

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204684Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204684	NDA Supplement #:S- Not Applicable	Efficacy Supplement Type SE- Not Applicable
Proprietary Name: IMPAVIDO Established/Proper Name: miltefosine Dosage Form: Capsule Strengths: 50 mg		
Applicant: Paladin Therapeutics, Inc. Agent for Applicant: Jonathan Berman, M.D., Fast Track Drugs and Biologics, LLC		
Date of Application: April 19, 2013 Date of Receipt: April 19, 2013 Date clock started after UN: Not Applicable		
PDUFA Goal Date: December 19, 2013		Action Goal Date (if different): Same
Filing Date: June 18, 2013		Date of Filing Meeting: May 16, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME (1)		
Proposed indications: Treatment of cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and visceral leishmaniasis (VL)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: Not Applicable	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of BLA: Not Applicable	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input checked="" type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): Not Applicable				
List referenced IND Number: 105430				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		Not Applicable
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="201 1488 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 7 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? (<i>351(a)BLAs only</i>) <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement if exclusivity has not yet been granted. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> eCTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Revised on 2/21/14
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan Designation-Granted 10/10/06.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT-IRT, MHT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date: January 13, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-NDA January 13, 2012 & Type A Meeting: January 8, 2013
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 16, 2013

BLA/NDA/Supp #: Not Applicable

PROPRIETARY NAME: IMPAVIDO

ESTABLISHED/PROPER NAME: miltefosine

DOSAGE FORM/STRENGTH: Capsule 50 mg

APPLICANT: Paladin Therapeutics, Inc.

PROPOSED INDICATIONS: Treatment of cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), and visceral leishmaniasis (VL)

BACKGROUND:

NDA 204684 was submitted by Paladin Therapeutics, Inc. (foreign applicant) and has selected Fast Track Drugs and Biologics, LLC as their U.S. Agent. The Applicant is requesting a 6 month Priority Review for NDA 204684. NDA 204684 for IMPAVIDO (miltefosine) corresponds to the information submitted to FDA under **IND 105430**. IND 105430 was granted Orphan Product Designation on 10/10/06, Fast Track Designation on 5/21/10, and a Proprietary Name Request was determined to be Conditionally Acceptable as stated in a 2/8/11 FDA communication. NDA 204684 would be considered a new molecular entity (NME) and an Advisory Committee is planned for this review cycle. NDA 20684 was submitted on 9/26/12, however after a filing review the Review Team determined the NDA was not acceptable for filing. On 11/26/12, FDA issued a Refuse-to-File (RTF) letter to the Applicant. On 12/3/12, the Applicant submitted a type-A meeting request to discuss the RTF issues with FDA and on 1/8/13, FDA and the Applicant met to discuss the Applicant's concerns. The Applicant then submitted NDA 204684 on 4/19/13, for FDA review. Since IMPAVIDO (miltefosine) is a New Molecular Entity (NME) NDA application that was submitted after 10/1/12, it qualifies to be reviewed under the "Program" as outlined under PDUFA V.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gregory F. DiBernardo	Y
	CPMS:	Maureen P. Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Thomas Smith		Y
Clinical	Reviewer:	Hala Shamsuddin	Y

	TL:	Thomas Smith	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Shukal Bala	Y
	ATL:	Kerry Snow	Y
Clinical Pharmacology	Reviewer:	Seong Jang	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Lan Zeng	Y
	TL:	Karen Higgins	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	James Wild	Y
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:	Not Applicable	
	TL:		
CMC Biopharmaceutics	Reviewer:	Mark R. Seggell	Y
	TL:	Angelica Dorantes	N
Product Quality (CMC)	Reviewer:	Maotang Zhou Anamitro Banerjee	Y Y
	TL:	Dorota Matecka	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Bryan Riley	N
	TL:	Stephen E. Langille	N
CMC Labeling Review	Reviewer:	Not Applicable	
	TL:		
Facility Review/Inspection	Reviewer:	Pending	
	TL:		

OSE/DMEPA (proprietary name)	Reviewer:	Alexander Winiarski	Y
	TL:	Jamie Wilkins Parker	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	Y
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Not Applicable	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Susan D. Thompson, M.D., Kassa Ayalew, M.D., M.P.H.		
Other attendees	Edward Cox, John Farley, David Roeder, Sumati Nambiar, Katherine Laessig, Frances LeSane, Naysea Minor		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments 	<input type="checkbox"/> Not Applicable

List comments: No Comments	
CLINICAL Comments: No Comments for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA , include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: Fall 2013 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY Comments: No Comments for 74-day letter	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments: No Comments for 74-day letter</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: No Comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: No Comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: No Comments for 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <ul style="list-style-type: none"> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments: There will be foreign site inspections</p>	<input type="checkbox"/> Not Applicable
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments: No Comments</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO • If so, were the late submission components all submitted within 30 days? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>Not Applicable</p>

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office of Antimicrobial Product Sign Off

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 19, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Since NDA will be reviewed under the “Program” as an NME Application, we will have a Mid-Cycle Communication, a Late-Cycle Meeting, and we will take NDA to an Advisory Committee Meeting.

Regulatory Project Manager, labeling format comments will be issued in 74-day letter.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

MAUREEN P DILLON PARKER
03/19/2014

PMR Development Template

NDA # 204684
Product Name: Impavido (miltefosine)

PMR Description: 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.

PMR Schedule Milestones:	Final Protocol Submission:	<u>March 2015</u>
	Study Completion:	<u>March 2025</u>
	Final Report Submission:	<u>March 2026</u>
	Other: 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	<u>March 2024</u>	

During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Miltefosine is teratogenic in animals at exposures lower than expected human exposure. There are no human data regarding pregnancy outcomes in women who become pregnant while exposed to Impavido.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The objective of the study is enhanced pharmacovigilance to collect pregnancy outcome data in women who become pregnant while exposed to miltefosine. Because the half-life of the drug is approximately 30 days, pregnancy outcome data is requested for the duration of therapy and for 5 months (5 half-lives) after end of therapy.

Impavido is for the treatment of leishmaniasis, a disease that is very rare in the United States and that disproportionately affects poor disadvantaged people mainly in South East Asia and South America. The anticipated use in the US is for military personnel or returning travelers. Impavido use in the US is anticipated to be less than 50 individuals per year and mostly men.

If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study will be enhanced pharmacovigilance to collect pregnancy outcome data in women who become pregnant while exposed to Impavido

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR Development Template

NDA # 204684

Product Name: Impavido (miltefosine)

PMR Description: 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.

PMR Schedule Milestones: Final Protocol Submission: March 2015

Study Completion: March 2018

Final Report Submission: March 2019

During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Miltefosine impaired spermatogenesis and fertility in male animals at exposures similar to human exposures. The clinical studies submitted in support of the NDA included evaluation of spermatogenesis in a small subset of patients and a retrospective survey of male fertility in patients receiving Impavido for the treatment of visceral leishmaniasis. These evaluations were deemed inadequate to assess the effects of the drug in human males. Because Impavido is an oral treatment for a life-threatening disease (visceral leishmaniasis) and fills an unmet medical need for the treatment of cutaneous and mucosal leishmaniasis, a study to evaluate the effects of the drug on male reproductive health was required post-approval rather than pre-approval.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study objective is to evaluate the effects of Impavido on male reproductive health: semen volume, sperm count, concentration and motility and levels of total testosterone and FSH.

Miltefosine caused impaired spermatogenesis and impaired fertility in male animals at exposures similar to human exposures. A study to evaluate these effects in healthy subjects is not feasible: the drug requires approximately 4 weeks to achieve steady state, has a long half-life, and is associated with renal impairment and frequent nausea and vomiting. This PMR study will be conducted in patients with leishmaniasis, using historical WHO reference values for comparison.

If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be conducted in male patients with leishmaniasis treated with Impavido. Evaluations will include semen volume, sperm count, sperm concentration and motility, and total testosterone and FSH.

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR Development Template

NDA # 204684

Product Name: Impavido (miltefosine)

PMR Description: 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.

PMR Schedule Milestones: Final Protocol Submission: March 2015

Study Completion: March 2018

Final Report Submission: March 2019

During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The effects of Impavido on QT interval were not thoroughly investigated pre-approval (also see response to the second question). Because no ECG findings and no cardiovascular deaths were noted during clinical trials that were already conducted prior to NDA submission, and because Impavido was a new oral drug to treat a life-threatening infection (visceral leishmaniasis) and fills an unmet medical need for visceral, mucosal and cutaneous leishmaniasis, the Division of Special Pathogens and Transplant Products (currently Division of Anti-Infective Products) agreed to a post-approval dedicated QT study.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The objective of this PMR is to provide information regarding potential effects of Impavido on QT interval.

The effects of Impavido on QT interval were not thoroughly evaluated prior to approval. Impavido requires approximately 4 weeks to achieve steady state, has a long half-life, and a narrow therapeutic window: it is teratogenic and associated with adverse reproductive effects in animal studies at doses similar to human therapeutic dose, it may cause renal impairment, and the incidence of nausea and vomiting increases as the dose increases. For these reasons, a thorough QT study was deemed unfeasible due to concerns regarding administration of the drug to healthy subjects. The ECGs conducted during the conduct of the clinical trials did not link ECG findings with PK data.

This PMR is for a dedicated QT study to be conducted in leishmaniasis patients treated with Impavido. The required study is to be large enough to exclude > 20 msec QTc interval prolongation.

If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study will be conducted in patients with leishmaniasis receiving Impavido for treatment. ECGs and PK samples will be obtained to identify potential effects of Impavido on QT interval or other ECG parameters.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial (Please note that the study is a dedicated QT study for the reasons outlined earlier in this document).
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-

Other

Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMC Development Template

NDA # 204684

Product Name: Impavido (miltefosine)

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

PMC Schedule Milestones: Final Protocol Submission: March 2015

Study Completion: March 2020

Final Report Submission: March 2021

Other: Interim Report Submission March 2016

Interim Report Submission March 2017

Interim Report Submission March 2018

Interim Report Submission March 2019

During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Impavido is indicated for the treatment of visceral, mucosal and cutaneous leishmaniasis (VL, ML and CL respectively). Impavido is approved at 100 mg daily for patients weighing less than 45 kg, and 150 mg daily for patients weighing more than 45 kg. For each of these indications, a dose lower than 2.5 mg/kg was associated with lower efficacy in clinical trials. The mean weight of adult VL patients enrolled in clinical trials that supported drug approval was 40 kg and no patient exceeded 70 kg. No adult ML or CL patient exceeded 82 kg. Because US patients receiving the drug are likely to have higher body weight (and thus lower mg/kg dose) compared to the clinical trial population, long-term effectiveness data in patients with higher body weight is needed.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This will be an observational descriptive study to collect effectiveness outcomes and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

This will be an observational descriptive study to collect effectiveness outcomes and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

This will be an observational descriptive study to collect effectiveness outcomes and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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
03/07/2014

HALA H SHAMSUDDIN
03/07/2014

JOSEPH G TOERNER
03/07/2014

**Division of Bone, Reproductive and Urologic Products (DBRUP) Consult:
Comments on Sponsor's Proposal for Postmarketing Requirement (PMR)**

To: Hala Shamsuddin, M.D., Medical Officer, DAIP
Thomas Smith, M.D., Clinical Team Leader, DAIP
Through Gregory DiBernardo, Regulatory Project Manager, DAIP

From: Guodong Fang, M.D., Medical Officer, DBRUP
Mark S. Hirsch, M.D., Medical Team Leader, DBRUP
Audrey Gassman, M.D., Deputy Director, DBRUP

Date: February 6, 2014

1. Background

On September 6, 2013 and January 15, 2014, DBRUP provided Urology consultant's reviews to the Division of Anti-Infective Products (DAIP) for NDA 204,684 Impavido (miltefosine).

DAIP again requests input from DBRUP in regard to a postmarketing sperm study.

On January 24, 2014, DAIP conveyed a Postmarketing Requirements Information Request to Sponsor. DAIP requested two postmarketing clinical trials: a sperm study and an assessment of the QT interval.

On January 29, 2014, the Sponsor informed DAIP that they were working on milestone dates for the postmarketing requirements. Sponsor stated that a sample size determination for the sperm study was key to their milestone date for study completion.

On January 31, 2014, the Sponsor submitted a protocol synopsis for a single clinical trial that would address both the QT and sperm issues. (b) (4)

DAIP now seeks input from DBRUP on the sample size for the sperm study and thus, the milestone date for completion of the in-life part of the study. (b) (4)

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

/s/

GUODONG FANG
02/06/2014

MARK S HIRSCH
02/06/2014
I concur.

AUDREY L GASSMAN
02/06/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	IMPAVIDO (miltefosine) capsules, for oral use
Applicant	Paladin Therapeutics Inc.
Application/Supplement Number	NDA 204684
Type of Application	Original
Indication(s)	Indicated in adults and adolescents ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for treatment of: <ul style="list-style-type: none"> • Visceral leishmaniasis due to <i>Leishmania donovani</i> • Cutaneous leishmaniasis due to <i>Leishmania braziliensis</i>, <i>Leishmania guyanensis</i>, and <i>Leishmania panamensis</i> • Mucosal leishmaniasis due to <i>Leishmania braziliensis</i>
Office/Division	OAP/DAIP
Division Project Manager	Gregory DiBernado
Date FDA Received Application	April 19, 2013
Goal Date	March 9, 2014
Date PI Received by SEALD	February 3, 2014
SEALD Review Date	February 4, 2014
SEALD Labeling Reviewer	Abimbola Adebowale
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *The horizontal line separating the TOC from the FPI is missing. Insert.*

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *All the headings from Indications and Usage through Use in Specific Populations in HL are not presented in the center of the horizontal line. Center them.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is extra white space before the Indications and Usage heading in HL. Recommend decreasing so that it is consistent with the white space before the other major headings in HL.*

Selected Requirements of Prescribing Information

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: The numerical identifier in parentheses (13.1) is in the middle of the summarized statement for the second bullet under the Warnings and Precautions section in HL. The preferred format is for the numerical identifier in parentheses to be at the end of the summarized statement or topic and not in the middle.

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The verbatim statement in the Highlights Limitation Statement includes the name of the drug product and the dosage form (i.e. IMPAVIDO capsules) instead of the name of the drug product alone. Delete the dosage form (i.e. capsules).

Selected Requirements of Prescribing Information

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The 4-digit year in the verbatim statement included in the Initial U.S. Approval in HL is currently written as “XXXX.” Change to 4-digit year (i.e. year in which the FDA will approve the new molecular entity) prior to approval action.*

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- NO** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment: *The words in the heading of the Boxed Warning in HL are not all in upper case letters. Change all the words to uppercase letters i.e. “WARNING: EMBRYO-FETAL TOXICITY” instead of “WARNING: Embryo-Fetal Toxicity.”*

- YES** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *The required statement under the Indications and Usage heading in HL should read as “IMPAVIDO is an antileishmanial drug indicated...” instead of [REDACTED] (b) (4) [REDACTED] (Only the proprietary name should be included in the statement as shown in Appendix A).*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Selected Requirements of Prescribing Information

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.

Comment:

- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

- NO** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *The bolded heading for the BW (i.e. WARNING: Embryo-Fetal Toxicity) INDICATIONS AND USAGE) that appears at the beginning of the TOC is not in upper case letters and it has the Indications and Usage section heading attached to it. Change the heading for the BW to uppercase letters and move the Indications and Usage section heading to its proper location in the TOC.*

- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *The subsection heading “5.1 Embryo-fetal toxicity” in the TOC is not in title case. Change to title case (i.e. Embryo-Fetal Toxicity).*

- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Match the following subsection headings in the TOC with those in the FPI:

Comment: *The TOC subsection heading “5.1 Embryo-fetal toxicity” does not match the FPI subsection heading “5.1 Embryo-Fetal Toxicity.”*

The TOC subsection heading “14 CLINICAL STUDIES” does not match the FPI subsection heading “14 CLINICAL TRIALS.”

- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the

Selected Requirements of Prescribing Information

following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: The bolded subsection heading “14 CLINICAL TRIALS” in the FPI should read as “14 CLINICAL STUDIES” instead as noted above.

Selected Requirements of Prescribing Information

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Comment: *Under subsection 5.2 Reproductive Effects in the FPI, the cross-reference should read as “[see Adverse Reactions (6.3)]” instead of (b) (4) i.e. section heading not subsection heading.*

*Throughout the FPI the entire cross-references enclosed within the brackets are not in italics (specifically, the word “see”). Italicize the entire cross-reference. For example, the cross-references in the Boxed Warning in the FPI should read as “[see *Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.8) and Nonclinical Toxicology (13.1)*]” instead of “[see *Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.8) and Nonclinical Toxicology (13.1)*]”.*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- NO** 36. In the BW, all text should be **bolded**.

Comment: *The summary text in the Boxed Warning in the FPI is not bolded. Bold.*

- NO** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment: *The words in the heading of the Boxed Warning in the FPI are not all in upper case letters. Change all words to uppercase letters i.e. “WARNING: EMBRYO-FETAL TOXICITY” instead of “WARNING: Embryo-Fetal Toxicity.”*

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *There is no reference to FDA-approved patient labeling (i.e. Medication Guide) at the beginning of Section 17 (Patient Counseling Information section). Include a reference at the beginning of Section 17 with the type of FDA-approved patient labeling. For example, “Advise the patient to read the FDA-approved patient labeling (Medication Guide).”*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ABIMBOLA O ADEBOWALE
02/04/2014

ERIC R BRODSKY
02/04/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**Division of Bone, Reproductive and Urologic Products (DBRUP) Consult:
Recommendations for a Postmarketing Requirement (PMR)**

To: Hala Shamsuddin, M.D., Medical Officer, DAIP
Thomas Smith, M.D., Clinical Team Leader, DAIP
Through Gregory DiBernardo, Regulatory Project Manager, DAIP

From: Guodong Fang, M.D., Medical Officer, DBRUP
Mark S. Hirsch, M.D., Medical Team Leader, DBRUP
Audrey Gassman, M.D., Deputy Director, DBRUP

1. Background

On September 6, 2013, DBRUP provided a Urology consultant's review to the Division of Anti-Infective Products (DAIP) for NDA 204,684 Impavido (miltefosine). The consult had the following conclusion:

- 1) The consultants found that the signal of male reproductive toxicity in animals is potentially clinically relevant, especially when considering that the nonclinical toxicity was observed in two species and at systemic miltefosine exposures similar to clinical therapeutic exposures. It is particularly notable that severe testicular toxicity in rats did not fully reverse at miltefosine exposures similar to mean maximum clinical therapeutic miltefosine concentrations. Further, the nonclinical data suggest an unevaluated possible anti-androgen effect of miltefosine.
- 2) The consultants also found that the available human data, including a small number of subjects who provided semen for analyses and one retrospective survey of "reproductive potential", are not sufficient to relieve the concern of potential clinical relevance. The consultants note that there has not been an adequate assessment of miltefosine on human spermatogenesis and there has been no assessment of potential effects on sex hormones in adult males.

Regarding potential human studies male reproductive toxicity of miltefosine, DBRUP had the following comment:

For drugs with a nonclinical testicular toxicity signal, we currently recommend a randomized, double-blind, placebo-controlled, non-inferiority study design. For chronically administered drugs, we advocate at least 12 weeks treatment, with semen analyses and male sex hormones measured at baseline, at the end of treatment, and after a 13-week off-treatment period. Because the human spermatogenic cycle is approximately 74 days, any potential adverse effects on sperm may not be observed immediately following treatment, but rather after 12-weeks off-treatment. Therefore, the primary endpoint is assessed at Week 26 of the study. As primary endpoint, we have advocated the percentage of subjects in each group with at least 50% reduction in sperm

concentration. Using a non-inferiority margin of 20%, such a study usually requires 100 subjects per arm.

DAIP intends to approve miltefosine in the treatment of visceral, mucosal and cutaneous leishmaniasis. Labeling will describe the reproductive toxicity observed in nonclinical studies. A postmarketing study to evaluate the effects of miltefosine on human spermatogenesis is being considered. DAIP requests the advice of DBRUP in the basic design for such a study.

DBRUP and DAIP have previously discussed the potential for a PMR study for miltefosine. DAIP noted that studies in normal volunteers would not be feasible because miltefosine has a risk of renal injury. Further, a concurrent active control would be difficult, if not impossible, because the currently available product for these conditions associated with leishmaniasis (amphotericin B) is also highly toxic. Thus, DAIP observed that the current standard “sperm study” would not be feasible in this circumstance. DBRUP agreed with DAIP that a “standard sperm study” for mitefosine is not feasible because:

- a) Miltefosine causes severe renal insufficiency in healthy volunteers;
- b) Miltefosine is not for chronic use, the total treatment period is around 4 weeks (28 days);
- c) It is not appropriate to use other approved anti-leishmaniasis drugs, such as amphotericin B, as an active control, due to their own various toxicities.

DAIP is again requesting a DBRUP consult to provide a brief proposal for a PMR for a male reproductive toxicity study.

2. Urology Consultant’s Recommendation for a PMR

2.1 Study design for this PMR:

Due to the study design constraints described in Section 1 of this memo, we currently advise a single arm, open-label, observational study in patients who require therapy with miltefosine for treatment of leishmaniasis. The course of treatment will be 4-weeks. Changes-from-baseline analyses will be performed for semen volume, sperm count, sperm concentration, normal morphology, and forward progression. Semen samples will be obtained from each patient at baseline, at the end of treatment and at 12-weeks following the end of treatment. In subjects with $\geq 50\%$ reduction from baseline in sperm concentration after 12 weeks, additional semen samples will be obtained at 26-weeks following the end of treatment. Serum concentrations of total testosterone and FSH will also be measured at baseline, at the end of treatment, and 12-weeks following the end of treatment.

2.2 Preferred method for evaluating semen parameters

Changes-from-baseline in semen and hormonal parameters will be analyzed using descriptive statistics (e.g., mean, standard deviation, etc). In addition, “responder analyses” for semen parameters will be conducted using various cut-points, including:

- The percentage of patients with $\geq 50\%$ reduction from baseline in sperm concentration from the baseline;

- The percentage of patients with <20 million sperm/mL at end of treatment, at Week 12 or at Week 26.
- The percentage of patients with significant changes from baseline in motility and normal morphology in sperm from the baseline (to be determined).
- The percentage of patients with motility and morphology below the lower limit of normal at end of treatment, at Week 12 or at Week 26.

2.3 Potential control groups

Although this study will be designed and analyzed primarily as a single arm, open-label, observational study, it is preferred to construct a control group for exploratory comparisons to the treated group. For example, possible control groups could include:

- Historical controls from recent published literature that use the most recent World Health Organization reference values for human semen characteristics
- Semen analysis in a group of untreated, age-matched, normal volunteers, using the same semen collection methods and schedule as for patients.

2.4 Other internal comments for DAIP's consideration

- It is difficult to provide a recommendation for study sample size. Sponsor should propose a sample size based on the expected change-from-baseline in sperm concentration from their safety database.
- DBRUP would be pleased to review the draft postmarketing study protocol and provide comments on the proposed sample size determination, design and statistical analysis plan.
- Other appropriate safety monitoring, including renal function tests, should be included in the proposed draft protocol and submitted for review.

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/s/

GUODONG FANG
01/15/2014

MARK S HIRSCH
01/15/2014
I concur.

AUDREY L GASSMAN
01/16/2014



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 24, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Gregory DiBernardo, RPM
DAIP

Subject: QT-IRT Consult to NDA 204684

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated December 6, 2013 regarding sponsor's re-submission and Post-marketing requirement. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT consult review for IND 105,430 (TQT waiver request, January 29, 2010)
- QT-IRT consult review for IND 105430 (November 4, 2010, addendum)
- QT-IRT consult review (February 24, 2011)
- QT-IRT consult review (August 12, 2013)

QT-IRT Comments for DAIP

The main features of a dedicated QT assessment are the following:

- Adequate sample size to exclude large effects on the QT interval (>20 ms)
- ECGs should be collected in replicated and be read centrally
- Time matched ECGs and PK samples should be collected at adequate number of time points in the dosing interval to detect immediate and delayed effects on the QT interval

- For more information refer to the article published in Am Heart J 2009; 157:827-836. Ask the sponsor to submit a QT assessment protocol to the Agency for review by QT-IRT.

BACKGROUND

The Division of Anti-Infective Products intends to approve miltefosine in the treatment of visceral, mucosal and cutaneous leishmaniasis. A TQT waiver was granted for miltefosine and QT-IRT recommended that the sponsor perform a dedicated QT study to be conducted in the target population to characterize the effects of miltefosine on QT effect, but deferred the timing of such a study to the review division. The dedicated QT study will be a postmarketing requirement.

The review division is requesting the specifics of the dedicated QT study to draft the PMR.

Thank you for requesting our input into the development of this product under NDA 204684. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

MONICA L FISZMAN
12/24/2013

NORMAN L STOCKBRIDGE
12/24/2013



Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Memorandum

Date: November 21, 2013

From: Miriam Dinatale, D.O., Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Lead – Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Anti-Infective Products (DAIP)

Drug: Impavido (Miltefosine) Tablets for oral use

NDA: 204684

Applicant: Paladin Therapeutics, Inc.

Subject: Pregnancy Labeling

Materials Reviewed:

- Applicant NDA submission, April 19, 2013
- Proposed labeling with DAIP revisions
- Nonclinical Review, October 4, 2013

Consult Question:

“DAIP requests consultation regarding labeling and pregnancy category, specifically as it relates to use in pregnancy and in women of childbearing age. Because of the different risk/benefit for the treatment of the various leishmania syndrome described earlier in the consult, we would also greatly appreciate your insight in input regarding the possibility of assigning a different pregnancy category for each indication.”

INTRODUCTION

On April 19, 2013, Paladin Therapeutics, Inc. re-submitted New Drug Application (NDA 204684) for Impavido (Miltefosine) Tablets for oral use for the treatment of visceral, mucosal, and cutaneous leishmaniasis. The NDA was originally submitted on September 27, 2012; however, a Refuse-To-File Letter was issued on November 26, 2012, because the application was not sufficiently complete to permit a substantive review. Miltefosine was granted orphan designation on October 10, 2006, for the treatment of leishmaniasis. The Agency granted a Priority Review for the application; however, the applicant submitted a major CMC Amendment on October 15, 2013, and the review clock was extended until March 19, 2014.

The Division of Anti-Infective Products (DAIP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS - MHT) on October 4, 2013, to provide input on Impavido pregnancy labeling and the appropriate pregnancy category classification for each indication, as well as provide recommendations for females of reproductive potential. Furthermore, DAIP requested recommendations for the collection of postmarketing pregnancy data.

This review contains PMHS-MHT’s recommended Impavido pregnancy and nursing mothers labeling revisions, as well as the recommendations for the new subsection, “Females and Males of Reproductive Potential,” to include information on contraception and infertility.

BACKGROUND

Miltefosine is an alkylphospholipid analogue that has cytostatic and immunomodulatory effects and was originally developed as an anti-neoplastic drug. Miltefosine is currently approved in other countries for the treatment of cutaneous, mucosal and visceral leishmaniasis. Leishmaniasis is not endemic to the United States; therefore, Impavido will not likely be used extensively in this country. However, deployed military members and travelers to or from endemic areas (e.g., Afghanistan, India) who have contracted leishmaniasis may be prescribed this product

Leishmaniasis is caused by a protozoan parasite of the genus *Leishmania* and is transmitted through the bite of an infected female sand fly.¹ Impavido is proposed for the treatment of visceral leishmaniasis (VL), mucosal leishmaniasis (ML) and cutaneous leishmaniasis (CL). The major clinical symptoms for VL are characterized by prolonged and irregular fever, weight loss, splenomegaly, and hepatomegaly. If untreated, VL can be fatal. CL causes skin ulcers that are self-healing and typically resolve in several months. ML is potentially life threatening and is a complication of CL. ML affects the mucosal region of infected individuals causing progressive destruction of nasopharyngeal structures with resultant disfigurement.

During pregnancy, VL is life-threatening for the mother and may lead to adverse outcomes for the fetus. If VL is untreated in the mother, this may result in severe anemia, spontaneous

¹ Selvapandiyan, Angamuthu, et al. Immunity to Visceral Leishmaniasis Using Genetically Defined Live-Attenuated Parasites. *Journal of Tropical Medicine*, 2007

abortion, congenital VL due to vertical transmission, and a small for date newborn.² CL during pregnancy is characterized by larger lesions with a highly atypical, exophytic appearance. There is concern that CL may cause a higher rate of preterm births and stillbirths.³

Since the 1940s, the pentavalent antimony compounds, sodium antimony gluconate and meglumine antimoniate, have been the mainstays of antileishmanial therapy. The standard regimen duration for pentavalent antimonials is 20-30 days. Treatment results in an overall cure rate of 95% worldwide. However, sodium antimony gluconate is only 60% efficacious in the Indian subcontinent due to acquired drug resistance. The adverse effects following antimonial therapy include cardiotoxicity, pancreatitis, hepatic and renal toxicity and arthralgia. Other therapies for leishmaniasis include parenteral and intramuscular formulations such as Amphotericin B deoxycholate or liposomal amphotericin B and paromomycin, respectively. Although liposomal amphotericin B is more than 95% effective and generally well tolerated, it is a parenteral agent with a long duration of therapy (38 days).^{4,5,6} Miltefosine is the only oral treatment available for leishmaniasis.

Miltefosine caused embryo-fetal toxicity, including death and teratogenicity in animal reproduction studies with rats and rabbits at doses lower than the maximum recommended human dose (MRHD), based on body surface area. The applicant submitted information on three cases of miltefosine-exposed pregnancies reported in Phase 4 clinical trials in India. One woman was exposed in her second week of treatment with miltefosine, one woman was exposed two weeks post-therapy and one woman was exposed two months post-therapy. All three infants were born without congenital defects, or other observable adverse effects.

In addition to embryo-fetal toxicity, fertility effects were observed in animal studies in both females and males with administration of miltefosine at doses less than and equal to the MRHD. In female rats and dogs, estrus cycle arrest and follicular atresia were observed and effects were fully reversible in dogs 6 weeks after drug dosing. In male rats the primary target of miltefosine appears to be the seminiferous epithelium causing atrophic changes resulting in tubular atrophy and germ cell loss. At the highest dose level, only partial reversibility of effects was observed in rats after dosing ended. However, animal studies are not always predictive of human response. There have been postmarketing reports of males successfully fathering children after miltefosine therapy. In addition, there have been postmarketing reports of scrotal pain and decreased or absent ejaculation during miltefosine therapy.

² Pagliano, Pasquale, et al. Visceral leishmaniasis in pregnancy: a case series and systemic review of the literature. *Journal of Antimicrobial Chemotherapy*, 2005; 55, 229-233.

³ Morgan, Daniel, et al. Cutaneous Leishmaniasis during Pregnancy: Exuberant Lesions and Potential Fetal Complications. *CID*, 2007; 45, 478-482.

⁴ Jha, T.K. et al. Miltefosine, an Oral Agent, for the Treatment of Indian Visceral Leishmaniasis. *The New England Journal of Medicine*. 1999; 341: 1795-1800

⁵ <http://www.niaid.nih.gov/topics/leishmaniasis/Pages/preventionTreatment.aspx>

⁶ Sarfaraz Ahmad Ejazi et al. Developments in diagnosis and treatment of visceral leishmaniasis during the last decade and future prospects. *Expert Reviews Anti Infectious Therapy*. 2013; 11 (1), 79-98.

DISCUSSION

Pregnancy Category

Choice of a pregnancy category and inclusion of required risk statements are defined by the current labeling regulations described in 21 CFR 201.57. Each category is defined by the findings from all available reproductive and developmental toxicity studies in animals and studies of drug use during human pregnancy. The pregnancy category definitions for pregnancy categories C, D, and X include a required consideration of both the potential risks and benefits of maternal drug use during pregnancy (see Appendix A for pregnancy category definitions).

The risk of using a drug must always be weighed against its potential benefit and for a pregnant woman, the potential benefit/risk must also include evaluation of potential risk to the fetus. Therefore, drug pregnancy category classification must be evaluated in the context of a specific indication. PMHS-MHT recommends a pregnancy category C, based on data from animal studies and a potential benefit to a pregnant woman, for VL and ML because these conditions can be life-threatening to the mother. A pregnancy category C or X can be considered for CL. CL is not life-threatening to a pregnant woman; however, because of the concern for an increased risk in preterm births and stillbirths in a pregnant woman with untreated CL, one cannot conclude that the potential benefit to the mother would never outweigh the potential fetal risks. Therefore, PMHS-MHT also recommends a pregnancy category C classification for the CL indication.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the Pregnancy and Lactation Labeling Rule (PLLR) and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

Pregnancy Exposure Data

New drugs generally have little or no human pregnancy experience prior to approval, unless the drug is specifically indicated for a pregnancy-related condition or problem. Thus, collection of safety data on use during human pregnancy is often performed post-approval.

In 2002, FDA published, “Guidance for Industry on Establishing Pregnancy Exposure Registries.” In this guidance, a pregnancy exposure registry is defined as a prospective observational study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes and is one method of collecting data on drug exposure during pregnancy before pregnancy outcomes are well established. Pregnancy exposure registries proceed from the point of drug exposure and pregnant women are enrolled before the outcome of pregnancy is known. Medical products that are considered good candidates for pregnancy exposure registries include those that have a high likelihood of use by women of childbearing potential. Pregnancy exposure registries are unlikely to be warranted when the product is not used or rarely used by women of childbearing potential. The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the sample size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups.⁷ An internal and/or external (in certain situations) control group is required for pregnancy exposure registries.

Alternative options for collecting meaningful postmarketing pregnancy exposure data include the use of a pregnancy surveillance program or enhanced pharmacovigilance. A pregnancy surveillance program is set up much like a pregnancy exposure registry; however, there are no control groups and data is collected both prospectively and retrospectively. Healthcare providers or patients must enroll in a pregnancy exposure registry or pregnancy surveillance program. With enhanced pharmacovigilance, applicants encourage the reporting of pregnancies, follow-up on all reports, and submit reports to FDA on a pre-established timeline.

A pregnancy exposure registry or a pregnancy surveillance program is not likely feasible for Impavido. Impavido will rarely be used in females of reproductive potential in the U.S. and most use occurs in third world counties in which program enrollment and data collection can be challenging. An enhanced pharmacovigilance program is likely the best method for collecting meaningful pregnancy exposure data with Impavido exposure.

CONCLUSIONS

PMHS-MHT recommends pregnancy category ^(b)₍₄₎ as the appropriate classification for visceral, mucosal and cutaneous leishmaniasis because there is potential benefit for the mother for these conditions despite the potential fetal risks identified in animal studies. The pregnancy subsection should be structured in the proposed PLLR format in order to assist prescribers with benefit/risk decision making, as well as still complying with the current pregnancy labeling regulations. Female contraception information and information on potential infertility for females and males should be placed in the females and males of

⁷ See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002

reproductive potential subsection. Impavido labeling should include a Boxed Warning for embryo-fetal toxicity to highlight and emphasize the concern for use in pregnant women and in females of childbearing potential. The applicant should conduct enhanced pharmacovigilance to collect meaningful data with intended or unintended Impavido pregnancy exposure.

RECOMMENDATIONS

The following are PMHS-MHT recommendations for pregnancy, nursing mothers, and females and males of reproductive labeling for Impavido labeling.

PMHS-MHT recommended and discussed the following Impavido labeling revisions at a labeling meeting with DAIP held on November 5, 2013:

- Highlights of Prescribing Information
- Boxed Warning
- Warnings and Precautions (5.1, 5.2, 5.7)
- Use in Special Populations (8.1, 8.3, 8.8)
- Patient Counseling Information (17.2)

Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Warning: Embryo-Fetal Toxicity
Fetal death and teratogenicity occurred in animals administered miltefosine. IMPAVIDO may cause fetal harm (b) (4) Advise use of effective contraception during and after therapy (5.1, 8.1, 8.8).

-----USE IN SPECIFIC POPULATIONS-----

- Nursing Mothers: Discontinue drug or nursing depending on importance of drug to mother (8.3).
- Females and Males of Reproductive Potential: Advise use of effective contraception during therapy and for 5 months after therapy. Potential impaired fertility (5.1, 5.2, 8.8).

FULL PRESCRIBING INFORMATION

WARNING: Embryo-Fetal Toxicity

(b) (4)

IMPAVIDO may cause fetal harm. Embryo-fetal toxicity, including death and teratogenicity, occurred in animals administered miltefosine at doses lower than the (b) (4) recommended human dose. Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after therapy [see *Warnings and Precautions (5.1) and Use in Special Populations (8.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Miltefosine may cause fetal harm. (b) (4)

(b) (4) Embryo-fetal toxicity, including death and teratogenicity, was observed in animals administered miltefosine prior to mating, during early pregnancy, and during organogenesis at doses lower than the maximum recommended human dose (MRHD). Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after completion of therapy [see *Boxed Warning, and Use in Specific Populations (8.1, 8.8)*].

5.2 (b) (4)

Females

Miltefosine caused impaired fertility in (b) (4) rats and dogs at doses approximately 1.0 and 0.2 times (b) (4) [See Nonclinical Toxicology (13.1)]. (b) (4) effects on female fertility have not been studied.

Males

Miltefosine caused testicular atrophy and impaired fertility in rats at doses approximately 1.0 times the maximum recommended human dose. (See Nonclinical Toxicology 13.1). Scrotal pain and decreased or absent ejaculation during therapy have also been reported during IMPAVIDO therapy (See (b) (4) 6.2). The (b) (4) effects of IMPAVIDO on male fertility have not been studied. Advise females and males of potential impaired fertility with IMPAVIDO therapy.

5.7 Absorption of Oral Contraceptives

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect the absorption of oral contraceptives, and therefore compromise their efficacy. If vomiting and/or diarrhea occur during IMPAVIDO therapy, advise females to use additional non-hormonal or alternative method(s) of effective contraception.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category (b) (4)

Risk Summary

IMPAVIDO may cause fetal harm. Human pregnancy data are not available, however, embryo-fetal toxicity including death and teratogenicity, was observed in rats and rabbits administered miltefosine during organogenesis at doses 0.06 and 0.2 times, respectively, the maximum recommended human dose (MRHD). Numerous visceral and skeletal fetal malformations were observed in a fertility study in female rats administered miltefosine prior to mating through day 7 of pregnancy at doses 0.3 times the MRHD. (b) (4)

Clinical Considerations

(b) (4)

During pregnancy, visceral leishmaniasis is life-threatening for the mother and may result in adverse fetal outcomes, including spontaneous abortion, congenital disease due to vertical transmission, small for gestational age newborn, and severe anemia. During pregnancy, (b) (4) cutaneous and mucosal leishmaniasis are characterized by larger and atypical appearing lesions and may increase the risk for adverse fetal outcomes, including preterm births and stillbirths.

Animal Data

Miltefosine administration in rat embryo-fetal toxicity studies during early embryonic development (Day 6 to Day 15 of gestation) caused embryo-fetal toxicity including death and teratogenicity at dosages of ≥ 1.2 mg/kg/day (0.06 times the maximum recommended human dose (MRHD based on body surface area (BSA) comparison). Teratogenic effects included undeveloped cerebrum, (b) (4) hemorrhagic fluid filling the lumina of the skull, cleft palate and generalized edema. Embryo-fetal toxicity was also observed in rabbits after oral administration of miltefosine during organogenesis (Day 6 to Day 18 of gestation) at doses ≥ 2.4 mg/kg/day (0.2 times the MRHD based on BSA comparison). In both rats and rabbits, there were no viable litters at miltefosine doses ≥ 6.0 mg/kg/day (0.3 or 0.6 times the MRHD based on BSA comparisons for rats and rabbits respectively).

In a separate female fertility study in rats, miltefosine doses ≥ 6.81 mg/kg/day (0.3 times the MRHD based on BSA comparison) administered for four weeks before mating and up to Day 7 of pregnancy produced numerous visceral (misshapen cerebral structures, dilated ventricles filled with brown masses, misshapen spinal cord, misshapen and malpositioned eyes, hypophysis, and absent inner ear) and skeletal (cleft palate, dumbbell-shaped ossification of thoracic vertebral centers, markedly enlarged skullbones, and markedly dilated sutures) fetal malformations.

8.3 Nursing Mothers

It is not known whether IMPAVIDO is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from IMPAVIDO, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Breastfeeding should be avoided for 5 months (b) (4) after IMPAVIDO therapy.

8.8 Females and Males of Reproductive Potential

Contraception

IMPAVIDO may cause fetal harm when used during pregnancy. Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months (b) (4) after therapy is completed [see *Boxed Warning, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect absorption of oral contraceptives and therefore may compromise their efficacy. Advise females who use oral

contraceptives to use additional non-hormonal or alternative method(s) of effective contraception during IMPAVIDO therapy if vomiting and/or diarrhea occur during therapy [see *Warnings and Precautions (5.7)*].

Infertility

Females

Miltefosine caused impaired fertility in (b) (4) rats and dogs at doses approximately 1.0 and 0.2 times the maximum recommended human dose [see *Nonclinical Toxicology (13.1)*]. The (b) (4) effects of miltefosine on female fertility have not been studied.

Males

Miltefosine caused testicular atrophy and impaired fertility in (b) (4) rats at doses approximately 1.0 times the MRHD [see *Nonclinical Toxicology (13.1)*]. The (b) (4) effects of IMPAVIDO on male fertility have not been studied [see *Warnings and Precautions (5.2)*].

Advise females and males of potential impaired fertility with IMPAVIDO therapy.

17 PATIENT COUNSELING INFORMATION

17.2 Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after therapy ends [see *Boxed Warning and Use in Specific Populations (8.1, 8.8)*].
- Advise females who use oral contraceptives to use additional non-hormonal or alternative method(s) of effective contraception during IMPAVIDO therapy if vomiting and/or diarrhea occurs [see *Warnings and Precautions (5.7)* and *Use in Specific Populations (8.8)*].
- Advise nursing mothers not to breastfeed during IMPAVIDO therapy and for 5 months after therapy is completed [see *Use in Specific Populations (8.3)*].
- Advise females and males of potential impaired fertility with IMPAVIDO therapy [see *Warnings and Precautions (5.2)* and *Use in Specific Populations (8.8)*].

APPENDIX A: FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)	
Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

MIRIAM C DINATALE
11/21/2013

JEANINE A BEST
11/21/2013

LYNNE P YAO
11/25/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 18, 2013

To: Sumathi Nambiar, M.D.
Acting Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
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Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Christine Corser, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert and
Instructions for Use

Drug Name: IMPAVIDO (miltefosine)

Dosage Form and Route: capsules

Application
Type/Number: NDA 204684

Applicant Paladin Therapeutics, Inc. (Paladin)

1 INTRODUCTION

On April 19, 2013, Paladin submitted for the Agency's review an original New Drug Application (NDA) for IMPAVIDO (miltefosine) capsules, NDA 204684.

IMPAVIDO (miltefosine) capsules is an antileishmanial drug indicated in adults and adolescents ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for treatment of:

- Visceral leishmaniasis acquired in geographic regions where *Leishmania donovani* is known to be prevalent
- Cutaneous leishmaniasis acquired in geographic regions where *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis* are known to be prevalent
- Mucosal leishmaniasis acquired in geographic regions where *Leishmania braziliensis* is known to be prevalent

Reference is made to the July 31, 2013, mid-cycle teleconference between the Division of Anti-Infective Products (DAIP) and Paladin, during which the Agency requested Paladin submit a draft Medication Guide (MG) by August 9, 2013. On August 9, 2013, Paladin, submitted for the Agency's review a Response to Information Request-Safety Information Amendment for IMPAVIDO (miltefosine) capsules with a proposed MG.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the DAIP on August 19, 2013, and August 16, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for IMPAVIDO (miltefosine) capsules.

2 MATERIAL REVIEWED

- Draft IMPAVIDO (miltefosine) capsules Medication Guide (MG) received on August 9, 2013 and received by DMPP on November 8, 2013
- Draft IMPAVIDO (miltefosine) capsules Medication Guide (MG) received on August 9, 2013, and received by OPDP on November 8, 2013.
- Draft IMPAVIDO (miltefosine) capsules Prescribing Information (PI) received on August 9, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on November 8, 2013
- Draft IMPAVIDO (miltefosine) capsules Prescribing Information (PI) received on June 27, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on November 8, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
11/19/2013

CHRISTINE G CORSER
11/19/2013

ROBIN E DUER
11/19/2013

MELISSA I HULETT
11/19/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 18, 2013

To: Gregory DiBernardo, Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA #204684**
IMPAVIDO (miltefosine) capsules, for oral use

As requested in your consult dated August 16, 2013, OPDP has reviewed the draft PI and proposed carton and container labeling for IMPAVIDO (miltefosine) capsules, for oral use. Comments on the proposed Medication Guide will follow under separate cover.

OPDP's comments on the PI are based on the substantially complete version of the labeling titled, "11 08 13 draft-labeling w MHT edits.doc" received via email from DAIP on November 8, 2013. OPDP's comments are provided in the attached, clean version of the PI.

OPDP's comments on the carton and container labeling are based on the draft versions located at the following EDR link:

<\\CDSESUB1\evsprod\NDA204684\0000\m1\us\114-labeling\1141-draft>.

OPDP has reviewed the carton and container labeling and has no comments at this time.

Thank you for the opportunity to provide comments on the proposed labeling.

If you have any questions about OPDP's comments on the PI, please contact Christine Corser at 6-2653 or Christine.corser@fda.hhs.gov

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/s/

CHRISTINE G CORSER
11/18/2013

This is an addendum to document a correction to a statement contained in the September 5, 2013, DBRUP consult review.

The Reviewer Comment in Section IIIB, at the top of page 5, is incorrect:

Comment: Given the paucity of human data, the potential for impaired female fertility with miltefosine is defined at this time.

The correction is shown in bold font in the Comment below:

*Comment: Given the paucity of human data, the potential for impaired female fertility with miltefosine is **not** defined at this time.*

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/s/

CAREN KIESWETTER
10/17/2013

CHRISTINA Y CHANG
10/17/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 11, 2013

TO: Gregory DiBernardo, Project Manager
Hala Shamsuddin, Medical Officer
Division of Anti-Infective Products

FROM: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204684

APPLICANT: Paladin Therapeutics, Inc.
Corporation Trust Center
1209 Orange Street
Wilmington, DE 19801
Contact: Jonathan D. Berman, M.D., Ph.D.

DRUG: Impavido[®] (miltefosine) capsules
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: 1. Treatment of visceral leishmaniasis (VL)
2. Treatment of cutaneous leishmaniasis (CL)
3. Treatment of mucosal leishmaniasis (ML)

CONSULTATION REQUEST DATE: June 7, 2013

DIVISION ACTION GOAL DATE: December 19, 2013
PDUFA DATE: December 19, 2013

I. BACKGROUND:

Paladin Therapeutics, Inc. submitted a new drug application (NDA 204684) for Impavido[®] (miltefosine) 50 mg capsules requesting approval for the use of Impavido[®] (miltefosine) oral capsules in adolescents and adults ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for the treatment of VM, CM, and ML. The product was initially developed by Zentaris GmbH (Zentaris). The ownership of miltefosine was transferred from Zentaris GmbH (Zentaris) to Paladin Labs (USA), Inc. and Paladin Therapeutics, Inc. on September 12, 2012. The NDA submitted is owned by Paladin Therapeutics Inc. Paladin Labs (USA), Inc., and Paladin Therapeutics Inc. are U.S. subsidiaries of Paladin Labs Inc. (Montreal, Canada).

Miltefosine is an antileishmanial agent that is administered orally. The specific mode of action of miltefosine in leishmaniasis is unknown. The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids. Conventional treatments of VL must be administered parenterally. As of November 2011, miltefosine was approved for marketing in 14 countries for the VL and CL indications. Miltefosine is also accepted as an Essential Medicine by the WHO. Orphan drug designation was granted by FDA on October 10, 2006.

The Applicant submitted data from two pivotal clinical trials (Protocols #3154 and #3168) which they interpret as sufficient evidence to support the use of Impavido[®] (miltefosine) for the treatment of VL, CL, and ML. The two pivotal studies were completed over 10 years ago (between 1999 and 2002), and according to Dr. Jonathan Berman, Paladin Therapeutics Inc. appointed agent, the clinical sites in Guatemala and India are not operational and have been closed. Dr. Berman noted that the sponsor has stored/archived certified copies of source documents from all sites at a location in Montreal, Canada. The inspection assignment therefore requested inspection of both sponsor responsibilities as well as data verification for the selected clinical sites to be conducted at the sponsor site.

Based on the proposed label, Impavido[®] (miltefosine) is contraindicated in pregnancy and in women of childbearing potential who do not use reliable contraception during and up to (b) (4) months after treatment, anyone having Sjögren-Larsson-Syndrome, anyone having pre-existing severe or life-threatening damage of kidney or liver function, and in patients who are hypersensitive to this product or any excipients. The most common adverse reactions reported in the proposed label that are likely attributable to Impavido[®] (miltefosine) therapy in leishmaniasis patients are vomiting, diarrhea, abdominal pain, elevated levels of liver enzymes, and elevated levels of creatinine.

Brief descriptions of the pivotal protocols are provided in the following sections.

Study No. 0-18506-3154: Clinical trial to assess efficacy and safety of orally administered miltefosine in patients with visceral leishmaniasis. Control group: Amphotericin B

This was a randomized, active controlled, multicenter study that compared miltefosine (100 mg/kg/day for 28 days) and Amphotericin B (1 mg/kg every other day for 30 days) in the treatment of VL in India. The treatment groups were:

Group A

Miltefosine capsule (50 mg); administered orally for 28 days

Patients \geq 25 kg body weight: 100 mg/day (1 capsule in the morning, 1 capsule in the evening, following meals)

Patients < 25 kg body weight: 50 mg/day (1 capsule in the morning, following meal)

Group B

Amphotericin B powder (50 mg); administered as 15 intravenous infusions over 28 days 1 mg/kg as 6 hours continuous intravenous infusion every other day

Eligible patients were randomly allocated to treatment with miltefosine or amphotericin B (ratio 3:1). Patients in the miltefosine group were treated with miltefosine capsules for 28 days, patients in the amphotericin B group were treated with amphotericin B intravenously every other day over 30 days. At the end of treatment the initial cure rate and clinical response were determined. If initial cure was observed, patients were evaluated after a 6 month follow up period for final cure.

The trial was conducted at three centers in India: the Kala Azar Research Center, Muzaffarpur (Center 1; principal investigator Dr. TK Jha), the Kala Azar Medical Research Center, Muzaffarpur (Center 2; principal investigator Prof. S. Sundar), and at Balaji Utthan Sanastan, Patna (Center 3; principal investigator Dr. CP Thakur).

Endpoints

The primary endpoint was initial cure, defined as negative spleen or marrow aspirate for leishmania organisms at the end of 28 days of therapy, plus resolution/no relapse of signs and symptoms associated with VL at 6 months. Secondary endpoints of this trial included the assessment of initial (parasitological) cure and clinical response at end of treatment, as well as the characterization of the safety of the proposed miltefosine schedule.

Eligibility Criteria

Male and female, adolescent and adult patients (12 years of age and older) with newly diagnosed or resistant/relapsing VL, confirmed by splenic/bone marrow aspiration, and with clinical signs and symptoms compatible with VL, including fever, splenomegaly, and anemia, were enrolled in the trial.

Study Visits and Procedures

Evaluation of clinical response was to be based on signs and symptoms attributable to VL. Temperature was to be recorded at screening, daily during treatment, at end of treatment, and at final evaluation. In patients with clinical signs and symptoms during follow up, a full clinical evaluation was to be performed. Spleen size, WBC, hemoglobin, and platelets were assessed at screening, weekly during treatment, at end of treatment, and at final evaluation. In patients that demonstrated signs and symptoms attributable to VL during follow up, a parasitological examination was performed to verify whether VL (positive spleen or bone

marrow aspirate) or another disease (negative parasitology, to be followed by appropriate tests) was the cause, unless another disease clearly was the cause of the signs and symptoms. At the six month follow up visit, signs and symptoms attributable to VL must be absent to define a final cure or, if signs and symptoms were present, a parasitological examination had to be performed in any case (whether another disease could explain the signs or symptoms or not).

Brief Overview of Study 3154 Results

Of 400 planned subjects, 398 subjects with VL received at least one dose of study drug: 299 subjects received miltefosine and 99 received amphotericin B at three study centers in India between July 1999 and December 2000. The sponsor claims that similar cure rates were achieved after oral miltefosine treatment (100 mg/day for 28 days; 94.3%) and intravenous amphotericin B treatment (50 mg; 97%), with no significant difference noted between subjects pre-treated or not pretreated with pentavalent antimonial drugs. The most common adverse events were gastrointestinal disorders and transient increases in serum transaminases. Serious adverse events occurred in six miltefosine treated subjects and one amphotericin B treated subject; of these, a case of Stevens-Johnson syndrome (miltefosine group) and a case of renal insufficiency were considered to be drug-related. Four subjects in the miltefosine group (arthritis/rash, diarrhea, jaundice, and Stevens-Johnson syndrome) and two subjects in the amphotericin B group (thrombocytopenia and renal impairment) discontinued treatment prematurely due to lack of tolerability.

Study Protocol No. 3168: Clinical trial to assess efficacy and safety of orally administered miltefosine in patients with cutaneous leishmaniasis

The study was a double blind, placebo-controlled multicenter trial conducted in two countries, Colombia and Guatemala. The study plan was to recruit a total of 132 subjects, 88 subjects to be treated with miltefosine and 44 subjects to be treated with placebo group.

Subjects were treated with miltefosine (50 mg) or matching placebo capsules; administered orally for 28 days

- Patients \geq 45 kg body weight: 3 capsules per day (1 capsule in the morning, 1 capsule at lunch, and 1 capsule in the evening, following meals)
- Patients $<$ 45 kg body weight: 2 capsules per day (1 capsule in the morning and 1 capsule in the evening, following meals)

The duration of treatment per subject was to be 28 days with 6-month post-treatment follow up to assess definite cure. The principal investigator for the study in Guatemala (Universidad del Valle de Guatemala) was Dr. Byron Arana who was succeeded by Dr. M. Gilardi. Dr. Jaime Soto was the principal investigator in Columbia. The study was performed between 2000 and 2002.

Endpoints

The primary efficacy endpoint for this study was defined as the rate of patients with **apparent cure** and **definite cure** (lack of parasite positivity after treatment, lack of $>$ 50% enlargement of the cutaneous lesion, and complete re-epithelialization of the cutaneous lesion at 6 months after the end of therapy).

Apparent cure: Complete epithelialization of all ulcers, and complete disappearance of inflammatory induration from all lesions 2 weeks after end of treatment.

Definite cure: Complete epithelialization of all ulcers, and complete disappearance of inflammatory induration from all lesions at the end of the 6 months follow up period.

Clinical failure: Residual lesions with presence of parasites, appearance of any new lesions, or $\geq 50\%$ enlargement of previously documented lesions two weeks after end of treatment or at any time during follow up period.

Eligibility Criteria

The study included male and female patients older than 12 years of age who had newly diagnosed or relapsing CL without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer with a minimum area of 50 mm².

Study Visits and Procedures

Lesions are either ulcerations or inflammatory indurations of the skin. Each lesion was measured in size (two dimensional, largest diameters in mm), and ulcerated lesions were assessed for their grade of epithelialization, area of infiltration. A standardized photograph was taken according to the approved procedure at the site of the investigator. For each lesion that was not completely epithelialized or showed an inflammatory induration, a parasitologic analysis was done at screening (diagnosis).

Patients were followed up (up to six months after end of treatment). Each patient who was not clinically cured at two months after the end of treatment was to receive rescue treatment with parenteral standard treatment. Safety was assessed based on treatment-emergent adverse events, the results of routine clinical laboratory tests, and physical examination.

Brief Overview of Study 3168 Results

There were 133 subjects with CL who were enrolled in the study: 89 subjects received miltefosine and 44 received placebo at two study centers (Guatemala and Columbia) between June 2000 and December 2002. The sponsor claims that cure rates were significantly higher after oral miltefosine treatment at six month follow-up (50 mg/day for 28 days; 69.7% cure rate) than after placebo treatment (31.8% cure rate). The most common adverse events in the miltefosine treatment group were gastrointestinal disorders, motion sickness, and headache.

II. RESULTS (by Site):

As noted above, the clinical investigator sites listed below were closed. Therefore, certified copies of the clinical investigator's site records were inspected at the sponsor, and an inspection of the sponsor was done, as well.

Name of CI	Protocol # and # of Subjects enrolled	Inspection Date	Final Classification
T.K. Jha, M.D. Kala-azar Research Center, Brahmpura, Muzaffarpur, India 842003	Protocol # 3154 Site #1 145 subjects	8/5/13 – 8/14/13	NA
C.P. Thakur, M.D. Balaji Utthan Sanastan Fraser Road, (Uma Complex) Atna 800001, India	Protocol #3154 Site #3 109 subjects	8/5/13 -8/14/13	NA
Byron A. Arana M.D. Medical Entomology Research and Training Unit Guatemala Center for Health Studies Universidad del Valle de Guatemala 18 Av. 11-95 Zona 15, Vista Hermosa III Apartado Postal No. 082 Guatemala	Protocol #3168 Site #2 60 subjects	8/5/13 – 8/14/13	NA
Paladin Labs Inc. 100 Blvd. Alexis Nihon, Suite 600 St-Laurent, Quebec H4M 2P2	Protocols #3154 and 3168	8/5/13 – 8/14/13	Pending NAI

Key to Classifications

NA = Not applicable since not all elements of Compliance Program 7348.811 could be performed.

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. T.K. Jha, M.D.

**Kala-azar Research Center,
Brahmpura, Muzaffarpur, India 842003**

- a. **What was inspected:** Copies of the records from Dr. Jha's study site are currently kept at corporate headquarters in Montreal, Canada. Dr. Jha certified that the source data copies that were sent to headquarters were true and accurate copies. Study records reviewed included Patient Registration Forms and Logs,

informed consent documents, monitoring reports, source data related to eligibility, concomitant medications, efficacy endpoints, and adverse events for 50 of the 145 subjects that were enrolled/randomized at this site. At this site, 142 subjects completed the study.

- b. **General observations/commentary:** Source data for eligibility, concomitant medications, efficacy endpoints, and adverse events for the 50 subjects reviewed were verifiable and agreed with the data on the line listings. Many of the informed consent documents were signed with a thumbprint, which was allowed by the protocol for illiterate subjects. The investigator signed an agreement indicating that he would conduct the studies under GCPs, although the study was not conducted under an IND. No underreporting of adverse event reporting was noted. The records that were reviewed indicated that the subjects were randomized and treated in accordance to protocol guidelines. Study endpoints of treatment success or failure were verifiable. The signed and dated monitoring reports for this site indicated that the monitors verified source records against data that was recorded on the CRFs and that the investigator was appropriately counseled on protocol deviations, such as removing a subject from study due to laboratory abnormalities. The site responded to data queries in a timely manner.
- c. **Assessment of data integrity:** Inspection of certified copies of the data from Dr. Jha's site revealed no significant regulatory violations. The data in support of the clinical efficacy and safety at Dr. Jha's site are considered reliable and acceptable in support of the application.

2. **C.P. Thakur, M.D.**
Balaji Utthan Sanastan
Fraser Road, (Uma Complex)
Atna 800001, India

- a. **What was inspected:** Copies of the records from Dr. Thakur's study site are currently kept at corporate headquarters in Montreal, Canada. Dr. Thakur certified that the source data copies that were sent to headquarters were true and accurate copies. Study records reviewed included informed consent documents, monitoring reports, source data related to eligibility, efficacy endpoints, and adverse events for 57 of the 109 subjects that were enrolled and received drug at this site. At this site, 104 subjects completed the study. Three subjects were lost to follow-up (Subjects 052, 069, and 092). Subject 038 died from meningitis during treatment, and Subject 030 died from malaria during follow-up.
- b. **General observations/commentary:** Source data for eligibility, efficacy endpoints, and adverse events for the 57 subjects reviewed were verifiable and agreed with the data on the line listings. The medical source records were in

- English. Subjects at this site signed informed consent forms in both Hindi and English. The investigator signed an agreement indicating that he would conduct the studies under GCPs, although the study was not conducted under an IND. Adverse events including serious adverse events were adequately reported. The records that were reviewed indicated that the subjects were randomized in accordance to protocol guidelines. Study endpoints of treatment success or failure were verifiable. The signed and dated monitoring reports for this site indicated that the monitors verified source records against data that was recorded on the CRFs. The site responded to data queries in a timely manner.
- c. **Assessment of data integrity:** Inspection of certified copies of the data from Dr. Thakur's site revealed no significant regulatory violations. The data in support of the clinical efficacy and safety at Dr. Thakur's site are considered reliable and acceptable in support of the application.
3. **Marco Gilardi M.D.**
Medical Entomology Research and Training Unit
Guatemala Center for Health Studies Universidad del Valle de Guatemala
18 Av. 11-95 Zona 15, Vista Hermosa III
Apartado Postal No. 082
Guatemala
- a. **What was inspected:** Copies of the records from Dr. Arana's study site are currently kept at corporate headquarters in Montreal, Canada. During the study the principal investigator at this site changed from Dr. Byron Arana to Dr. Marco Gilardi. Dr. Gilardi certified that the source data copies that were sent to headquarters were true and accurate copies. Study records reviewed included monitoring reports and source data related to eligibility, efficacy endpoints, and adverse events for 31 of the 60 subjects that were enrolled at this site. Review of informed consent documents is not specifically mentioned. Four subjects (012, 016, 023, and 031) were lost to follow-up, and 56 subjects completed the study at this site.
- b. **General observations/commentary:** Source data for eligibility, efficacy endpoints, and adverse events for the 31 subjects reviewed were verifiable and agreed with the data on the line listings. The investigator signed an agreement indicating that he would conduct the studies under GCPs, although the study was not conducted under an IND. Adverse events including serious adverse events were adequately reported, with the exception of two non-SAEs: Subject 005 had painful edema due to lesions in both feet, and Subject 012 had pain and edema due to lesions. This subject also received acetaminophen which was not recorded as a concomitant medication in the CRF and line listing. The records that were reviewed indicated that the subjects were randomized in accordance to protocol guidelines. Study endpoints of treatment success or failure were verifiable. There were pictures/slides of the subject's lesions at the site. The signed and dated monitoring reports for this site indicated that the monitors

verified source records against data that was recorded on the CRFs. The site responded to data queries in a timely manner.

- c. **Assessment of data integrity:** Inspection of certified copies of the data from Dr. Alana/Gilardi's site revealed no significant regulatory violations. The data in support of the clinical efficacy and safety at this site are considered reliable and acceptable in support of the application.

4. **Paladin Labs Inc.**
100 Blvd. Alexis Nihon, Suite 600
St-Laurent, Quebec H4M 2P2

- a. **What was inspected:** The inspection was conducted in at Paladin Labs Inc. and reviewed conduct and procedures of Protocols 3154 and 3168. The inspection occurred between August 5, 2013 and August 14, 2013. Records related to monitoring practices, verification of key safety and efficacy endpoints, test article accountability, adverse events, delegation of responsibilities, and contractual agreements were reviewed.
- b. **General observations/commentary:** Paladin Labs Inc. was founded in 1996 and is headquartered in the Montreal, Canada area; they are the parent company of the wholly owned subsidiaries Paladin Labs-Barbados, Paladin Therapeutics-Delaware, USA, and Paladin Labs USA-Delaware, USA. The original development of the test article miltefosine that was used in Studies 3154 and 3168 was conducted between 1999 and 2002 by ASTA Medica, which was acquired by Aeterna Zentaris in 2002. For both studies, meeting minutes indicated that Study Initiation Investigator Meetings were conducted, covering GCP requirements, informed consent, laboratory procedure requirements, and monitoring. For both studies, it was determined that subjects were randomized to study drug in accordance with the protocol, and the inspector noted that there were no records to indicate why more females were randomized than males. A note to the file is included in the exhibits which indicates that the enrollment and screening logs for the study sites that conducted the study under Protocol 3154 were not contained in the Master File. Records showed that monitoring activities included review for protocol compliance, CRF completion, drug accountability, and source data verification and indicated that sites were monitored frequently. Accountability records for the investigational product(s) were reviewed and appeared accurate and complete for both studies.

An FDA 483 was not issued at the close of the inspection. Two verbal observations were discussed with the sponsor: (1) Late filing of financial disclosure information, and (2) the lack of documented continuing IRB review/approvals in the study files for the study sites reviewed.

- c. **Assessment of data integrity:** The data collected and maintained at the sponsor's site

as it pertains to the three clinical sites audited appear consistent with that submitted to the agency as part of and in support of NDA 204684. Review of randomization procedures did not reveal any discrepancies in these procedures. The observations of late filing of financial reports and lack of documented continued IRB approval are unlikely to significantly impact subject safety or study outcome.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the records from the audited sites of Drs. Jha, Thakur, and Arana/Gilardi demonstrated that the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents showed that the subjects exist, met eligibility criteria, received assigned study medication, adhered to the protocol, and signed informed consent documents. Randomization appears to have been conducted appropriately. There were no significant regulatory violations noted during the sponsor inspection; the discussion items noted above should not influence subject safety or efficacy outcome. The studies conducted at this site appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

{See appended electronic signature page}

Susan D. Thompson, M.D.

Team Leader

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.

Acting Branch Chief

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

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/s/

SUSAN D THOMPSON
10/15/2013

KASSA AYALEW
10/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 13, 2013

Reviewer(s): Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Miltefosine, 50 mg per Capsule

Application Type/Number: NDA 204684

Submission Number: S-12

Applicant/sponsor: Paladin Therapeutics

OSE RCM #: 2013-1181

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	INTRODUCTION	1
1.1	Regulatory History	1
1.2	Product Information	1
2	METHODS AND MATERIALS REVIEWED	1
2.1	Labels and Labeling	2
3	MEDICATION ERROR RISK ASSESSMENT	2
3.1	Integrated Summary of Medication Error Risk Assessment	2
4	Discussion	2
5	CONCLUSIONS	2
6	RECOMMENDATIONS	3
6.1	Comments to the Division	3
6.2	Comments to the Applicant	4
	Appendices	6

1 INTRODUCTION

This review evaluates the proposed blister label, carton and insert labeling for Miltefosine, NDA 204684, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Miltefosine was granted orphan drug designation for the treatment of leishmaniasis on October 10, 2006 and for topical treatment of cutaneous lymphoma encompassing cutaneous manifestations of T-cell lymphoma and B-cell lymphoma on March 18, 2009. The Applicant submitted an NDA on September 26, 2012, however the Agency refused to file the application on November 26, 2012, citing clinical, statistical, and dataset deficiencies. The NDA was subsequently resubmitted by the Applicant on April 19, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 10, 2013 proprietary name submission.

- Active Ingredient: Miltefosine
- Indication of Use: Impavido (miltefosine) capsules are indicated in adolescents and adults ≥ 12 years of age weighing ≥ 30 kg (66 lbs) for the treatment of mucosal leishmaniasis due to *L.v. braziliensis*.
- Route of Administration: Oral
- Dosage Form: Capsule
- Strength: 50 mg
- Dose and Frequency: 28 day treatment

Weight	Dosage and Administration
30 to 44 kg	50 mg twice daily with food
45 kg or greater	50 mg three times daily with food

- How Supplied: A folded peel/push-through blister card each containing 14 capsules, with 2 cards per carton, each carton containing a total of 28 capsules
- Storage: Room temperature, protect from moisture

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Miltefosine medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the Miltefosine labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Labels submitted September 27, 2012 (Appendix B)
- Carton Labeling submitted September 27, 2012 (Appendix C)
- Insert Labeling submitted June 27, 2013
- Medication Guide submitted August 7 2013

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Miltefosine product design as well as the associated label and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Based on the two proposed dosing regimens (50 mg twice or three times daily), the blister label and carton labeling are adequately designed for the outpatient setting when a 28 day course of therapy (either 2 or 3 cartons) is prescribed. However, the packaging is not well designed for situations where an individual blister may be separated from the blister card, because the individual blisters are not labeled.

Therefore, DMEPA recommends adding labeling to each individual blister. Additionally, we provide comments to the Applicant and the Division to further improve the labels and labeling, our recommendations are listed below in sections 5.1 and 5.2.

4 DISCUSSION

The current blister card

(b) (4)

(b) (4)

the capsules would not be easily identifiable, which may lead to medication errors. Thus, DMEPA recommends that the individual blisters should be labeled individually.

DMEPA and ONDQA discussed the recommendation to label individual blisters and ONDQA concurred with our recommendation.

5 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to mitigate any confusion or to clarify information.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for the Division to consider implementing prior to approval of this NDA:

A. Highlights of Prescribing Information, Dosage and Administration

1. Revise the weigh ranges to only include kilograms (kg), as providing both kilogram and pound ranges may be misinterpreted for the other and cause dosing errors.
2. Revise the “ \geq 45 kg” statement with “45 kg or greater”, as the greater than symbol has been identified on the Institutes for Safe Medications Practices (ISMP’s) list of error-prone abbreviations². Additionally, replace the hyphen in the “30-44 kg” statement with the word “to” and add the unit of weight after the number 30 to appear as: “30 kg to 44 kg”.

B. Highlights of Prescribing Information, Dosage Forms and Strengths

1. To clarify that each capsule contains 50 mg of miltefosine and for consistency with the full prescribing information, revise the following statement: (b) (4) to appear as: “Each Impavido capsule contains 50 mg miltefosine.”

C. Full Prescribing Information Dosage and Administration

1. See A1 and A2 above.
2. Remove the word (b) (4) from the following statement “One 50 mg capsule (b) (4) twice daily with food (breakfast and dinner)”, as it is confusing.

D. Full Prescribing Information Patient Counseling Information

1. Counseling instructions to the patient typically do not include weight specific dosing directions as it may cause the patient to change their individual dose or confuse the patient, especially when both kilograms and pounds are provided. Revise the following statements:

(b) (4)

² <http://www.ismp.org/tools/errorproneabbreviations.pdf>, Accessed July 31, 2013.

To read:

Take the IMPAVIDO capsules as prescribed, either:

- 1 capsule with breakfast and 1 capsule with dinner each day for 28 days

OR

- 1 capsule with breakfast, 1 capsule with lunch, and 1 capsule with dinner each day for 28 days.

E. Medication Guide

1. The “How should I take IMPAVIDO” instructions are confusing and provide specific weight based dosing to the patient, which may influence the patient to change their prescribed dose. Revise the following statement:



To read:

Take the IMPAVIDO capsules as prescribed, either:

- 1 capsule with breakfast and 1 capsule with dinner each day for 28 days

OR

- 1 capsule with breakfast, 1 capsule with lunch, and 1 capsule with dinner each day for 28 days.

6.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Blister Labels

1. The current blister card configuration  (b) (4)  they would be unidentifiable. Revise the blister label so that each individual capsule blister contains a 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.

B. 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.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

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

/s/

ALEKSANDER P WINIARSKI
09/13/2013

JAMIE C WILKINS PARKER
09/13/2013

Division of Bone, Reproductive and Urology Products (DBRUP)
Urology Consultation in Response to Request from the Division of Anti-Infective Products
(DAIP) for NDA 204,684

To: Hala Shamsuddin, M.D., Medical Officer, DAIP
Thomas Smith, M.D., Clinical Team Leader, DAIP
Wendelyn Schmidt, Ph.D., Nonclinical Team Leader, DAIP
James Wild, Ph.D., Nonclinical Reviewer, DAIP
Through Gregory DiBernardo, Regulatory Project Manager, DAIP

From: Guodong Fang, M.D., Medical Officer, DBRUP
Mark S. Hirsch, M.D., Medical Team Leader, DBRUP
Audrey Gassman, M.D., Deputy Director, DBRUP

Subject: DAIP asks DBRUP: 1) To evaluate male and female reproductive toxicities observed in nonclinical studies, 2) To evaluate the risk of infertility associated with miltefosine use, 3) To provide labeling recommendations for such risk, and 4) To provide advice for postmarketing studies or surveillance that may be required.

Tracking # 470

This urology consultation pertains *only* to male reproductive toxicities. A separate consultation relevant to female reproductive toxicity is being conducted by one of the DBRUP reproductive teams.

Date: September 6, 2013

Urology Consultant's Review in Response to Request from DAIP for NDA 204,684
Impavido (miltefosine)

1. Background

General Background Information

NDA Submission Date: April 19, 2013
PDUFA Goal Date: December 19, 2013
Advisory Committee Meeting Planned: October 18, 2013

Drug	Impavido (miltefosine), a structural analog of alkylphospholipids
Indication	Visceral (VL), mucosal and cutaneous (ML/CL) leishmaniasis
Formulation	Oral capsule containing either 10 mg or 50 mg miltefosine
Dose	2.5 mg/kg/day
Duration of treatment	28 days

Mechanism of action: The specific mode of action of miltefosine in leishmaniasis is unknown. Miltefosine may inhibit the metabolism of phospholipids (phosphocholine synthesis) in the cell membrane of the leishmania parasite.

Background Information Provided by DAIP in the Consult

Nonclinical:

- 1) “Miltefosine is teratogenic and fetotoxic in female mice, rats and rabbits at exposures similar to clinical exposure”;
- 2) “Exposures similar to clinical exposure(s) also result in testicular atrophy and impaired fertility in male rats and in atretic follicles in female rats.”

Consultant’s comment: *This consultation pertains only to testicular atrophy and impaired fertility in male rats. Data from dog studies and from human males is also reviewed as part of this consultation.*

Clinical PK:

“In human subjects, elimination follows a 2-compartment disposition model, with first elimination half-life of 7 days and terminal elimination half-life of 31 days.”

Approved European Labeling:

“The European product labeling for Impavido® contraindicates administration to pregnant women and advises women of child bearing potential to use effective contraception during treatment and for 3 months after discontinuation.”

Relevant Human Experience:

“The Applicant planned to evaluate the effects of miltefosine on male fertility by having spermograms performed in clinical trials. This was not acceptable to the study population due to cultural reasons. The Applicant did submit a dataset with such analysis for 15 subjects who participated in Study 3168 that compared miltefosine to placebo in the treatment of CL. In Study 3154 that compared miltefosine to amphotericin B in the treatment of VL, the Applicant compared the rate of live births (in) female partners of male subjects exposed to miltefosine or amphotericin B during treatment and at one year follow-up and found no difference.”

2. Brief Review of Male Findings in Nonclinical Studies

2.1 In Rats

In a Segment 1 study of fertility and reproductive performance, male Wistar rats received miltefosine via oral gavage at doses of 0, 3.16, 8.25 and 21.5 mg/kg/day for 4 weeks, followed by mating. Report Number 3000919528 provides the following summary of results related to male reproductive toxicity:

1. At the high dose of 21.5 mg/kg (equivalent to 129 mg/m²/day), massive degenerative atrophic changes of the seminiferous tubules were observed, resulting in diffuse tubular

atrophy and loss of germ cells, with a “*Sertoli cell only*” appearance in the majority of tubular cross sections. These changes led to marked reduction in sperm number and sperm viability, adverse effects on sperm morphology, and infertility in male rats. Only 60% of high dose males were able to successfully mate. Importantly, these changes did not demonstrate reversal during the drug-free recovery period. After 6 weeks, beginning re-proliferation of spermatogenic cells was observed in single tubules only. After 15 weeks, 11 of 24 high dose rats demonstrated a “*tendency to reversibility*”, with varying proportions of tubular cross sections demonstrating regenerated epithelium with Sertoli cell only appearance still present.

2. At mid-dose of 8.25 mg/kg (49.5 mg/m²/day), adverse effects of miltefosine on the seminiferous tubules and sperm were again observed, but these findings were less pronounced compared to the high dose group. In addition, the findings were reversible during the drug-free recovery period, with full restoration of reproductive capacity. Overall, 95% of the mid dose males were able to successfully mate.
3. At the lowest dose of 3.16 mg/kg (determined to be the NOAEL in this study, equivalent to 19.0 mg/m²/day), there were no observations of seminiferous tubule atrophic degeneration and no adverse effects on male fertility.
4. Thus, a dose-dependent effect of miltefosine on the male reproductive system was observed, at doses which showed little other systemic toxicity.

Male reproductive toxicity, including both seminiferous tubule injury and an apparent anti-androgen effect, was observed in rats in the 8-week and the 52-week oral toxicity studies. Key findings from these two studies were:

From the 8-week oral toxicity study in rats (Study Report #3000864494):

- The testes showed moderate to marked tubular degeneration and necrosis accompanied by a secondary hyperplasia of the interstitial cells in Groups 4 (21.5 mg/kg) and 5 (46.4 mg/kg) males;
- The prostate and seminal vesicles were atrophic in Groups 3 (10 mg/kg), 4 (21.5 mg/kg), and 5 (46.4 mg/kg) males, respectively.

From the 52-week oral toxicity study in rats (Study Report #3000861344):

- The testes, epididymides, prostate, and seminal vesicles all showed massive atrophy in Groups 3 (10 mg/kg) and 4 (21.5 mg/kg) males, but a “tendency” was also seen in low dose (4.64 mg/kg) group males. The weights of these organs were reduced.
- In the high dose group (21.5 mg/kg), the testicular atrophy was usually combined with focal mineralization of seminiferous tubules and diffuse and focal hyperplasia of Leydig cells.
- In individual animals, Leydig cell adenomas were observed.
- While “complete atrophy” of the testes was observed after the 52-week treatment period in high dose (21.5 mg/kg) group males, a tendency to reversibility with

beginning re proliferation of spermatogenic cells in single tubules was observed after the 6-week recovery period.

- Another predominant finding in the high dose (21.5 mg/kg) males, was complete atrophy of the epididymides. During the development of this atrophy, spermatogenic granulomas occurred in a higher incidence than in controls. When the development of this atrophy was slower, as in mid-dose (10 mg/kg) group males, a much higher incidence of spermatogenic granulomas occurred compared to group 4 (21.5 mg/kg) rats.

Consultant's comments: In the high and mid-dose groups in male Wistar rats in the Segment I study, the evidence is clear that 4 weeks of miltefosine was associated with testicular injury and resultant adverse effects on sperm, and in the high dose group, an adverse effect on male fertility. It is particularly notable that loss of germ cells and seminiferous tubule atrophy showed little reversal in the high dose group (21.5 mg/kg). These adverse effects were present, but less pronounced and fully reversible in the mid dose group (8.25 mg/kg). Finally, it is notable that no adverse effects were observed in the low dose group (3.16 mg/kg, or 19 mg/m²/day), thus, the study did generate a NOAEL for testicular toxicity in rats.

The seminiferous tubular atrophy observed in the 8-week and 52-week rat toxicity studies confirmed the findings in the 4-week reprotox study. In addition, the findings of atrophic epididymides, prostate, and seminal vesicles, as well as Leydig cell hyperplasia and Leydig cell adenomas, suggest a clinically important anti-androgen effect of miltefosine. The mechanism for such an effect is unknown, but a similar clinical picture can occur with testosterone receptor blockade.

2.2. In Dogs

In a chronic oral toxicity study, beagle dogs received miltefosine at doses of 0, 1.00, 3.16, and 6.19 mg/kg/day for 52 weeks. The following are Sponsor's summary results for this study (from Study Report #3000873450):

1. Multifocal atrophy and degeneration of seminiferous tubules, associated with focal mononuclear infiltrates, were observed in individual high dose (6.19 mg/kg/day) males. The findings returned to normal in the recovery period. The mean maximum miltefosine plasma concentration in the high dose group was 69.7 µg/mL, similar to plasma concentrations measured in patients taking 100 to 150 mg per day.
2. Testicular toxicity was not reported in the mid dose (3.16 mg/kg/day) group nor in the low dose (1.00 mg/kg/day) group. The mean maximum miltefosine plasma concentration in the mid dose group was 40.6 µg/mL.
3. The Sponsor purports that the low-dose in this study (1.00 mg/kg/day, equivalent to 20.0 mg/m²/day), represents a "nontoxic dose", with the exception of reversible ovarian changes. ***(Reviewer's comment: For a discussion of female reprotox, the reader is referred to the DBRUP/Reproductive consult).***

Male reproductive toxicity, including both seminiferous tubule atrophy and an apparent anti-androgenic effect, was observed in dogs in a 13-week toxicity studies. Key findings from this study (Study Report 3000859408) are shown in Table 1 and summarized here:

- Seminiferous tubule atrophy was observed. In the control group, one dog (Dog #4) had seminiferous tubular atrophy in association with a “retained testicle”, while one other control dog (Dog #3) had moderate to marked tubular atrophy with focal mononuclear cell infiltrates. One recovery control animal (Dog #34) showed moderate to marked tubular atrophy. In comparison, three dogs administered milfetosine showed moderate to marked tubular atrophy, including one in the 3.16 mg/kg group (Dog #20), one in the 10 mg/kg group (Dog #28), and one in the high-dose recovery group (Dog #37).
- Atrophy of the prostate, with decreased prostate weights was observed. In the control group, just one dog (Dog #4) showed minimal prostate atrophy (left side only). In comparison, six dogs administered milfetosine showed moderate to marked prostate atrophy, including two dogs in the 3.16 mg/kg group (Dogs #19 and #20), 2 dogs in the 10 mg/kg group (Dogs #25 and #28), and one in the high dose recovery group (Dog #38)

Table 1: Male Reproductive Findings from A 13-Week Toxicity Study in Beagle Dogs (Study Report 3000859408)

Groups	Control	Recovery Control	Low dose (1 mg/kg)	Mid dose (3.16 mg/dose)	High dose (10 mg/kg)	Recovery High
N	n = 4 (#1- 4)	n = 2 (#33, 34)	n = 4 (#9-12)	n = 4 (#17-20)	n = 4 (#25-28)	n = 2 (#37, 38)
Macro: Prostate weight decreased	#4 (left side only)			#19, 20 (moderate to marked)	#25, 28 (moderate to marked)	#38 (moderate to marked)
Histopathol:						
Prostate atrophy	#4 (minimal)			#19, 20 (moderate to marked)	#25, 28 (moderate to marked)	#38 (minimal)
Testes: (retained testicle with typical tubular atrophy)	#4					
Testes: Moderate to marked tubular atrophy+ maturation disturbance in spermatogenesis+ focal infiltrates of mononuclear cells	#3	#34		#20	#28,	#37

Consultant’s comments: It is notable that seminiferous tubule atrophy and degeneration were noted in the high dose group in beagle dogs at plasma milfetosine concentrations similar to those expected in patients. Although the Sponsor states that “morphologically similar changes are occasionally seen in control dogs”, we believe that the findings of seminiferous tubule degeneration in two species (rat and dog), at similar exposures, provides strong evidence of an association between milfetosine and testicular injury in animals. It is also notable that

prostate atrophy was observed in rats and in dogs, again suggesting an anti-androgen effect of miltefosine.

2.3 Exposure Comparisons Between Humans and Animals

2.3.1 Comparisons Based Upon Dose

Table 2 provides estimates of safety margins between doses at which testicular toxicity was observed in animals and therapeutic doses in humans.

The proposed clinical therapeutic dose is 100 – 150 mg per day, based on a mg/kg-based dose of 1.75 to 2.0 mg/kg/day. This is equivalent to an exposure of 62.9–92.5 mg/m²/day in a 60 kg human. Severe and potentially irreversible testicular toxicity was observed in rats at 129 mg/m²/day. Reversible testicular toxicity was observed in rats at 49.5 mg/m²/day.

Based on the Sponsor-determined NOAELs for general toxicity in rats and dogs, we calculated human equivalent doses (HED) of 45 mg and 102 mg, respectively. When these HEDs are compared to the proposed starting clinical dose of 100 mg, there is no apparent safety margin for the testicular toxicity findings.

Table 2: Estimation of Safety Margins Based on NOAEL and HED Conversion

Species	Study Duration	Single (SD) / Multiple (MD) Dose	NOAEL (mg/kg/d)	HED Conversion ¹ (mg)	Fold Safety Margin ² (Comparison to HED dose)
Rat	8 weeks	MD	4.64	44.54	0.45
Dog	13 weeks	MD	3.16	102.38	1.02

¹ Human equivalent dose (HED) determined from conversions of animal doses based on body surface area calculated for a 60 kg human. The conversion factors used: Mouse (0.08), Rats (0.16), and Dog (0.54), are described in the CDER July 2005 Guidance for Industry, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers."

² Fold safety margin calculated by dividing the HED by the proposed clinical start dose.

2.3.2 Comparisons Based Upon Plasma Concentrations

When comparing plasma concentrations, the conclusion reached for dose-based comparisons is confirmed.

In the rat, testicular toxicity was observed at miltefosine doses of 8.25 mg/kg and higher. In rats, a plasma concentration of approximately 52 µg/mL was observed following 52 weeks of miltefosine 10 mg/kg/day. Thus, the plasma concentration at which testicular toxicity was observed in rats is approximately the same as the clinical therapeutic miltefosine plasma concentration (70 µg/mL). Plasma concentrations in rats at a dose of 21.5 mg/kg/day (a dose at which testicular toxicity was severe and did not show reversal), were similar to mean maximum plasma concentrations (83 µg/mL) observed in patients in **Study 3109** who were administered miltefosine 3.8 mg/kg/day, a dose slightly greater than the planned clinical therapeutic dose of 2.5 mg/kg/day.

In the dog, multifocal atrophy and degeneration of seminiferous tubules was observed at a dose of 6.19 mg/kg/day. The mean maximum miltefosine plasma concentration at that dose was 69.7 µg/mL, which is virtually the same as the plasma concentration in patients taking 100 to 150 mg per day (70–80 µg/mL).

2.4 Summary Statement Regarding Testicular Toxicity Findings in Nonclinical Studies

Studies in rats demonstrated a clear association of miltefosine with severe testicular injury and adverse impact on male fertility, at doses and exposures *lower* than the human equivalent therapeutic dose. A potential for irreversibility of the testicular toxicity was observed at high doses in rats. Studies in dogs also demonstrated the testicular toxicity signal, albeit at a safety margin of approximately 1-fold. For human risk assessment, the Sponsor believes that it is important to consider that the rat is the most sensitive species, and that the rat exhibited toxicities in various tissues and organs that have not been observed in humans to date.

It is also notable that male reproductive organs that are known to atrophy when the effect of testosterone is withdrawn (e.g., prostate, seminal vesicles, epididymis) demonstrated atrophy in rats and in dogs under the influence of miltefosine. Leydig cell hyperplasia and Leydig cell adenomas were also observed in rats. In total, these findings suggest a potential anti-androgen effect of miltefosine.

In summary, based upon the nonclinical data, the Urology consultation team has serious concerns in regard to the male reproductive toxicity findings observed in animals.

3. Brief Review of Relevant Male Data from Clinical Studies

According to the DAIP consult, the Sponsor acknowledged that testicular toxicity was observed in nonclinical studies and they planned to conduct semen analyses in males in the controlled efficacy and safety studies. However, the consult further notes that the planned semen analyses were not conducted because the study population was reluctant due to cultural reasons. Therefore, the available relevant human data are limited, and are comprised of the following:

1. Semen analyses in 15 subjects in Study 3168, a multicenter, double-blind, placebo-controlled trial of orally administered miltefosine (100 mg/day for 28 days) to assess efficacy and safety of orally administered miltefosine in patients with CL. The study was conducted in Columbia and Guatemala.
2. A retrospective assessment of male reproductive potential, based on the rate of live births in partners of former male study participants in Studies 0033, 3089, 3109, 3127 and 3154. These clinical trials of miltefosine were completed and had been performed in India. The Sponsor refers to this retrospective analysis as “Study Z005”.

3.1 Semen Analyses in Study 3168

Study 3168 was a multicenter, double-blind, placebo-controlled trial of orally administered miltefosine (100 mg/day for 28 days) to assess efficacy and safety of orally administered

miltefosine in patients with cutaneous leishmaniasis (CL). The study was conducted at investigative sites in Columbia and Guatemala from 25-June-2000 to 15-Dec-2002. Patient recruitment for this trial was completed in Guatemala but was ongoing in Colombia at the time when the Sponsor and the World Health Organization (WHO) concluded that the potential impact of oral treatment with miltefosine on male fertility should be investigated prospectively. The study procedures were amended to include semen analyses (Sponsor refers to these as “spermiograms”) according to the study flow chart shown in Table 3.

Table 3: Flow Chart for Semen Analyses

Assessment	Visit # (Day)					
	1	2	3	4	5	6
	Before Treatment	weekly during treatment (Day 7, 14, 21)	Day 28 or end of treatment	2 weeks after end of treatment	2 month after end of treatment	6 month after end of treatment
Semen analyses ^a	X			X		X

^a Semen analyses should be taken from at least 15 male patients at center 1.

Study 3168 was designed to test a treatment duration of 28 days and included a 6-month post-treatment follow-up period to assess for “definite cure”. Dosage was either 150 mg per day or 100 mg per day, based upon patient weight:

- Patients \geq 45 kg body weight: 3 capsules per day (1 capsule in the morning, 1 capsule at lunch, and 1 capsule in the evening, following meals)
- Patients $<$ 45 kg body weight: 2 capsules per day (1 capsule in the morning and 1 capsule in the evening, following meals)

The study included a total of 132 patients (88 miltefosine and 44 placebo); however, semen analyses were conducted in just 15 patients, of whom 11 received miltefosine treatment. Semen analyses were to be conducted prior to treatment, 2 weeks after the end of treatment and 6 months after the end of treatment. Semen analyses included the following assessments: semen volume, sperm concentration, progressive sperm motility, live sperms, and sperm morphology. The Sponsor stated the recruitment of patients for the semen analysis procedure turned out to be more difficult than anticipated, for a variety of reasons. As a consequence, completion of the trial was significantly delayed. Semen analyses were performed in a total of 11 miltefosine patients (MIL) patients and 4 placebo patients (PLA), all at Center 1. The examinations were performed at screening, 2 weeks after end of treatment (in all patients), and at 6 months after end of treatment (in 10 miltefosine patients and in just 1 placebo patient).

Table 4 below provides mean (\pm SD) data for sperm characteristics in the 15 patients who underwent semen analysis assessments at Center 1 in Study 3168.

Table 4: Semen Analyses Data (Mean±SD) from Study 3168

Variable	Treatment	N	Values			Changes to baseline	
			Screening	+2 wks	+6 M*	+2 wks	+6 M*
Volume [ml]	PLA	4	2.6±0.8	1.9±0.3	2.0 (n=1)	-0.8±0.9	–
	MIL	11	3.2±1.3	2.3±1.0	3.3±0.7	-1.0±0.9	-0.1±1.1
Concentration [10^6 /ml]	PLA	4	76.3±25.3	106.3±54.4	86.0 (n=1)	30.0±29.7	–
	MIL	11	64.9±31.5	79.9±40.8	82.1±25.0	15.0±25.8	14.8±40.9
Progressive Motility [†] [%]	PLA	4	60.0±8.2	57.5±5.0	60.0 (n=1)	-2.5±5.0	–
	MIL	11	49.1±12.2	54.5±16.3	57.5±17.2	5.5±15.1	7.5±15.1
Sperms alive [%]	PLA	4	93.3±2.6	91.0±1.4	96.0 (n=1)	-2.3±3.4	–
	MIL	11	92.8±3.6	91.4±3.0	94.6±2.8	-1.5±3.7	1.9±3.7
Normal morphology [%]	PLA	4	59.8±6.9	64.3±1.0	75.0 (n=1)	4.5±6.9	–
	MIL	11	70.9±10.2	62.3±9.6	66.8±7.5	-8.6±12.3	-2.7±16.3

* N = 9-10 for MIL, N = 1 for PLA (not shown)

[†] Grade IV or greater motility, as per WHO grading criteria (highest grade = highest motility).

The semen analysis results submitted by Sponsor and presented in Table 4 show some variability in sperm characteristics between patients, but in this very limited sample, lacking adequate control group at the 6 month post-treatment time point, pre-treatment to post-treatment comparisons do indicate a major adverse change for any of the 11 miltefosine patients or for any mean change in individual sperm characteristics.

The direction of the mean changes for placebo and for miltefosine differed (1) for the rates of motile sperm with a progressive motility of grade IV, and (2) for the rates of sperm with normal morphology. In both cases, a larger difference at baseline disappeared during the course of observation, and very similar values were reached post-treatment. The Sponsor believes that the results suggest a “regression-to-the-mean” phenomenon rather than a specific treatment-related effect. Further, the Sponsor concludes that these data support the assumption that a 28-day course of oral miltefosine in human patients has no clinically relevant effect on sperm viability or on spermatogenesis.

Reviewer’s comment: A comparison of observed changes between treatments is problematic due to the small number of patients (n=15), especially few placebo patients (n=4), and a generally high variation in concentration and motility which are key predictors. Due to small sample size and large standard deviations within the groups, and particularly inadequate sample size and control group at the more critical 6 month timepoint, we judge the results from this study to be inconclusive, and we do not agree with the Sponsor’s conclusion about this data.

3.2 Retrospective Analysis of Male Reproductive Potential (Study Z005)

Study Z05 was a retrospective analysis of male patients who had previously participated in Studies 0033, 3089, 3109, 3127, and 3154, which had been conducted at investigative sites in India. In these studies, male subjects had received oral miltefosine for the treatment of visceral leishmaniasis (VL).

The Sponsor decided to conduct this retrospective after the treatment phases of all efficacy and safety studies in VL in India had completed. This study was undertaken only after discussions involving the study principal investigators and the World Health Organization.

Study Rationale: Study Z005 recruited male subjects who had participated in clinical trials of miltefosine in India and who were aged 18 years and older. The data from this retrospective study was intended to support the hypothesis that oral use of miltefosine in the efficacy and safety studies did not lead to a clinically relevant impairment of fertility in these male patients in the post-treatment period.

Study Design and Procedures: The Sponsor's data base was searched for eligible male subjects and each study center was provided with lists identifying the subjects to be contacted and re-assessed. After providing the subjects with information about the purpose of the re-evaluation, the subjects was queried for sexual activity and "reproductive performance" since the end of miltefosine study in which they had participated. The key data to be collected were the subjects' description of pregnancies in the partners of former study participants.

Study Endpoints:

- a) Number of pregnancies and live births in partners of male subjects who stated that they had a female sexual partner and did not use contraceptive measures during the entire period since the end of study treatment.
- b) Occurrence of birth defects in babies born to partners of male subjects.

Reviewer's comment: There are clear limitations in the study design and methodology:

- ***This was a retrospective study, based on the recollection of male participants in previous miltefosine studies***
- ***There is no information on "reproductive performance" in the male subjects prior to drug exposure***
- ***Study 3154 included patients with a lower age limit of 12 years, the youngest patients were not expected to contribute evaluable data. Therefore, a minimal age of 18 years at the time of re-evaluation was selected as a cut-off, which further limited the amount of data that could be analyzed.***

Results: A total of 345 patients were identified in the database that matched the eligibility criteria for this retrospective analysis. Of these, 197 subjects had received miltefosine and 23 had received amphotericin B.

In total, information for 341 of 345 (98.8%) former study participants was retrieved for the evaluation of reproductive performance in the post-treatment period. Assessments were done between 11 and 57 months after initiation of miltefosine treatment (median 34 months) and between 19 and 28 months after initiation of amphotericin B treatment (median 24 months). In total, the Sponsor identified 220 study participants who defined the "relevant population" for this fertility assessment.

Table 5 summarizes the data for the overall retrospective study, for each study, and for each of the three participating centers in the multicenter studies 3109 and 3154. In the table, "c1" refers to Dr. Jha's center, "c2" to Dr. Sundar's center, and "c3" to Dr. Thakur's center.

The table has 6 columns. The columns entitled "Total", "Relevant population", "Proven fertility" and "Ongoing pregnancies" are defined herein:

- "Total" – refers to the total number of males meeting the eligibility criteria for reproductive performance assessment. For studies in which there were multiple centers, the respective "total numbers" are provided for each center. The other studies were single center only (clinical investigative site "c2" only).
- "Relevant population" – refers to the number of patients who were not without a sexual partner and/or did not use contraceptives all of the time.
- "Proven fertility" – refers to the number of patients in whom a female partner had at least one delivery or one ongoing pregnancy reported. The percentages of "proven-fertile" subjects relative to the total number of "relevant population" subjects are shown in parentheses.
- "Ongoing pregnancies" – refers to the number of pregnancies that were reported as ongoing at the time of the assessment.

Table 5: Summary Results from Study Z005: A Retrospective Analysis of Male Reproductive Potential in Phase 1 to 3 Miltefosine Studies Conducted in India

Study/ Treatment	Number of Male Patients			Number of		
	Total ^a	Relevant population ^b	Proven fertility: any delivery or pregnancy ^c	Deliveries	Babies	Ongoing pregnancies ^d
0033/ miltefosine	30	16	16 (100%)	16	21	0
3089/ miltefosine	33	22	18 (82%)	18	23	0
3109/ miltefosine	64 c1: 23 c2: 19 c3: 22	39 c1: 12 c2: 11 c3: 16	24 (62%) c1: 7 (58%) c2: 11 (100%) c3: 6 (38%)	25 c1: 7 c2: 11 c3: 7	26 c1: 7 c2: 13 c3: 6	3 c1: 1 c2: 0 c3: 2
3127/ miltefosine	32	24	21 (88%)	20	21	1
3154/ miltefosine	141 c1: 64 c2: 46 c3: 31	96 c1: 35 c2: 33 c3: 28	56 (58%) c1: 15 (43%) c2: 31 (94%) c3: 10 (36%)	52 c1: 14 c2: 31 c3: 0	53 c1: 14 c2: 32 c3: 0	7 c1: 1 c2: 0 c3: 1
ALL/ miltefosine	300	197	136 (69%)	131	144	11
3154/ amphotericin B	41 c1: 20 c2: 14 c3: 7	23 c1: 7 c2: 9 c3: 7	12 (52%) c1: 2 (29%) c2: 9 (100%) c3: 1 (14%)	11 c1: 2 c2: 9 c3: 0	10 c1: 1 c2: 9 c3: 0	1 c1: 0 c2: 0 c3: 1

^a Total - total number of males meeting the eligibility criteria for the reproductive performance assessment (for multicenter trials, the respective numbers per individual center are included as well; the center of Prof. Sundar, who conducted the single center studies, was assigned center number 2 in the multicenter studies).

^b Relevant population - number of patients who were not without sexual partner and/or did not use contraceptives all of the time.

^c Proven fertility - number of patients in whom a female partner had at least one delivery or ongoing pregnancy reported; the percentages of "proven-fertile" subjects relative to the "relevant population" subjects are shown in parentheses.

^d Ongoing pregnancies - number of pregnancies that were reported as ongoing at the time of the assessment.

Overall 69% (136 of 197 males) of the "relevant population" of miltefosine-treated patients had "proven fertility", as documented by at least one delivery or ongoing pregnancy in their female partner. In Study 3154 only, 58% (56 of 96 males) of the "relevant population" of miltefosine-treated patients had "proven fertility". In this same study, the "proven fertility" rate for amphotericin B was 52% (12 of 23 males). Thus the Sponsor concludes that the "proven fertility" rates were similar for both treatment arms in Study 3154.

There were marked differences in the reproduction rate between centers. The "proven fertility" rate in center 2 was distinctly higher than the other centers, both for the single and multi-center studies. The "proven fertility" rate for center 2 ranged between 82% and 100%, as compared to the "proven fertility" rates for center 1 (43% or 48%) and center 3 (36% or 38%).

Subjects who reported deliveries or pregnancies were considerably younger on average than Subjects who did not report pregnancies. The mean ages were 32 versus 38 years in center 1, 32 versus 43 years in center 2, and 34 versus 42 years in center 3, for subjects reporting deliveries or pregnancies, versus those not reporting deliveries or pregnancies.

Participants were queried as to the occurrence of congenital abnormalities or birth defects. One patient (study 3154 center 3, Patient ID 3) reported an abortion of a first pregnancy, which was followed by a currently ongoing second pregnancy. No malformations or other birth defects were noted.

Although semen analyses were not part of the protocol, center 3 provided summary results from semen analyses collected in 13 subjects (12 treated with miltefosine, and 1 treated with amphotericin B). In 10 of the 12 subjects treated with miltefosine, the semen analyses was described as "completely normal" with regard to sperm count, sperm viability, and sperm morphology. One miltefosine subject was reported to show "oligospermia" but this subject also reported 2 partner pregnancies in the post-study period. One other miltefosine subjects, aged 35 years at treatment and 38 years at time of semen analysis was found to have "oligospermia, decreased sperm motility, and an increased percentage of abnormal (60%) or degenerated (25%) sperm".

Conclusions of the Retrospective Study (Z005): The Sponsor concluded that the results of this retrospective re-evaluation provided strong evidence that orally administered miltefosine is unlikely to induce infertility in male patients treated for leishmaniasis. The Sponsor provides the following summary points:

- Male study participants were found to show a high reproduction rate in the post study period, both for patients treated with miltefosine and for patients treated with amphotericin B.
- Differences noted between individual centers in subject reproductive potential are possibly related to factors other than drug treatment, e.g., differences in age and socio-economic status of the patient populations.

In addition, the Sponsor believes that this conclusion is supported by post-treatment-only semen analyses that were conducted in 13 subjects (12 miltefosine and 1 amphotericin B) who had been treated for VL at center 3 in Indian trials. In 10 of the miltefosine subjects, semen analyses were reported as normal; one miltefosine subject had oligospermia but was reportedly fertile, and there was one subject in whom oligospermia was found 3 years after end of treatment.

Consultant's comments:

- 1) ***The limitations of study methodology for this retrospective analysis are obvious based on data collected through retrospective interview from the study participants using a post-study survey on reproduction rate.***
- 2) ***The support provided by such a retrospective observational survey is quite weak.***

4. Consultant's Summary Conclusions

The consultants find that the signal of male reproductive toxicity in animals is potentially clinically relevant, especially when considering that the nonclinical toxicity was observed in two species and at systemic miltefosine exposures similar to clinical therapeutic exposures. It is particularly notable that severe testicular toxicity in rats did not fully reverse at miltefosine exposures similar to mean maximum clinical therapeutic miltefosine concentrations. Further, the nonclinical data suggest an unevaluated possible anti-androgen effect of miltefosine.

The consultants also find that the available human data, including a small number of subjects who provided semen for analyses and one retrospective survey of "reproductive potential", are not sufficient to relieve the concern of potential clinical relevance. The consultants note that there has not been an adequate assessment of miltefosine on human spermatogenesis and there has been no assessment of potential effects on sex hormones in adult males.

Optimally, the clinical therapeutic dose of miltefosine should provide an exposure that provides a reasonable margin of safety from the exposure in animals that was associated with male reproductive toxicity. However, the Phase 3 efficacy and safety studies have already been completed using doses that provide little or no margin of safety. If it is impossible to repeat the Phase 3 studies using lower doses, then the options remaining for addressing the issue at this point appear to include the following:

1. Conduct additional pre-marketing studies in animals, for example, in primate, to further elucidate the male reproductive toxicity. The use of primate is limited by number of animals that can be studied.
2. Conduct a randomized, placebo-controlled, double-blind, pre-marketing study in healthy volunteers using the clinical therapeutic doses in order to directly assess the effect of 28 days of miltefosine on human spermatogenesis and male sex hormones. In this situation, it may be possible to enroll men who are planning to undergo elective sterilization, or men willing to enroll despite the risk of permanent sterility.
3. Provide major warnings in the product labeling regarding the nonclinical male reproductive toxicity findings, with a requirement to conduct a postmarketing study of the effect of miltefosine on human spermatogenesis and male sex hormones in the target population.

5. Labeling Recommendations

At this time, rather than providing specific recommendations for labeling, the consultants have provided options for addressing the unresolved safety issue (see Section 4 of this memo) and we would be pleased to engage in further discussion as necessary.

6. Recommendation for Postmarketing Studies

A clinical study, whether pre- or post-marketing, is one option to address the safety issue of male reproductive toxicity that was observed in nonclinical studies. The trial would be designed to directly assess the effects of milfetosine on human spermatogenesis and male sex hormones.

For drugs with a nonclinical testicular toxicity signal, we currently recommend a randomized, double-blind, placebo-controlled, non-inferiority study design. For chronically administered drugs, we advocate at least 12 weeks treatment, with semen analyses and male sex hormones measured at baseline, at the end of treatment, and after a 13-week off-treatment period. Because the human spermatogenic cycle is approximately 74 days, any potential adverse effects on sperm may not be observed immediately following treatment, but rather after 12-weeks off-treatment. Therefore, the primary endpoint is assessed at Week 26 of the study. As primary endpoint, we have advocated the percentage of subjects in each group with at least 50% reduction in sperm concentration. Using a non-inferiority margin of 20%, such a study usually requires 100 subjects per arm.

We refer you to the following publication for further details of such a “sperm study”, “*An evaluation of semen characteristics in men 45 years of age or older after daily dosing with tadalafil 20 mg: results of a multicenter, randomized, double-blind, placebo-controlled, 9-month study.* Hellstron WJ, Gittelman, M, Jarow J, Steidle C, McMurray J, Talley D, Watts S, Mitchell CL and McGill, JM. *European Urology* 2008 May;53(5):1058-65.”

In addition, although we are aware that there are cultural differences that may preclude sperm collection in some communities, we are prepared to share with you possible solutions that the Sponsor may adapt to increase enrollment.

Thank you for the opportunity to participate in this review. We look forward to working with you further to address any remaining issues.

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/s/

GUODONG FANG
09/10/2013

MARK S HIRSCH
09/10/2013
I concur.

AUDREY L GASSMAN
09/10/2013

**Division of Bone, Reproductive, and Urologic Products (DBRUP)
Response to Consult Request**

Tracking # 470

NDA: 204684

Drug: Miltefosine 50mg oral capsules
Applicant: Paladin Therapeutics, Inc

Date: 9/5/13

To: Sumathi Nambiar, MD,
Division Director, Division of Anti-Infective Products (DAIP)

Hala Shamsuddin, MD
Medical Officer, DAIP

From: Caren Kieswetter, MD, MPH
Medical Officer, DBRUP

Through: Christina Chang, MD, MPH
Clinical Team Leader, DBRUP

Christine P. Nguyen, MD
Deputy Director for Safety, DBRUP

I. Background:

This is a consultative review in response to the DAIP request dated June 17, 2013, concerning miltefosine. Miltefosine, a structural analog of alkyllysophospholipids, is the subject of an NDA currently under review in DAIP. It is administered orally (at a dose of 2.5 mg/kg/day and treatment duration of 28 days) for the treatment of visceral, mucosal, and cutaneous leishmaniasis.

Leishmaniasis is caused by protozoan parasites of the genus *Leishmania* and is typically transmitted through the bite of an infected female sand fly. It is endemic in 98 countries and territories with an annual incidence of 0.5 million cases of visceral leishmaniasis (VL) and 1.5 million cases of cutaneous leishmaniasis (CL).¹ Although VL has a worldwide distribution, over 90% of cases are found in five countries: India, Bangladesh, Nepal, Sudan, and Brazil.² VL is the most serious manifestation of the disease and can result in death. CL has a broad spectrum of severity but can be self-limiting. In India, the ratio of infected males to females is 4:1 and most patients are between 10 and 30 years of age.³ Most cases of leishmaniasis in the United States are diagnosed in individuals who have traveled or lived in endemic areas, for example,

¹ WHO Technical Report Series 949: Control of the Leishmaniases: Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010.

² Sundar S, Olliaro PL. Miltefosine in the treatment of Leishmaniasis: Clinical evidence for informed clinical risk management. *Therapeutics and Clinical Risk Management*. 2007;3(5):733-740.

³ Paladin Therapeutics, Inc, ASTA Medica AG. Study Report: Clinical Trial to Assess Efficacy and Safety of Orally Administered Miltefosine in Patients with Visceral Leishmaniasis, Study 3154, p 10, 5/28/1999. NDA 204684, SN0000, Module 5.3.5.1 (p 646), Original NDA Submission.

U.S. military personnel returning from Iraq or Afghanistan. Occasional cases of cutaneous leishmaniasis have been acquired in Texas and Oklahoma. No cases of visceral leishmaniasis are known to have been acquired in the United States.⁴

Currently available therapies for leishmaniasis include parenteral and intramuscular formulations, such as amphotericin B deoxycholate or liposomal amphotericin B and paromomycin, respectively. Pentavalent antimonials are no longer used due to widespread disease resistance. The only orally available treatment for leishmaniasis is miltefosine. It received marketing authorization abroad in 2002.⁵ Based upon total patient exposures reported to the German Regulatory Authorities (BfArM), approximately 90,000 patients received miltefosine from 2002 through 2011.⁶ While miltefosine's route of administration (oral) has widened access to treatment, important questions remain regarding its potential teratogenicity, reproductive toxicity in both women and men, and risk of impaired fertility in women of child-bearing age.

II. Requests From DAIP

DAIP seeks DBRUP's input on the four items listed below; DBRUP's responses are provided in the subsequent section.

- A. Evaluate the risk for female reproductive toxicities associated with Miltefosine.
- B. Evaluate the risk of female infertility associated with Miltefosine.
- C. Provide labeling recommendations for female reproductive toxicities/risk of infertility.
- D. Provide any recommendations for further postmarketing studies or surveillance that may be required.

Comment: DAIP also requests input on the impact of miltefosine on the male reproductive tract. This issue will be addressed in a separate consult.

III. DBRUP's Responses

A. Evaluate the risk for female reproductive toxicities associated with Miltefosine.

Nonclinical Data:

1. Adverse Fetal Effects: Nonclinical studies have shown that, at exposures similar to clinical exposures, miltefosine is embryotoxic and fetotoxic in rats and rabbits, and teratogenic in rats but not in rabbits.⁷ Teratogenic effects observed in fetal rats included primarily central nervous system abnormalities, cleft palate, and misshapen eyes.⁸ Given these findings and miltefosine's long terminal elimination half life of 31 days in humans, the proposed labeling (like the German labeling, Impavido®) contraindicates administration to pregnant women and advises

⁴ http://www.cdc.gov/parasites/leishmaniasis/gen_info/faqs.html

⁵ Sundar S, Olliaro PL. Miltefosine in the treatment of Leishmaniasis: Clinical evidence for informed clinical risk management. *Therapeutics and Clinical Risk Management*. 2007;3(5);733-740.

⁶ Paladin Therapeutics, Inc, Clinical Overview, p 43, 4/2013. NDA 204684, SN 0006, Module 2.5, 4/19/2013, SD 7.

⁷ Sindermann H, Engel J. Development of Miltefosine as an oral treatment for leishmaniasis. *Trans R Soc Trop Med Hyg*. Dec 2006;100 Suppl 1;S17-S20. ePub 26 May 2006.

⁸ Paladin Therapeutics, Inc, Study Report: Examination of the influence on the Fertility and General Reproductive Performance as well as the Early Embryonic Development after Oral Administration in Female Wistar Rats. Module 4.2.3.5.1, Original NDA Submission.

- women of child bearing potential to use effective contraception during treatment and for (b) (6) months after discontinuation.⁹
2. Reproductive Tract Tumors: We defer this to the DAIP pharmacology/toxicology and clinical teams.

Comment: Findings from the nonclinical data are included in the proposed labeling submitted in this NDA.

Clinical Trial Data: All but one of the pivotal clinical studies included in the Applicant's NDA submission enrolled female subjects greater than 11 years of age. In these studies combined there were 144 such female subjects (89 in Study 3154, 21 in Study Z022, 8 in Study Z020a, 9 in Study Z020b, 9 in Study Soto, and 8 in Study 3168).¹⁰ In all these studies, miltefosine was given at a target dose of 2.5 mg/kg/day for 28 days regardless of whether the indication was cutaneous, mucosal, or visceral disease. All women were required to use some form of birth control for the duration of treatment and for 2 months post treatment. The duration of these studies was 7 months—1 month of treatment plus 6 months of follow up. However, at site #2 of Study 3154, patients were followed for an additional 6 month (a total of 12 months follow-up post-treatment). Thus, the 43 female patients at this site (30% of the female subjects in the overall clinical program) had a total of 12 months follow-up post-treatment.

Comments: In the clinical trials, data relevant to the impact of miltefosine on pregnancy are extremely limited for the following reasons:

1. *Women were required to use a form of birth control both during and post-treatment.*
2. *No pregnancies were reported in any of these pivotal clinical studies during the treatment or follow-up period.*¹¹

Postmarketing Data: Three pregnancies were reported in the 1st Periodic Safety Update Report (PSUR 1) to the German Regulatory Authority (BfArM).¹² These pregnancies occurred in female patients who received miltefosine in Phase IV studies. However, the total number of females enrolled in these studies is not provided. No case report forms or details were included in the Applicant's NDA submission. The pregnancy data are summarized in Table 1 below:

Table 1 Pregnancy Information (Postmarketing)

Investigator / Study	Pat ID / Pat. No.	Treatment period	Estimated time of conception	Pregnancy outcome
Dr. Nath, (Z013, India)	(b) (6)	8 Feb – 8 Mar 2003	(b) (6) after end of treatment period	(b) (6) healthy child birth (gest. wk: 39)
Dr. Mukherjee, (Z013, India)	(b) (6)	27 Apr – 19 May 2003	(b) (6) after end of treatment period	(b) (6) healthy child birth (gest. wk: 40)
Dr. Rijal, I(Z013b, Nepal)	(b) (6)	21 Mar – 17 Apr 2004	(b) (6) (calculated from ultrasound)	(b) (6) healthy child birth (gest. wk: 42)

⁹ Paladin Therapeutics, Inc, Annotated Draft Labeling, Module 1.14.1.2, 4/19/13, SD 7.

¹⁰ Paladin Therapeutics, Inc, Response to IR, dated 8/13/13, SD 16.

¹¹ *Ibid.*

¹² Paladin Therapeutics, Inc, Zentaris, Impavido 1st Periodic Safety Report, submitted under NDA 204684, received 9/27/2012; Module 5.3.6, Original NDA Submission.

Outcomes of pregnancy for all three cases were reportedly healthy neonates without apparent abnormalities. However, the small number of reported pregnancies provides little reassurance to disregard the potential risks indicated by nonclinical studies.

To date, it is estimated that approximately 100,000 patients have received treatment for leishmaniasis with miltefosine and it is likely that about 20,000 of these patients have been women, taking into account a lesser incidence among women. Among approximately 20,000 women, it is expected that more than the three reported pregnancies have occurred, considering the failure rate of birth control even under conditions of optimal access and typical use. Additionally, under-reporting is likely because reporting pregnancies that occur while on miltefosine is voluntary outside the setting of clinical trials. It is not possible to make any assumptions regarding the outcome of pregnancies that may have occurred post-marketing.

Comment: The potential for human teratogenic effect associated with miltefosine exposure cannot be determined from limited data on the three reported pregnancies during clinical studies. At this time, without additional data, we remain concerned about the potential for human fetal embryotoxicity and teratogenicity, especially because of a lack of safety margin and the fact that the target population will include women of reproductive age potential. See our responses to questions #3 and #4 for our recommendations on risk mitigation and assessment, respectively.

B. Evaluate the risk of female infertility associated with Miltefosine.

Nonclinical Data: Nonclinical studies have also shown that, at exposures less than or similar to clinical exposures, miltefosine results in atretic follicles in female dogs.¹³ At higher exposures female dogs (and rats) appeared morphologically anestrus.^{14, 15} The appearance of follicles and the estrus cycle both returned to normal during a 6-week recovery period.¹⁶ These nonclinical studies raise concerns that loss of ovarian follicles may occur in humans, which may subsequently result in decreased fertility. However, they also suggest that effects on ovarian follicles are reversible following cessation of miltefosine. This information should be included in the product labeling.

Clinical Trial Data: It is not feasible to assess miltefosine's effect on female fertility because of concomitant use of contraception, which is indicated given miltefosine's potential teratogenic effects.

Postmarketing Data: Under-reporting of pregnancies hinders this assessment. The three pregnancies reported in postmarketing clinical studies (see Table 1), occurred during treatment or shortly thereafter. Three case reports are insufficient to enable assessment of any effect of miltefosine use on fertility. It is important to note, however, that it is not feasible to perform a clinical study of miltefosine's effect on female fertility given its potential teratogenic effects.

¹³ Paladin Therapeutics, Inc, Nonclinical Overview, pp 20-21. Module 2.4, Original NDA Submission.

¹⁴ Paladin Therapeutics, Inc, Study Report: Examination of the influence on the Fertility and General Reproductive Performance as well as the Early Embryonic Development after Oral Administration in Female Wistar Rats. Module 4.2.3.5.1, Original NDA Submission.

¹⁵ Paladin Therapeutics, Inc, Nonclinical Overview, pp 20-21. Module 2.4, Original NDA Submission.

¹⁶ *Ibid.*

Comment: Given the paucity of human data, the potential for impaired female fertility with miltefosine is defined at this time. In general, the effect on fertility cannot be inferred from drug effect on ovarian follicles. Fertility depends on multiple factors, including function of the pituitary-gonadal axis, structural integrity of the female reproductive tract, maternal health status, and male factors. Assessing for drug-related effect on fertility would need to adequately control for all of these factors.

For miltefosine, we are reassured by the reversibility of ovarian atresia and resumption of estrus cycle in the animals off drug. Because the proposed dosing regimen for miltefosine is 28 days (i.e., not chronic), we do not have significant concerns of permanent infertility, assuming ovarian atresia occurs in humans. Furthermore, women must use effective contraception during and for a period of time after treatment. Therefore, we do not believe any temporary fertility impact from reduced ovarian follicles, if that occurs in humans, would be a relevant risk to women requiring treatment with miltefosine.

C. Provide labeling recommendations for female reproductive toxicities/risk of infertility.

If miltefosine is approved in this review cycle, DBRUP has the following recommendations for labeling.

Adverse Fetal Effects:

1. Over all, we agree with the proposed labeling related to adverse fetal effects in the Contraindications, Warnings/Precautions, and Pregnancy sections. In addition:
 - a. The Warnings and Precautions should be revised with the subtitle “Adverse Fetal Effects” in place of (b) (4). The Warning verbiage should be revised to clearly describe the adverse fetal effects seen in animals and the importance of effective contraception. The Warning should advise women to use effective contraception during miltefosine treatment and to continue effective contraception for the recommended duration following completion of miltefosine treatment. Recommendations regarding duration of female contraceptive use following treatment with miltefosine vary. Optimal duration for post-treatment contraceptive use appears to be 4 months.¹⁷ However, we defer to Clinical Pharmacology for the final determination of the recommended time interval (b) (4).
 - b. The section on “Use in Specific Populations” should be revised in the spirit of the near final Pregnancy and Lactation Labeling Rule. Consultation with the Pediatric and Maternal Health Staff is recommended.
 - c. The information on adverse fetal effects and the need for effective contraception should appear in the section on “Patient Counseling Information.”
2. We note that three reported pregnancies are insufficient to enable assessment of miltefosine’s effect pregnancy outcome. Such a small number of reported pregnancies provides little reassurance to disregard the potential risks indicated by

¹⁷ Dorlo TPC, et al. Translational pharmacokinetic modeling and simulation for the assessment of duration of contraceptive use after treatment with miltefosine. *J Antimicrob Chemother.* 2012;67:1996-2004.

nonclinical studies. Therefore, we do not suggest the inclusion of data from these 3 pregnancies in labeling.

Finally, we recommend a Medication Guide under 21 CFR 208 to inform patients of adverse fetal effects and the importance of effective contraception.

Ovarian Follicle Atresia:

We do not believe the nonclinical findings of ovarian follicular atresia, which were reversible off drug, warrant inclusion under Warnings. This information would most appropriately appear in section 8.3, in the spirit of the near-final Pregnancy and Lactation Labeling Rule. We suggest including the following statement in section 8.3: "There is insufficient information to adequately assess the potential for impaired fertility associated with the use of miltefosine."

D. Provide recommendations for any further postmarketing studies or surveillance that may be required.

Adverse Fetal Effects:

- Establish a voluntary pregnancy and birth registry to capture postmarketing data, including data from current or future studies. We suggest consulting the Pediatric and Maternal Health Team regarding details of planning for the registry. The following specific data would be useful to obtain from this registry to assess human teratogenic effects:
 - Number of Women of Childbearing Age Enrolled
 - Form of Birth Control During Treatment
 - Dates of Treatment Period
 - Pregnancy During the Year Following Treatment
 - Estimated Date of Conception
 - Pregnancy Outcome
- Enhanced Pharmacovigilance: We recommend that the sponsor proactively collected cases of pregnancy occurring within 9 months of drug exposure and submit case reports and analysis of data with each PSUR submission.
- We recommend the following postmarketing requirement if miltefosine is approved: a drug-drug interaction (DDI) study to evaluate the effect of miltefosine on hormonal contraceptive exposure and efficacy. It is expected that the concomitant use of hormonal contraceptives and miltefosine would be common practice. Consultation with your Clinical Pharmacology team regarding the design of this study is suggested.

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/s/

CAREN KIESWETTER
09/05/2013

CHRISTINA Y CHANG
09/05/2013

CHRISTINE P NGUYEN
09/05/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 12, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Gregory Dibernardo RPM
DAIP

Subject: QT-IRT Consult to NDA 204684

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated June 14, 2013 regarding labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT consult review for IND 105,430 (TQT waiver request, January 29, 2010)
- QT-IRT consult review for IND 105430 (November 4, 2010, addendum)
- QT-IRT consult review (February 24, 2011)

QT-IRT Comments for DAIP

As we previously stated, material submitted from study 3154 is insufficient to rule out a clinically relevant effect of miltefosine on the QT interval. Once the post-marketing study is submitted we will provide labeling language according to the results of the QT assessment.

BACKGROUND

QT-IRT granted a waiver for a formal TQT study because of safety and tolerability issues.

On November 4, 2010 the team reviewed the material submitted from study 3154 and concluded that this information was insufficient to rule out a clinically relevant effect of miltefosine on the QT interval. QT-IRT advised that a QT assessment be considered as part of a post-marketing requirement (please refer to QT-IRT consult February 24, 2011). The review division determined that a dedicated QT study could be conducted as a post-marketing requirement.

Thank you for requesting our input into the development of this product under NDA 204, 684 . We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

MONICA L FISZMAN
08/12/2013

KEVIN M KRUDYS
08/12/2013

NORMAN L STOCKBRIDGE
08/12/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204684	NDA Supplement #: Not Applicable	Efficacy Supplement Type: Not Applicable
Proprietary Name: Impavido Established/Proper Name: (miltefosine) Dosage Form: Capsule Strengths: 50 mg		
Applicant: Paladin Therapeutics, Inc. Agent for Applicant: Fast Track Drugs and Biologics, LLC		
Date of Application: September 26, 2012 Date of Receipt: September 27, 2012 Date clock started after UN: Not Applicable		
PDUFA Goal Date: March 27, 2012	Action Goal Date (if different): Same	
Filing Date: November 26, 2012	Date of Filing Meeting: November 1, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME (1)		
Proposed indications: Treatment o of cutaneous, mucosal and visceral leishmaniasis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track-Granted 5/21/10 <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation-Granted 10/10/06 <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): Not Applicable				
List referenced IND Numbers: 105430				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>		X		
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				Not Applicable
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Signed by Samira Sakhia. Paladin Therapeutics, Inc.

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 7</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	
Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> eCTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible</p>		X		Data from one study was not submitted

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	NDA submitted on 9/26/12, received 9/27/12.
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			Revised and updated submitted on 10/10/12 received 10/12/12.
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			Signed by Samira Sakhia. Paladin Therapeutics, Inc.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				

<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674." <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></i>	X			Signed by Samira Sakhia. Paladin Therapeutics, Inc.
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></i>	X			Signed by Samira Sakhia. Paladin Therapeutics, Inc.
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	Clinical Filing Review made designation, this requirement is not applicable.
Pediatrics	YES	NO	NA	Comment

PREA Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>		X		Orphan Designation-Granted 10/10/06.
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Submitted on 11/8/12 to NDA (IND 105430) Proprietary Name Request Conditionally Acceptable 2/8/11.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		X		Due to Refuse to File
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)		X		Due to Refuse to File
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?		X		Due to Refuse to File
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)			X	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date: Pre-NDA Meeting occurred on 1/13/12.	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 1, 2012

NDA #: 204684

PROPRIETARY NAME: Impavido

ESTABLISHED/PROPER NAME: miltefosine

DOSAGE FORM/STRENGTH: Capsules, 50 mg

APPLICANT: Paladin Therapeutics, Inc.

PROPOSED INDICATIONS: Treatment of cutaneous, mucosal, and visceral leishmaniasis

BACKGROUND:

NDA 204684 was submitted by Paladin Therapeutics, Inc. (foreign applicant) and has selected Fast Track Drugs and Biologics, LLC as their U.S. Agent. The Applicant is requesting a 6 month Priority Review for NDA 204684. NDA 204684 for Impavido (miltefosine) corresponds to the information submitted to FDA under **IND 105430**. IND 105430 was granted Orphan Product Designation on 10/10/06, Fast Track Designation on 5/21/10, and a Proprietary Name Request was determined to be Conditionally Acceptable as stated in a 2/8/11 FDA communication. NDA 204684 would be considered a new molecular entity (NME) and an Advisory Committee would be needed for this review cycle.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gregory F. DiBernardo	Y
	CPMS:	Maureen P. Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	Pending		
Clinical	Reviewer:	Hala Shamsuddin	Y
	TL:	Thomas Smith	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	Not Applicable	

	TL:	Not Applicable	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Shukal Bala	Y
	Acting TL:	Lynette Berkeley	N
Clinical Pharmacology	Reviewer:	Seong Jang	Y
	TL:	Kimberly Bergman	Y
Biostatistics	Reviewer:	Lan Zeng	Y
	TL:	Karen Higgins	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	James Wild	Y
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
Product Quality (CMC Drug Product)	Reviewer:	Mark Seggel	Y
	TL:	Dorota Matecka	Y
Product Quality (CMC Drug Substance)	Reviewer:	Anamitro Banerjee	Y
	TL:	Dorota Matecka	Y
CMC Biopharmaceutics	Reviewer:	Mark Seggel	Y
	TL:	Angelica Dorantes	N
Facility Review/Inspection: OC/OSI/DGCPC/GCPAB	Reviewer:	Kassa Ayalew	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Alek Winiarsk	Y
	TL:	Todd Bridges	N
OSE/OMEPRM/DRISK (REMS)	Reviewer:	Kate Heinrich Oswell	Y
	TL:		

OSE/PMS	Reviewer:	Karen Townsend	Y
	TL:		
OSE/OPE/DEPIII	Reviewer:	Andrew Mosholder	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Not Applicable	
	TL:	Not Applicable	
Bioresearch Monitoring (OSI)	Reviewer:	Not Applicable	
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Not Applicable	
	TL:		
CMC Labeling Review	Reviewer:	Not Applicable	
	TL:		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: Comments regarding Data Sets will be communicated to Applicant in Refuse to File Letter.</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Information request sent to Applicant on 10/23/12, Applicant Response submitted on 11/12/12.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Clinical comments to be included in Refuse to File letter.	
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: NME, Priority Review Application will trigger Advisory Committee. <i>If no, for an NME NDA or original BLA , include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: Scheduled for 2/26/13, prior to Refuse to File <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY Comments: Information request sent to Applicant on 10/23/12, Applicant Response submitted on 11/12/12. Clinical Microbiology comments to be included in Refuse to File letter.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments: No comments to be issued to Applicant	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>BIostatISTICS</p> <p>Comments: Biostatistics will communicate Refuse to File issues to Applicant in Refuse to File letter.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input checked="" type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: No comments to be issued to Applicant, but labeling will eventually need revisions.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: CMC comments to be included in Refuse to File letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments: No EA submitted.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology</u> (for sterile products)</p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: No labeling comments at this time.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Edward Cox, M.D., Director Office of Antimicrobial Products</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 12/27/12 (Due to Refuse to File, no meeting will occur)</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: (Due to Refuse to File, no additional NDA meetings will occur)</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input checked="" type="checkbox"/>	<p>The application is unacceptable for filing. Explain why: The submitted datasets do not allow a meaningful review of the efficacy and safety data, see Refuse to File letter for additional details.</p>
<input type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p>

	<input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input checked="" type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
11/26/2012

MAUREEN P DILLON PARKER
11/26/2012