

Subject: NDA 204684

Total no. of pages including cover: 5

Comments:

Information request for submission dated, September 26, 2012

Confirm receipt of this communication at gregory.dibernardo@fda.hhs.gov

Document to be mailed: YES NO

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Dear Dr. Berman,

Please refer to your New Drug Application (NDA) 204684 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) for visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis.

We have the following requests on your September 26, 2012, NDA submission:

On cursory review of your submission, we identified the following issues that may impact the fileability of the NDA. Please submit the following items, or a rationale for inability to submit:

Clinical:

1. Submit the datasets for Study Z020a
2. Submit analysis datasets for Studies 3168 and 3154. These should include a unique subject ID, visit number, clinical response, parasitic response, population flag, treatment assigned, and duration of therapy
3. The Adverse Events for Studies 3168 and 3154 were classified using WHO (World Health Organization) classification, while Studies Z020b and SOTO were classified using MedDRA. Please reclassify adverse events for all the submitted studies using MedDRA
4. Resubmit datasets for studies 3168 and 3154 with a separate column for unique subject ID
5. For ease of navigation of the laboratory datasets, please specify the laboratory parameter by name instead of a code
6. Please clarify the visit days in your datasets. For example, in Study 3168, visits are designated 0, 55 and 70. These do not correlate to the timing of assessments as per the protocol or with the days as designated in the tv dataset.

Clinical Microbiology:

It would be helpful if the following information would be submitted for review:

1. It appears that parasitology data were included for only 2 clinical trials (Z020b and Z022) and the results were presented as positive by either microscopy or PCR. For study Z020b, *Leishmania* species identified was specified for some of the patients only. Please include parasitology data including *Leishmania* species identified for all patients in all the datasets.
2. Please format the datasets including all of the above in one Sas Transport file as shown in the attached Table 1 for each of the studies (3154, Z025, 3168, Soto, Z020b, and Z022). Please note that Table 1 is based on study report 3168. The *Leishmania* species will vary based on the country where trial was

performed. Additionally, the testes used for parasitological response may vary in different laboratories. Therefore, changes to the Table should be made as appropriate.

3. Please provide summary Tables (as shown in Table 2) of the results by baseline *Leishmania* species in the treatment arms. Patients with a single baseline pathogen and those patients with mixed infection should be shown separately. A separate summary Table should be included for each study.
4. Please provide details of all the parasitological methods used for identification of *Leishmania* species as well as measuring parasitologic response at follow up visits (e.g., 2 weeks, 2 months and 6 months after end of treatment for study 3168). Other than microscopy and culture, it appears that all the other tests used such PCR and immunofluorescent testing are not FDA cleared and considered experimental assays. Please clarify. As discussed in meeting on January 13, 2012 (for details see meeting minutes dated February 9, 2012) if the tests are FDA cleared, then test brochure should be provided for our review. If these are experimental assays then details of the methods used in the laboratory where testing was performed and performance characteristics of the assays including appropriate quality control measures in that laboratory should be provided for an independent review.
5. It appears that photographs were taken of the parasitological findings. It will be helpful if some of these are included in the submission.
6. It also appears that cytokines were measured in some of the studies such as Z027. Please provide details of the methods used and the results for our review.

APPEARS THIS WAY ON ORIGINAL

Table 1: CL Clinical microbiology dataset sample template

Pt ID	Center (Colom /Gaut)	Trt Grp	Durat of Trt	ITT/PP Flag	Phase	Specimen Source/Lab	Test used for species identification and results by lab				Clinical Response	Lesion Size	Parasitological Response	Status of Leishmania (Relap/New/U nresponsive)
							Stain*	Culture	PCR	IFA				
101		M			Baseline	Aspirate								
101		M			2 weeks after the last dose	Aspirate								
101		M			2 mths after the last dose	Smear								
101		M			6 mths after the last dose	Aspirate								
<u>102</u>		M			Baseline	Smear								
<u>102</u>		M			2 weeks after the last dose	Smear								
<u>102</u>		M			6 mths after the last dose	Smear								
103		P			Baseline	Biopsy								
103		P			2 weeks after the last dose	Biopsy								
103		P			6 mths after the last dose	Biopsy								
103		P			Baseline	Aspirate								
103		P			2 weeks after the last dose	Aspirate								
103		P			6 mths after the last dose	Aspirate								

*If different stains were used then those should be specified; If more than one species was identified in a specimen from a patient then that should be identified
M= miltefosine; P = placebo

Table 2: Summary Tables by the method used (stain, PCR, culture, etc):

Treatment Group/Species	End of Therapy n /N (%)			Follow-Up at 2 and 6 months n /N (%)		
	Clinical Success	Proven Parasitologic Eradication	Presumed Parasitologic Eradication	Clinical Success	Proven Parasitologic Eradication	Presumed Parasitologic Eradication
ITT						
Miltedfosine						
Colombia						
<i>L. vianna panamensis</i>						
Guatemala						
<i>L. v. braziliensis</i>						
<i>L. mexicana mexicana</i>						
Total						
Placebo						
Colombia						
<i>L. vianna panamensis</i>						
Guatemala						
<i>L. v. braziliensis</i>						
<i>L. mexicana mexicana</i>						
Total						
Total						
PP						
Miltedfosine						
Colombia						
<i>L. vianna panamensis</i>						
Guatemala						
<i>L. v. braziliensis</i>						
<i>L. mexicana mexicana</i>						
Total						
Placebo						
Colombia						
<i>L. vianna panamensis</i>						
Guatemala						
<i>L. v. braziliensis</i>						
<i>L. mexicana mexicana</i>						
Total						

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/s/

GREGORY F DIBERNARDO
10/23/2012
Clinical and Microbiology Information Request



NDA 204684

NDA ACKNOWLEDGMENT

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President, Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

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: Impavido (miltefosine) Capsule, 50 mg

Date of Application: September 26, 2012

Date of Receipt: September 27, 2012

Our Reference Number: NDA 204684

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 November 26, 2012, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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
10/12/2012



IND 105430

MEETING MINUTES

Paladin Labs, Inc. (USA)
c/o Fast-Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph. D.
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for miltefosine.

We also refer to the meeting between representatives of your firm and the FDA on January 13, 2012. The purpose of the meeting was to discuss a New Drug Application (NDA) for leishmaniasis.

A copy of the official minutes of the 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 Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 13, 2012, 11:00 to 12:00 pm (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 105430
Product Name: Impavido (miltefosine)
Indication: visceral, mucosal, and cutaneous leishmaniasis
Sponsor/Applicant Name: Paladin Labs Inc. (USA)

Meeting Chair: John Farley, MD, MPH
Meeting Recorder: Caroline D. Fukuda, MHA

FDA ATTENDEES

Division of Anti-Infective Products (FDA)

Sara Alizai	Pharmacy Student
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
John Farley, MD, MPH	Acting Director
Caroline D. Fukuda, MHA	Regulatory Project Manager
Karen M. Higgins, ScD	Statistical Team Leader
Seong Jang, PhD	Clinical Pharmacology Reviewer
Katherine A. Laessig, MD	Deputy Director
Francis V. LeSane	Chief, Project Management Staff
Sumati Nambiar, MD, MPH	Deputy Director for Safety
Anne E. Purfield, PhD	Clinical Microbiology Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Hala H. Shamsuddin, MD	Medical Officer
Thomas Smith, MD	Clinical Team Leader
Kerry Snow, MS	Clinical Microbiology Reviewer
James S. Wild, PhD	Pharmacology/Toxicology Reviewer
Andrew B. Yu, PhD	Chemistry Reviewer
Lan Zeng, PhD	Statistical Reviewer

Division of Regulatory Review Support/Office of Business Informatics

Valerie M. Gooding	Regulatory Information Specialist
--------------------	-----------------------------------

Office of New Drug Quality Assessment

Minerva Hughes	Chemist
Rapti Madurawe, PhD	Branch Chief

Office of Orphan Products Development

Henry Startzman, MD Medical Officer

SPONSOR ATTENDEES

Paladin Labs, Inc. (USA) [Paladin]

Ms. Sylvie Ducharme Director, Regulatory Affairs
Ms. Stephanie Peika Director, Quality Services
Dr. Robert K. Vinson Director, Product Development

SPONSOR CONSULTANTS

Fast-Track Drugs and Biologics, LLC

Dr. Jonathan D. Berman Vice President for Clinical Affairs

(b) (4)

(b) (4)

1.0 BACKGROUND

On October 3, 2011, Paladin Labs requested a pre-NDA meeting to discuss a New Drug Application (NDA) for leishmaniasis. Paladin Labs submitted a meeting package on December 1, 2011. The meeting package included 19 questions. Preliminary responses were sent to Paladin Labs on January 11, 2012, in preparation for the January 13, 2012 meeting. Paladin Labs accepted the FDA's responses to questions 5-8, 10-13, and 15-19. Questions 1-3, 4, 9, and 14, as well as the Microbiology Additional FDA Comments, were discussed during the meeting. The minutes below include Paladin Labs' (referred to as Paladin) original questions in **bold** font, FDA's response in normal font, and meeting discussion and additional recommendations in *italics*.

2. DISCUSSION

Paladin gave a history of miltefosine development, global marketing authorizations, and the status of miltefosine development and designation in the United States. Paladin stated their goals: to expand access to miltefosine and replace parenteral with non-parenteral therapy. Paladin described bias against miltefosine in Visceral Leishmaniasis (VL) studies, specifically Study 3154 in which six months after treatment 27 patients in the miltefosine study arm were tapped at six month follow-up, but none of the patients in the amphotericin B study arm were tapped.

2.1. CLINICAL

Question 1: Is the clinical dossier consisting of study reports as described for studies 3154 and Z025 sufficient as pivotal studies to review in support of an NDA for visceral leishmaniasis?

Question 2: Does the Agency agree that study 3154 plus studies Z025/033/3089/3109/3127 and Phase 4 literature reports are sufficient to review in support of an NDA for visceral leishmaniasis?

FDA Response to Questions 1 and 2: Studies 3154 and Z025 were open-label, randomized, controlled trials comparing miltefosine to an active comparator, amphotericin B, in Study 3154 and stibogluconate (SSG) in Z025. The open-label nature of the studies could introduce serious bias and weaken study conclusions.

Study 3154 was designed as a non-inferiority trial; a justification for the non-inferiority margin should be provided (See discussion on Question 3 for more detail). In addition, patient level data generated from this study should be provided.

Study Z025 was not explicitly described as a non-inferiority trial; however if the efficacy of miltefosine will be determined based on similar efficacy as the control, then a non-inferiority margin justification will be required for this study as well. For Study Z025, please clarify if the patient level data related to efficacy and safety evaluations are available for those with severe adverse events, deaths, and discontinuations. The lack of a complete dataset for this study may adversely affect our ability to perform an adequate review. In addition, for Study Z025, please provide ancillary (e.g., literature) data to support the utility of antimonials in the treatment of African VL, specifically whether resistance to antimonials has limited their utility, and thus the adequacy of these agents as active comparators, similar to the situation in India. The resistance issue may be of importance in interpreting whether the higher death rates in SSG recipients were possibly related to resistance or possibly related to toxicity.

Studies 033, 3089, 3109 and 3127 were not randomized or blinded. While these studies may be supportive of efficacy, we are not optimistic that they would be found to be adequate and well-controlled upon review.

When all the proposed studies are submitted to an NDA, please also provide an assessment of the potential for development of resistance to miltefosine. It is also important to include all protocols and amendments, the statistical analysis plans, if applicable, as well as any information regarding any interim analyses conducted and data safety monitoring boards. Additionally, complete electronic data from the studies will need to be submitted. The datasets should be able to support the analyses contained in the clinical study reports. Please describe the formats of your datasets for review.

Discussion: *Paladin stated that the pivotal studies for visceral leishmaniasis (VL) are studies 3154 and Z025 and added that all requested Study 3154 data will be provided in the NDA; Paladin has access to source and electronic data. Paladin described Study Z025 as an*

investigator-initiated trial for which Paladin lacks access to primary data (i.e. informed consent forms); patient-level data is only available for patients who were reported to have a serious adverse event(s) and drug discontinuation. Additionally, Paladin stated that the antimony comparator is supported 100% by the literature; failure in the study was due to patient problems, not parasite problems.

In response to the Agency's previous advice, given during the pre-Investigational New Drug Meeting, to file for VL and to consider the FDA's Guidance for Industry, "Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention" published August 2011 and the Non-Inferiority Clinical Trials Draft Guidance published March 2010, Paladin described their view of their two options for providing adequate evidence of efficacy for VL:

- *Reliance on studies 3154 and Z025, or*
- *Reliance solely on Study 3154.*

The FDA confirmed that there are circumstances when one trial with supportive data can stand alone. The FDA recommended that Paladin refer to the November 3-4, 2011 Advisory Committee briefing documents which discusses supportive evidence which may be helpful in anti-infective drug development.

Question 3: Does the Agency agree that because this value of 9.6% is less than the 10%-15% value specified in the 2010 draft guidance document, study 3154 generated a statistically persuasive result and this single pivotal trial is sufficient to review in support of an NDA for VL?

FDA Response to Question 3: For Study 3154 to be considered an adequate and well-controlled trial as part of substantial evidence of the efficacy for miltefosine for this indication, we will require an adequate non-inferiority margin justification. As with all non-inferiority studies, you will need to discuss how the efficacy of your drug can be determined based on the results of this non-inferiority study. We recommend that this information be included as part of the study report. We recommend that you address the following three pieces of information, as outlined in the guidance documents International Conference on Harmonization (ICH)-E9 and in more detail in ICH-E10, to explain "why the drugs should be considered effective in the study" as described at 21CFR314.126.

(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)

1. Evidence of the historical sensitivity to drug effect. This would include a data-driven estimate of the smallest effect size (as specified in ICH-E10) that the control would have over what would have been expected from a placebo arm in this study, if one had been included. The non-inferiority (NI) margin used in this study would need to be no larger than this smallest effect size. This information ideally would be obtained from past placebo-controlled trials of the active control. If you plan on collecting this information from a literature search, we recommend including an outline of the criteria used for the literature search, databases searched, key words, etc. The variability of the effect size estimated should be taken into account, typically by considering the lower bound of the 95% confidence interval of the difference between the active control and placebo.

2. An explanation why the chosen magnitude of the loss of effectiveness would be clinically acceptable (for instance, why a drug that might be as much as 10% less effective would be still clinically acceptable).
3. An evaluation of the constancy of the effect of the control in the current trial, e.g., definitions of disease, definitions of endpoints, timing of endpoints etc., as they were used in the previous trials that were used to determine a margin (point 1 above) and how they relate to the current trial under review.

If a placebo effect cannot be determined from historical or literature references, you may wish to consider using the response to antimonials in Bihar, India as a “pseudo-placebo”. The difference between this value and the aggregate response to amphotericin could be used to determine the treatment effect, or M1.

Discussion: *The FDA recommended that Paladin submit their non-inferiority (NI) margin justifications for all studies and all indications prior to NDA submission so that the FDA can review and provide any guidance, if necessary. Additionally, the FDA suggested that Paladin outline their literature search. Paladin stated that they will provide literature data available on antimonial resistance (lack thereof) in African VL. The FDA recommended that Paladin refer to the FDA’s response to Question 3, specifically the last paragraph that describes a potential method of using a pseudo-placebo if a placebo rate could not be found. Also, the FDA referred Paladin to the Non-Inferiority Clinical Trials Draft Guidance, published March 2010, for examples of how to justify non-inferiority margins. The FDA recommended that Paladin consider the timing of the primary endpoint and consider the placebo rate at the time point used in the study.*

Question 4: **Does the Agency agree that studies 3168, Z020a, Z020b, and “Soto study” are sufficient to review in support of NDA for cutaneous leishmaniasis?**

FDA Response to Question 4: Study 3168 compared miltefosine to placebo. It is not clear from the current submission whether randomization was employed to allocate patients into each group in Study 3168. If Study 3168 is submitted along with other studies to an NDA, provide an explanation for the apparent geographic variation in treatment response in patients infected with *L. braziliensis*. It will be important to include all protocols and amendments, the statistical analysis plans, if applicable, as well as any information regarding any interim analyses conducted and data safety monitoring boards. Additionally, complete electronic datasets from the studies will need to be submitted. The datasets should be able to support the analyses contained in the clinical study reports. Please describe the formats of your datasets for review.

The statistical hypotheses for studies Z020, Z020b and the Soto study are not clear. If these studies are of a non-inferiority design, please provide an NI margin justification.

Miltefosine is teratogenic and contraindicated in pregnancy. It can also affect male fertility. For the treatment of VL, a potentially fatal disease, the risk/benefit may be favorable for an effective drug. However, for cutaneous leishmaniasis (CL), the risk/benefit may not be favorable, especially if the *Leishmania* species is not one that causes mucosal leishmaniasis (ML). Please

provide a risk/benefit analysis and any data or plans regarding post-marketing monitoring of reproductive toxicity.

Discussion: *Paladin stated that studies 3168, Z020a, Z020b, and the “Soto Study”, all investigator-initiated and all NI studies, will be submitted as pivotal studies in the NDA for CL. Paladin added, they will submit post-hoc statistical analysis plans (SAPs) in the NDA.*

Paladin stated that challenges presented by geographic variation in response to treatment restrict the ability to generalize efficacy data between studies; the mechanism of response to treatment is unknown. Paladin added, no one knows if we can generalize the treatment benefit across species; we can only present the data as it exists.

Paladin stated that they will provide a risk/benefit analysis for CL in the NDA.

2.2. MICROBIOLOGY (Additional FDA Comments)

1. Please refer to the Guidance for Industry: Microbiological Data for Systemic Antibacterial Drug Products—Development, Analysis and Presentation (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf>) for general consideration of the type of nonclinical information that should be submitted with the NDA. We recognize that the guidance document is specific to development of antibacterial products; however, many of the types of microbiological studies, assessments and clinical trials are also appropriate to support an NDA for an antiparasitic drug product, including studies to assess intracellular concentrations of miltefosine or the potential effects on activity in vitro or in vivo when miltefosine is co-administered with other clinically relevant products, such as amphotericin B or anti-parasitic agents. In addition, please include studies in vitro or in animal models of infection that assess activity of any miltefosine metabolite.

Discussion: *Paladin stated that they will provide extensive literature on co-administration and resistance in the NDA; Paladin cited Simon Croft’s lab finding of a study conducted in Peru.*

2. Please include detailed study reports or publications for all preclinical studies conducted to describe miltefosine mechanism(s) of action and resistance, spectrum of activity in vitro and in animal models of New or Old World visceral, mucocutaneous and cutaneous *Leishmania* infection, and details for how drug activity and parasite susceptibility are measured. Study reports using animal models of infection should include details such as the size of inoculum, time of treatment, strain of pathogen(s), quality control parameters, strain of animal and method for assessing activity against relevant life stages of *Leishmania* spp.

Discussion: *Paladin stated that they will provide mechanism of action data on miltefosine in the NDA.*

3. Note that for inclusion in labeling, you will need to demonstrate activity of miltefosine in vitro against laboratory strains of *Leishmania* sp. and at least 100 fresh clinical isolates of each species to be included. We recognize that there are no standard methods to assess in vitro activity of miltefosine against *Leishmania* spp.; however experimental methods to assess drug activity against *Leishmania* spp. in vitro are described in published literature (Vermeersch et al., 2009. Antimicrobial Agents and Chemotherapy), and you should attempt to validate such an assay. Please include a description of adequate controls, comparators and performance characteristics for the assay in the laboratory where it is performed. Different concentrations of miltefosine should be tested to determine the optimal concentration effective for inhibiting growth and/or killing the parasite and the effect of miltefosine on different stages of the parasite.

Discussion: *Paladin described that in vitro and in vivo animal models have been investigated, but lack clinical relevance.*

Paladin stated that the requirement for testing 100 clinical isolates of each species will prevent NDA submission for miltefosine. The FDA explained that data such as this is helpful to monitor changes in miltefosine susceptibility and said that it would be ideal to have a validated in-vitro susceptibility test method for clinical isolates of different Leishmania species. The FDA stated that particular Leishmania species cannot be listed in the drug label without being studied. The FDA suggested that one alternative approach to testing 100 clinical isolates of each species is to compile what data is available and arrive at a mutually agreeable post-marketing requirement. The FDA is agreeable to further discussion of this issue.

4. A direct measure of parasitemia is an important endpoint in clinical studies. Study reports should include details of parasitologic assessment and microbiologic testing methods, such as microscopy, serological assessments, or molecular methods for speciation. If the tests used are FDA cleared, then please provide the test brochure for our review. If the tests used are not FDA cleared, then please include details of the methods used and the performance characteristics, including appropriate quality control measures, in the laboratory(ies) where the test was performed. We recognize that the clinical trials in support of your application may have been conducted without your oversight and details of the microbiologic methods may be limited in publications.

Discussion: *Paladin stated that they will provide details on parasitological endpoints in the NDA.*

5. The ability of *Leishmania* spp., to develop resistance or decreased susceptibility when subjected to drug pressure should be examined in appropriate in vitro and/or in vivo animal models of infection. It is important to identify the mechanism of resistance or potential cross-resistance with other anti-*Leishmania* drugs. You should evaluate the clinical significance of any changes in phenotype (e.g., in vitro susceptibility to

miltefosine) or genotype observed in preclinical studies by correlating such changes with clinical outcome.

Discussion: *In response to comments 3 and 5, Paladin described that there is not a correlation in this field between in vitro susceptibility data and clinical outcome. The FDA recommended that Paladin provide both a statement describing the lack of correlation between preclinical data and clinical outcomes in Leishmaniasis and data to support this statement.*

Paladin stated that they will provide published studies on Leishmania species resistance to miltefosine in the NDA.

2.3. PHARMACOKINETICS

Question 9: **Is the pharmacokinetic dossier sufficient to review in support of an NDA for visceral, cutaneous, and mucosal leishmaniasis?**

FDA Response to Question 9: We do not agree that the pharmacokinetics (PK) dossier is sufficient to review in support of the proposed NDA.

First, we do not agree that you addressed the issues *h* and *i* in the pre-IND minutes although we understand that you did not conduct any studies related to these issues. Regarding the issue *h*, we request that you provide any information related to the ability of miltefosine to inhibit and/or induce CYP450 enzymes. If you do not have such information, we recommend that you conduct in vitro studies to evaluate the potential of miltefosine as an inhibitor and/or an inducer of CYP450 enzymes. Regarding issue *i*, we request that you provide any supporting information/rationale for the statement “no signs of interactions with antiviral therapy were encountered.” If you do not have such information/rationale, we recommend you conduct a study to exclude the potential interactions of miltefosine with antiviral therapies.

Second, we request that you clarify the pre-IND issue *k*. According to the pre-IND meeting minutes, the 50 mg miltefosine capsule formulation that was used in all clinical studies (i.e., PK and efficacy/safety trials) is the final marketed formulation. However, the current submission states that supporting information will be submitted in the NDA detailing the comparison between the 50 mg miltefosine capsule formulation that was used in clinical trials and the final to-be-marketed formulation. If there were any changes between the 50 mg miltefosine capsule formulation that was used in clinical trials and the final to-be-marketed formulation (including manufacturer), the need for a clinical bioequivalence (BE) study must be addressed **prior to** NDA submission. It should be noted that the lack of information for bioequivalence between the clinical formulation and the final to-be-marketed formulation is an NDA filing issue.

Third, we recommend you provide all clinical pharmacology information that you plan to include in the labeling before you submit the NDA so that we can recommend what other clinical pharmacology information is needed.

Discussion: *In regards to issue h, Paladin stated that miltefosine does not inhibit or induce CYP450 3A4, thus there are no anticipated effect(s) on most antiviral therapies. The FDA stated that the need for further drug-drug interaction evaluation will be addressed upon review of the preclinical drug interaction data in the Investigator's Brochure (IB), specifically information related to the ability of miltefosine to inhibit and/or induce CYP450 enzymes. If such information does not adequately address the potential for drug interactions with miltefosine, in vitro studies to evaluate the potential of miltefosine as an inhibitor and/or an inducer of CYP450 enzymes may be warranted. Paladin agreed to submit the current IB to the FDA. In regards to issue k, Paladin stated that the formulation changes were very minor and the detailed information will be submitted in the NDA.*

2.4. CHEMISTRY, MANUFACTURING, and CONTROLS

Question 14: *Is this proposal acceptable to the Agency?*

FDA Response to Question 14: *This subject will be a review issue after NDA submission. We recommend the provision of stability data for the new packaging system.*

(b) (4)

(b) (4)

Additional Meeting Discussion: *The FDA asked Paladin when they expect to submit the NDA. Paladin aims to submit the NDA in early July, 2012. The FDA stated that because miltefosine is a new molecular entity for the United States, an Advisory Committee meeting will likely be organized. Whether the NDA is given a priority review will be determined at filing.*

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 POST-MEETING NOTE

Four business days after this meeting, Paladin asked if meeting minutes of the November 3-4, 2011, Advisory Committee (AC) Meetings are available. Paladin found the Briefing Document for the November 4, 2011, AC Meeting entitled "Endpoints and Clinical Trial Issues in Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia." The Agency provided the following two links containing the briefing documents from the November 3rd, 2011, AC meeting,

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm275821.htm>,

the slide sets, and the complete written transcripts of the November 4th, 2011 AC discussion,

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm>.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit current IB for FDA review	Paladin Labs	Submitted 01-25-2012; received 01-26-2012
Can the (b) (4) packaging change be handled as a postmarketing change?	FDA	See response below.

No, the (b) (4) packaging is required for a marketed drug product per the U.S. Consumer Product Safety Commission (CPSC) regulations (b) (4)

(b) (4)

6.0 ATTACHMENTS AND HANDOUTS

Paladin handed-out an 11-page presentation which they used to guide the meeting. The hand-out used in the presentation was officially submitted by Paladin to the IND on January 24, 2012.

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

/s/

JOHN J FARLEY
02/09/2012

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 204684

LATE-CYCLE MEETING MINUTES

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President for Clinical Affairs
5 Paramus Court
North Potomac, MD 20898

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) dated April 19, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Impavido (miltefosine) Capsule, 50 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 8, 2013.

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

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Thomas Smith, M.D.
Cross Discipline Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 8, 2013, at 9:00 A.M. to 10:30 A.M.
Meeting Location: White Oak Campus, Building 22, Room 1419
Application Number: NDA 204684
Product Name: Impavido (miltefosine) Capsules
Applicant Name: Paladin Therapeutics, Inc.
Meeting Chair: Thomas Smith, M.D.
Meeting Recorder: Gregory F. DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

Edward Cox, M.D., M.P.H. Director
John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H. Acting Director
Katherine Laessig, M.D. Deputy Director
Thomas Smith, M.D. Clinical Team Leader
Hala H. Shamsuddin, M.D. Medical Officer
Shukal Bala, Ph.D. Clinical Microbiology Reviewer
Wendelyn Schmidt, Ph.D. Pharmacology/Toxicology Team Leader
James S. Wild, Ph.D. Pharmacology/Toxicology Reviewer
Maureen P. Dillon-Parker Chief, Project Management Staff
Susmita Samanta, M.D. Safety Regulatory Project Manager
Gregory F. DiBernardo Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Philip Colangelo, Pharm.D., Ph.D. Clinical Pharmacology Team Leader
Seong H. Jang, Ph.D. Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Karen Higgins, Sc.D. Biostatistics Team Leader
Lan Zeng, M.S. Biostatistics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Rapti Madurawe, Ph.D.	Branch Chief
Dorota M. Matecka, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Lead
Anamitro Banerjee, Ph.D.	CMC Reviewer-Drug Product

Office of Surveillance and Epidemiology (OSE)

Division of Risk Management (DRISK)

Joyce Weaver, Ph.D.	Risk Management Reviewer
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Division of Epidemiology (DEPI II)

Natasha Chin-Ying Chen, Ph.D.	Visiting Scientist
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Division of Pharmacovigilance (DPV)

Mihaela Jason, Ph.D.	Safety Evaluator
Ronald T. Wassell, Ph.D.	Safety Evaluator

Office of Compliance (OC)

Division of Scientific Investigation

Susan Thompson, M.D.	Scientific Investigator
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Division of Marketing Product Quality (DMPQ)

Steven Hertz	Consumer Safety Officer
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Office of Strategic Programs (OSP)

Kimberly Taylor	Operations Research Analyst
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(b) (4)

APPLICANT ATTENDEES

Paladin Therapeutics, Inc.

Robert K. Vinson, Ph.D.	Director, Product Development
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Fast Track Drugs and Biologics, LLC

(b) (4)

Jonathan Berman, M.D., Ph.D.	Vice President Clinical Affairs
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(b) (4)

BACKGROUND

NDA 204684 was submitted on April 19, 2013 for Impavido (miltefosine) Capsules, 50 mg.

Proposed indications: Treatment of visceral, cutaneous, and mucosal leishmaniasis

PDUFA goal date: December 19, 2013 [See Post-Meeting note.]

FDA issued a background package to Paladin in preparation for the late cycle meeting on October 1, 2013. The FDA Advisors and Consultants Staff provided Paladin with the October 18, 2013, FDA Briefing Package for the scheduled Advisory Committee meeting in advance of the late cycle meeting.

FDA also notes that on September 25, 2013, a teleconference between FDA and Paladin occurred. The purpose of this teleconference was to inquire about the timing of Paladin's response to the outstanding request for information from the June 20, 2013, Chemistry, Manufacturing, and Controls (CMC), Information Request, specifically questions #7a, #7b, #7c, and #8. Paladin informed FDA that they were working on providing FDA responses to all of these requests by mid-October, 2013. Paladin inquired if it would be acceptable to submit their responses via email as the information became available. FDA agreed that Paladin could provide the information in this manner, but emphasized that FDA would need all of it submitted officially to the NDA before FDA could determine if Paladin's responses were acceptable. FDA also emphasized that the impact of such a submission could trigger a major amendment to the NDA. FDA explained to Paladin that if the official submission completely addressed the outstanding requests for information then FDA would review this material, but it would not occur under the current PDUFA goal date of December 19, 2013. If this new information was complete and the CMC reviewers determined that the response was adequate, a three-month extension of the PDUFA goal date would then occur. Paladin stated they understood these statements. FDA also emphasized that this information would be identified in the late cycle meeting. (Note: A major amendment was submitted to the NDA on October 15, 2013. FDA made the determination that this submission would allow for a PDUFA goal clock extension of 3 months. The new PDUFA Goal date is March 19, 2014. Paladin was issued a Review Extension-Major Amendment letter on November 8, 2013, detailing this information.)

1.0 DISCUSSION

1. Introductory Comments – 5 minutes (Thomas Smith, M.D.)

Welcome, introductions, ground rules, objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Chemistry, Manufacturing, and Controls (CMC) Quality:

1. HPTLC Method Deficiencies:

- a) With regard to the HPTLC method for (b) (4) impurities in the drug substance:

- i. As (b) (4) are potential degradants, validate the analytical method for quantitative testing rather than limit testing.
 - ii. Provide data from spiking studies to show that the HPTLC method can reliably detect OOS data for the impurities (b) (4)
 - b) With regard to the drug product analytical procedures in Section 3.2.P.5.2 of the NDA submission, we note the system suitability tests for all HPTLC methods use only a single system suitability test (i.e., RSD for repeatability). Both resolution and reproducibility should be evaluated as part of the system suitability test. Therefore:
 - i. Revise the acceptance criteria for repeatability tests (i.e., RSD) so that they are comparable to those required by USP <621>
 - ii. Include at least one additional parameter to verify the system's resolution capability.
 - c) As per ICH Q3, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products using samples subjected to relevant stress conditions (i.e., light, heat, humidity, acid/base hydrolysis, and oxidation), as appropriate. We note that you only performed a limited validation on the HPTLC method for degradant test by using miltefosine as a model due to lack of impurities samples. We also note that no degradant products were observed in your forced degradation study. However, it seems to us that you used relatively mild conditions (b) (4)
(b) (4) In order to confirm that the appropriate analytical procedures are truly stability-indicating:
 - i. Conduct a forced degradation study using more forceful conditions targeting approximately (b) (4) total degradation of the drug substance in order to determine the stability-indicating nature of the HPTLC method. The forced degradation study should be conducted under the following conditions, as appropriate: (b) (4)
(b) (4)
 - ii. Validate the HPTLC methods using appropriately stressed samples as described above.
 - a. Use appropriately stressed drug product samples to demonstrate that the proposed HPTLC methods are able to discriminate between compounds (i.e., impurities/degradants) of closely related structures which are likely to be present.
 - b. Compare the HPTLC test results to those from a second well-characterized procedure, i.e., pharmacopoeial method or other validated analytical procedure (e.g., independent procedure such as LC/MS, GC/MS, etc).
2. Please provide data to show the drug substance (b) (4) state form remains unchanged over the proposed shelf life of the drug product. In Section 3.2.S.3.1 of the NDA submission,

you state that the drug substance is hygroscopic (b) (4)

Please refer to CMC information request dated, June 20, 2013.

Discussion:

Paladin stated that as a follow-up to the September 25, 2013, teleconference, they had provided their responses to questions #7a, #7b, #7c, and #8 from the June 20, 2013, CMC Information Request to FDA via email. Paladin noted that the outstanding items from the June 20, 2013, CMC information request were the same items listed as the substantive review issues outlined in the late cycle meeting agenda. FDA agreed. Paladin understood that FDA will need all this information submitted to the NDA officially via the FDA electronic document room. Paladin stated the official submission was coming.

Pharmacology/Toxicology:

1. In order to verify that levels of (b) (4) in the drug substance remain within the qualification threshold amounts recommended in the ICH Q3A(R2) guidance, the HPTLC method deficiencies must be corrected as specified in the June 20, 2013, CMC information request.

Discussion:

Paladin inquired if a second submission to the NDA would be necessary to address the Pharmacology/Toxicology substantive review issues described. FDA stated that once the official submission is made to address the substantive CMC review issues, the Pharmacology/Toxicology team will review this information. No separate submission is needed. Paladin stated they were clear on this point.

Paladin stated that they expected to make their official submission of all elements to all substantive review issues on October 14, 2013.

FDA stated the impact of Paladin's submission to the NDA is that this new information will be considered a major amendment and will result in a three-month review clock extension if the CMC team determines it is adequate for review.

3. Discussion of Minor Review Issues – 30 minutes

Statistics:

- Blinding: There is a possibility that the pivotal Study 3168 was not completely blinded. The randomization list provided in the study report indicated that treatments were labeled as "A" or "B", which essentially allowed the study investigator to separate two groups of patients.
- Randomization: Although the randomization lists were provided for the studies, there was no randomization date in the submitted datasets. It is questionable if the randomization lists were fully complied with. Study Soto, in particular, appears not to have followed the randomization list to such a degree that we have concluded that we cannot rely on it being a randomized study. In Study 3168 when using the date of first medication

exposure as a surrogate for randomization date, the ID numbers were in order of medication start date for patients at the Guatemala site. At the Colombia site, however, subjects were not given ID numbers according to the order in the randomization list.

- Subgroup analysis: It appears that study Z020 was initially designed as one study with a planned analysis to pool the information from both countries and age groups. As such, analyses of Z020a and Z020b constitute subgroup analyses without planned control of the type I error. Though the results are supportive of the efficacy of miltefosine, we do not believe the type I error is controlled in these two sub-studies and we do not consider the results from Z020b as demonstrating the superiority of miltefosine over meglumine.

Discussion:

Paladin provided a handout showing “screening/enrollment log + patient identification list” and registration form for Study 3168. Paladin stated that pivotal Study 3168 was completely blinded and that the “A” and “B” codes were not used on the CRF or medical kits. The sites never saw a randomization list with labels of “A” or “B”. Paladin stated that the study maintained double blind, and neither subject nor investigator knew what they received. Paladin stated they did not record a randomization date, but they had the registration date (kit number). Paladin stated the registration date was not captured in the data set. FDA stated that they used the treatment start date to make sure randomization was followed correctly, and based on how this information was provided; it looked like the randomization was out of order. FDA asked Paladin to explain how the “A” and “B” designation worked. Paladin stated that patients were numbered sequentially, and as they were eligible they were entered. Paladin stated there were no envelopes. If a kit had a number on it, then the kit was assigned to the patient. The investigator took the kit off the shelf and gave it to the patient. Paladin said there was no mention of an “A” or “B”.

FDA stated that in the Soto study there were concerning issues regarding the randomization order. Paladin stated that they received a letter from Soto, and, based on that, they believe it is randomized. FDA asked Paladin if they assessed the order of treatment in subjects in Study Soto and Paladin stated they had not. FDA recommended that Paladin look at the data to make a determination themselves. FDA indicated that some numbers on the master randomization list were not used as planned. FDA also pointed out that 3 subjects previously treated with SSG were “randomized” to miltefosine and that 3 subjects previously treated with miltefosine were “randomized” to SSG. Paladin stated the only way to truly assess the situation would be to pull the data out of the trial master file, but since Study Soto was considered only a supportive study, it might not be worthwhile. FDA agreed.

Paladin presented an updated analysis combining adult patients from two sites and stated that the results were significantly in favor of miltefosine. FDA pointed out that this analysis was again a subgroup analysis because pediatric patients were excluded. FDA stated the problem was Study Z020 was planned as one study with two sites and included both adults and children. FDA could not consider the results looking at adults from one site only and consider the results as significant.

FDA stated that Paladin had not discussed a non-inferiority margin but may be able to say how miltefosine did compared to standard-of-care. Paladin stated that they planned to discuss clinical cure rather than statistical significance during their presentation to the

Advisory Committee. Paladin stated they planned to focus on Study Z020 as a whole, since it presented a cleaner way to present their data.

FDA also emphasized that these issues were not substantive review issues but wanted Paladin to be aware of their concerns with these data.

Clinical:

Reproductive toxicity issue: Assessment of effects of miltefosine on spermatogenesis

Discussion:

FDA stated that there was a significant signal from the animal studies regarding the effects of miltefosine on spermatogenesis. FDA stated that DAIP consulted the Division of Bone, Reproductive and Urologic Products (DBRUP) to evaluate whether this safety signal was appropriately evaluated in the clinical trials, which included spermatograms from a subset of patients in Study 3168 and fertility rates in male participants of Study 3154 and VL Phase 2 studies. DAIP informed Paladin that DBRUP's assessment concluded that adverse effects on male reproductive toxicity occurred at doses equivalent or lower than the human dose and that the clinical evaluation was not adequate to determine if the adverse effect was reversible. FDA was interested in hearing what Paladin thought could be done to address this issue as part of a postmarketing plan and if Paladin could propose labeling to address this concern. Paladin asked why FDA thought Paladin's current evaluation was inadequate. FDA stated that from the animal studies it appeared there was no safety margin and that the substantial variability in sperm counts in Study 3168 did not allow meaningful conclusions. Paladin stated that they did not agree with this assessment and they believed the underlying issue was that the FDA was using body surface area to correlate the human therapeutic dose to the dose from the rat and dog studies. Paladin stated that they believe that the human and animal dose should be correlated based on exposure, not body surface area. FDA stated that they would have used exposure as the basis to correlate the human and animal doses but the exposure information in the animal studies was sparse often not including C_{max} and AUC measurements that could be compared to similar measurements from human clinical trials. FDA asked Paladin if they believed an animal signal existed. Paladin stated they did believe there was a strong signal for the rat at 10 mg/kg and at 4.6 mg/kg, but they did not believe a strong signal existed in the dog study.

Paladin stated they believed a slight signal existed for the dog in the prostate gland at the mid dose in the 52 week study, but did not believe this was a clear signal in the dog. Paladin stated that the prospective spermogram data from Study 3168 which involved 11 miltefosine recipients and 4 placebo recipients indicated that there was no significant effect on spermatogenesis in humans. FDA indicated that the significant variability in sperm counts in this small subset of patients precluded meaningful conclusions. FDA also stated that they did consider the dog study findings a signal. Paladin stated it appeared they were trying to prove a negative result. FDA emphasized they were not asking Paladin to prove a negative, but wanted to better categorize what was actually occurring. FDA stated that for male patients they needed to determine if any adverse effects on sperm production or function were temporary or irreversible. FDA indicated that DBRUP thought a postmarketing study to

evaluate sperm counts may be an option, but stated that fertility rates were not a good measure to assess this issue. Paladin stated that they are open to further discussion. Paladin commented that they are collecting periodic safety reports (PSUR) for this AE in Europe and they are not seeing this AE in PSURs. FDA is concerned with underreporting and that the PSURs did report on men who complained of absent ejaculation during therapy. FDA stated the current label does not adequately address this issue.

Regarding miltefosine use during pregnancy, FDA stated that the risk-benefit analysis for CL versus VL patients may be different and more discussion may be needed. FDA stated that they are not in disagreement with regards to embryo lethality and FDA is considering how to label for this concern. FDA emphasized that in the real world, reproductive contraception is not always adequately followed and this presented a significant concern to ensure labeling is correct.

4. Additional Applicant Data – 10 minutes (Applicant)

Discussion:

Paladin stated that the requested information to address substantive review issues #1 and #2 above will be submitted to FDA by mid-October, 2013.

5. Information Requests – None

6. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

- Mortality at end of therapy as post-hoc primary endpoint for Study Z025: we do not consider this endpoint acceptable as it pertains to the claim that miltefosine is superior to sodium stibogluconate.

Discussion:

Paladin stated they only had access to the records of the patients who died in Study Z025; therefore it was hard not to focus on the significant p-values that indicated that miltefosine was superior to stibogluconate for mortality. Paladin stated that they intend to focus on this information as they prepare for the Advisory Committee meeting. FDA stated that they understood, but they are not convinced of the superiority of miltefosine given the lack of access to the study data and the lack of a clear biological basis for miltefosine to be better in this study. FDA pointed out that when the higher initial failure rates and higher subsequent relapse rates were considered, they did not support miltefosine superiority. FDA also added that the confounder in Study Z025 was the high prevalence of HIV in the study population and that there were more patients with HIV status unknown in the antimony arm.

Paladin also stated that the Advisory Committee may be concerned with the patient population in Ethiopia, but Paladin will try to focus on how the drug could be used in the U.S.

- Difference in renal safety data: We assessed creatinine elevations in relation to baseline, not in relation to upper level of normal.

Discussion:

Paladin stated that regarding this difference in renal safety data, they did not consider FDA's approach and that is the main difference. FDA stated that they looked at baseline levels and that a change from baseline was significant and therefore considered this a safety signal. However, Paladin and the FDA reached similar conclusions regarding renal safety.

- Provide a rough outline of the Advisory Committee presentations by both Paladin and FDA.

Discussion:

Paladin stated that for their two planned Advisory Committee presentations, they will need a minimum of 1 1/4 hours, but may need 1 1/2 hours. FDA stated this is acceptable. FDA stated that their planned presentation highlights the aspects of the review as provided in this meeting agenda.

7. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical Postmarketing Requirement:

- Complete a dedicated QT study to evaluate the effects of Impavido (miltefosine) on cardiac repolarization.

Discussion:

Paladin stated that conducting a dedicated QT study to evaluate the effects of Impavido (miltefosine) on cardiac repolarization will be a real challenge. Paladin proposed conducting a dog study instead of a standalone 40-patient study in humans. Paladin stated that if the dog study results were clean and they coupled this data with the data from Study 3154, this should be sufficient to address FDA's concerns on the effect of Impavido (miltefosine) on cardiac repolarization. FDA stated that this request will have to be discussed with FDA's internal QT-IRT group to determine if the proposed plan is acceptable. FDA emphasized that one of the limitations of such a plan is that there are no pharmacokinetic (PK) data in Study 3154 and the ECG tracings are of poor quality.

- Possible study to assess spermatogenesis

Discussion:

FDA stated that they had consulted DBRUP due to the animal signal discussed earlier for advice on how to assess this signal. DBRUP recommended that this signal be investigated. FDA requested that Paladin propose a study on how to assess this signal in men. Paladin stated that a study conducted in a healthy male population, like soldiers, may present a number of obstacles. Paladin did not have a proposal at this time and will need to discuss this more internally.

- Global Pregnancy Registry

Discussion:

FDA expressed concern that pregnancy may be underreported. FDA stated that there had been over 90,000 doses of miltefosine dispensed, mainly in India, and only three (3) pregnancies had been reported.

Paladin stated that the idea of a global pregnancy registry is a bit of a challenge and they stated they are not sure how to construct such a registry. Paladin suggested that global periodic safety update reports (PSUR) could address the FDA's concern of underreporting of pregnancy and adverse events. Paladin stated that they do not have a viable approach to collect data on pregnancy in the Indian sub-continent; therefore, the global PSUR may need to be considered. Paladin stated that they had planned on passive data collection in the U.S., and since miltefosine use in the U.S. will be low it is unlikely that this data will provide great numbers related to miltefosine use in pregnancy. Paladin stated that they plan to provide a contact number in the Medication Guide for questions and for reporting of miltefosine use during pregnancy. FDA stated they understand this is a challenge, and they will continue internal discussions on how they (Paladin) might address this issue.

CMC (Quality) Postmarketing Commitment:

- Develop an appropriate method (such as HPLC) for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules. Refer to CMC information request dated June 20, 2013. Please also note that the analytical method used for miltefosine assay in the dissolution test should also be updated with the new (i.e., HPLC) assay method.

Discussion:

Paladin does not have any concerns regarding this postmarketing commitment at this time.

8. Major labeling issues – 5 minutes

- Boxed Warning regarding embryo lethality and teratogenicity in pregnant women, the need for effective and reliable contraception in women of childbearing age during therapy and for 6 months post-therapy.

Discussion:

FDA stated that the September 23, 2013, labeling and PMR/PMC discussion comments letter included only a portion of the planned labeling revisions for the NDA. FDA stated they wanted Paladin to be aware of the proposal for a boxed warning for the Package Insert. FDA stated they plan to have more involved labeling discussions with Paladin over the next few months. Paladin stated they plan to submit their response to the September 23, 2013, letter next week. Paladin will propose revisions to the microbiology section of the labeling and will submit their additional references to support the revisions. FDA will review and provide comments on this information.

9. Review Plans – 1-5 minutes

- Review response to outstanding CMC information requests, once submitted, to determine if all issues have been addressed and the potential impact on review timelines.

Discussion:

FDA will review the submission of the CMC and Pharmacology/Toxicology information and determine if it is adequate and if it qualifies as a major amendment. (Note: Paladin was issued a Review Extension-Major Amendment letter on November 8, 2013). [See post meeting note.]

10. Wrap-up and Action Items – 1-5 minutes

Discussion:

FDA stated that the October 18, 2013, Advisory Committee meeting is still scheduled to occur as planned even under the current government shutdown status.

FDA stated that there are no action items from this meeting, but FDA will determine if the response from Paladin to the Substantive Review Issues identified above will allow for a major amendment to the NDA. Paladin again stated they plan to submit their response to the outstanding requests from the June 20, 2013, CMC Information request by mid-October, 2013.

This application has not yet been fully reviewed by the signatory authority, division director, and cross-discipline team leader; therefore, this meeting did not address the final regulatory decision for the application.

Paladin provided a handout for FDA to review at the late-cycle meeting; this handout is attached.

POST-MEETING NOTE: The review clock has been extended 3-months due to the Major Amendment submitted on October 15, 2013. The PDUFA due date for the NDA has been adjusted to March 19, 2014.

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

/s/

THOMAS D SMITH
12/02/2013



NDA 204684

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Paladin Therapeutics, Inc.
c/o Fast Track Drugs and Biologics, LLC
Attention: Jonathan D. Berman, M.D., Ph.D. (U.S. Agent)
Vice President, Clinical Affairs
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Berman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) Capsule, 50 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 8, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 8, 2013, 9:00 A.M. to 10:30 A.M.

Meeting Location: White Oak Campus, Building 22, Room 1415

Application Number: NDA 204684

Product Name: Impavido (miltefosine)

Indication: Treatment of cutaneous, mucosal and visceral leishmaniasis

Applicant Name: Paladin Therapeutics, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Chemistry, Manufacturing, and Controls (CMC) Quality:

The following deficiencies were communicated in the Agency Information Request letter dated June 20, 2013. These deficiencies remain outstanding.

1. HPTLC Methods:

- a) With regards to the HPTLC method for [REDACTED] (b) (4) impurities in the drug substance,
 - i. As [REDACTED] (b) (4) are potential degradants, validate the analytical method for quantitative testing rather than limit testing.
 - ii. Provide data from spiking studies to show that the HPTLC method can reliably detect OOS data for the impurities [REDACTED] (b) (4)

- b) With regard to the drug product analytical procedures in Section 3.2.P.5.2 of the NDA submission, we note the system suitability tests for all HPTLC methods use only a single system suitability test (i.e. RSD for repeatability). Both resolution and reproducibility should be evaluated as part of the system suitability test. Therefore,
 - i. Revise the acceptance criteria for repeatability tests (i.e., RSD) so that they are comparable to those required by USP <621>
 - ii. Include at least one additional parameter to verify the system's resolution capability.

- c) As per ICH Q3, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products using samples subjected to relevant stress conditions (i.e., light, heat, humidity, acid/base hydrolysis, and oxidation), as appropriate. We note that you only performed a limited validation on the HPTLC method for degradant test by using miltefosine as a model due to lack of impurities samples. We also note that no degradant products were observed in your forced degradation study. However, it seems to us that you used relatively mild conditions [REDACTED] (b) (4)
[REDACTED] In order to confirm that the appropriate analytical procedures are truly stability-indicating,
 - i. Conduct a forced degradation study using more forceful conditions targeting approximately [REDACTED] (b) (4) total degradation of the drug substance in order to determine the stability-indicating nature of the HPTLC method. The forced degradation study should be conducted under the following conditions, as appropriate: [REDACTED] (b) (4)
 - ii. Validate the HPTLC methods using appropriately stressed samples as described above.
 - a. Use appropriately stressed drug product samples to demonstrate that the proposed HPTLC methods are able to discriminate

between compounds (i.e., impurities/degradants) of closely related structures which are likely to be present.

- b. Compare the HPTLC test results to those from a second well-characterized procedure, i.e., pharmacopoeial method or other validated analytical procedure (e.g., independent procedure such as LC/MS, GC/MS, etc).

2. Please provide data to show the drug substance (b) (4) state form remains unchanged over the proposed shelf life of the drug product. In Section 3.2.S.3.1 of the NDA submission, you state that the drug substance is hygroscopic (b) (4)

Pharmacology/Toxicology:

In order to verify that levels of (b) (4) in the drug substance remain within the qualification threshold amounts recommended in the ICH Q3A(R2) guidance, the HPTLC method deficiencies must be corrected as specified in the June 20, 2013, CMC information request.

ADVISORY COMMITTEE MEETING

Date of AC meeting: October 18, 2013

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: September 20, 2013

Potential questions and discussion topics for AC Meeting are as follows:

Has the Applicant demonstrated the safety and effectiveness of miltefosine in the treatment of:

- Visceral leishmaniasis caused by *L. donovani*?
- Cutaneous leishmaniasis caused by members of the subgenus *viannia*?
- Mucosal leishmaniasis?

For each indication, if yes, are there specific issues that should be addressed in labeling? In particular, please discuss the reproductive risks associated with the use of miltefosine and whether the overall risks and benefits are different in the treatment of cutaneous versus visceral disease.

For each indication, if not, what additional data are needed?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted

two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

We do not anticipate requiring a REMS.

LCM AGENDA

1. Introductory Comments – 5 minutes (Thomas Smith, M.D.)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion.

Chemistry, Manufacturing, and Controls (CMC) Quality:

1. HPTLC Method Deficiencies:

- a) With regards to the HPTLC method for (b) (4) impurities in the drug substance,
 - i. As (b) (4) are potential degradants, validate the analytical method for quantitative testing rather than limit testing.
 - ii. Provide data from spiking studies to show that the HPTLC method can reliably detect OOS data for the impurities (b) (4)
- b) With regard to the drug product analytical procedures in Section 3.2.P.5.2 of the NDA submission, we note the system suitability tests for all HPTLC methods use only a single system suitability test (i.e. RSD for repeatability). Both resolution and reproducibility should be evaluated as part of the system suitability test. Therefore,
 - i. Revise the acceptance criteria for repeatability tests (i.e., RSD) so that they are comparable to those required by USP <621>
 - ii. Include at least one additional parameter to verify the system's resolution capability.
- c) As per ICH Q3, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products using samples subjected to relevant stress conditions (i.e., light, heat, humidity, acid/base hydrolysis, and oxidation), as appropriate. We note that you only performed a limited validation on the HPTLC method for degradant test by using miltefosine as a model due to lack of impurities samples. We also note that no degradant products were observed in your forced degradation study. However, it seems to us

that you used relatively mild conditions (b) (4)
(b) (4) In order to confirm that the appropriate analytical procedures are truly stability-indicating,

- i. Conduct a forced degradation study using more forceful conditions targeting approximately (b) (4) total degradation of the drug substance in order to determine the stability-indicating nature of the HPTLC method. The forced degradation study should be conducted under the following conditions, as appropriate (b) (4)
(b) (4)
 - ii. Validate the HPTLC methods using appropriately stressed samples as described above.
 - a. Use appropriately stressed drug product samples to demonstrate that the proposed HPTLC methods are able to discriminate between compounds (i.e., impurities/degradants) of closely related structures which are likely to be present.
 - b. Compare the HPTLC test results to those from a second well-characterized procedure, i.e., pharmacopoeial method or other validated analytical procedure (e.g., independent procedure such as LC/MS, GC/MS, etc).
2. Please provide data to show the drug substance (b) (4) state form remains unchanged over the proposed shelf life of the drug product. In Section 3.2.S.3.1 of the NDA submission, you state that the drug substance is hygroscopic (b) (4)
(b) (4)

Please refer to CMC information request dated, June 20, 2013.

Pharmacology/Toxicology:

In order to verify that levels of (b) (4) in the drug substance remain within the qualification threshold amounts recommended in the ICH Q3A(R2) guidance, the HPTLC method deficiencies must be corrected as specified in the June 20, 2013, CMC information request.

3. Discussion of Minor Review Issues – 30 minutes

Statistics:

- **Blinding:** There is a possibility that the pivotal Study 3168 was not completely blinded. The randomization list provided in the study report indicated that treatments were labeled as “A” or “B”, which essentially allowed the study investigator to separate two groups of patients. **Randomization:** Although the randomization lists were provided for the studies, there was no randomization date in the submitted datasets. It is questionable if the randomization lists were fully complied with. Study Soto, in particular, appears not to

have followed the randomization list to such a degree that we have concluded that we cannot rely on it being a randomized study. In Study 3168 when using the date of first medication exposure as a surrogate for randomization date, the ID numbers were in order of medication start date for patients at the Guatemala site. At the Colombia site, however, subjects were not given ID numbers according to the order in the randomization list. Subgroup analysis: It appears that study Z020 was initially designed as one study with a planned analysis to pool the information from both countries and age groups. As such, analyses of Z020a and Z020b constitute subgroup analyses without planned control of the type I error. Though the results are supportive of the efficacy of miltefosine, we do not believe the type I error is controlled in these two sub-studies and we do not consider the results from Z020b as demonstrating the superiority of miltefosine over meglumine.

Clinical:

Reproductive toxicity issue: Assessment of effects of miltefosine on spermatogenesis

4. Additional Applicant Data – 10 minutes (Applicant)
5. Information Requests – None
6. Discussion of Upcoming Advisory Committee Meeting – 15 minutes
 - Mortality at end of therapy as post-hoc primary endpoint for Study Z025: we do not consider this endpoint acceptable as it pertains to the claim that miltefosine is superior to sodium stibogluconate.
 - Difference in renal safety data: We assessed creatinine elevations in relation to baseline, not in relation to upper level of normal.
 - Provide a rough outline of the Advisory Committee presentations by both Paladin and FDA.
7. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical Postmarketing Requirement:

- Complete a dedicated QT study to evaluate the effects of Impavido (miltefosine) on cardiac repolarization.
- Possible study to assess spermatogenesis
- Global Pregnancy Registry

CMC (Quality) Postmarketing Commitment:

- Develop an appropriate method (such as HPLC) for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules. Refer to CMC information request dated, June 20, 2013. Please also note that the analytical method used for miltefosine assay in the dissolution test should also be updated with the new (i.e., HPLC) assay method.

8. Major labeling issues – 5 minutes

- Boxed Warning regarding embryo lethality and teratogenicity in pregnant women, the need for effective and reliable contraception in women of childbearing age during therapy and for ^(b)₍₄₎ months post-therapy.

9. Review Plans – 1-5 minutes

- Review response to outstanding CMC information requests, once submitted, to determine if all issues have been addressed and the potential impact on review timelines.

10. Wrap-up and Action Items – 1-5 minutes

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/s/

SUMATHI NAMBIAR
10/01/2013