

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204684Orig1s000

Trade Name: Impavido

Generic Name: Miltefosine

Sponsor: Paladin Therapeutics Inc.

Approval Date: March 19, 2014

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

- Visceral leishmaniasis due to *Leishmania donovani*.
- Cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*.
- Mucosal leishmaniasis due to *Leishmania braziliensis*.

Limitations of use: *Leishmania* species evaluated in clinical trials were based on epidemiologic data. There may be geographic variation in the response of the same *Leishmania* species to IMPAVIDO. The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

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APPROVAL LETTER



NDA 204684

NDA APPROVAL

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

Dear Dr. Berman:

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

We acknowledge receipt of your amendments dated June 7, 10, 11, 26, and 27, July 10 and 29, August 9, 13, 15, 19 and 22 (2), October 14, 17 and 23, November 13 and 15, 2013; and January 3, February 3, 7, 20 (2), 24, and 27, and March 5 (2), 2014.

This new drug application provides for the use of Impavido (miltefosine) Capsule, 50 mg, for treatment of visceral leishmaniasis due to *Leishmania donovani*, cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis* and mucosal leishmaniasis due to *Leishmania braziliensis*.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on February 24, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with six of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204684.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug or biologic application. When redeeming this priority review voucher, you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, **PRV 204684**. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, see FDA's guidance, *Tropical Disease Priority Review Vouchers*, at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf>.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Gregory F. DiBernardo
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6223
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

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

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of teratogenicity and impaired spermatogenesis, and to assess a signal of a serious risk of QT prolongation. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

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

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

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

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

Submit the protocols to your IND 105430, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

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

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

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

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

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

The timetable you submitted on March 5, 2014, states that you will conduct this study according to the following schedule:

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

Submit clinical protocols to your IND 105430 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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

Sincerely,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

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

/s/

JOHN J FARLEY
03/19/2014