

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY REVIEW**

Date: September 13, 2013

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Subject: Review to determine if a REMS is necessary

Drug Name(s): Impavido (miltefosine)

Therapeutic class & dosage form: Antileishmanial agent

OND Review Division: Division of Anti-infective Products

Application Type/Number: NDA 204684

Application received: April 19, 2013

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Applicant/sponsor: Paladin Therapeutics, Inc

OSE RCM #: 2013-1178

TSI #: n/a

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1 INTRODUCTION

This review by the Division of Risk Management evaluates if a Risk Evaluation and Mitigation Strategy (REMS) is needed for the antileishmanial agent Impavido (miltefosine). The proposed indications for miltefosine includes treatment of adult and adolescent patients with visceral, cutaneous or mucosal leishmaniasis.

Paladin Therapeutics, Inc did not submit a Risk Evaluation and Mitigation Strategy (REMS) or risk management plan.

1.1 BACKGROUND

Leishmaniasis is a disease caused by infection with *Leishmania* parasites, spread by bite from infected sand flies. Leishmaniasis disease can be cutaneous (involving skin) or visceral (involving internal organs). Cutaneous leishmaniasis can spread to the mucous membranes of the nose, mouth or throat, resulting in mucosal leishmaniasis.

Leishmaniasis is found on every continent except Australia and Antarctica. In the Eastern Hemisphere, leishmaniasis occurs in Asia, the Middle East, Africa, and southern Europe. In the Western Hemisphere, leishmaniasis occurs in Mexico, and Central and South America. Leishmaniasis generally does not occur in the United States (US), although rare cases of cutaneous leishmaniasis have been contracted in Texas and Oklahoma. Residents of the United States who contract leishmaniasis generally do so outside of the US, while on travel to endemic areas. Based on our conversation with an Army expert on leishmaniasis, the incidence of leishmaniasis in the US is likely fewer than 100 cases yearly, almost all cases are contracted outside the US.

Currently, AmBisome (liposomal amphotericin) is the only FDA-approved therapy for visceral leishmaniasis. There are no approved treatments for cutaneous leishmaniasis and mucosal leishmaniasis. Besides the use of AmBisome, treatment of leishmaniasis is accomplished off-label with high-dose fluconazole, and Pentostam (sodium stibogluconate) (not approved in the US; investigational drug used for recalcitrant cases). The FDA is considering an application for miltefosine, a new antileishmanial agent that inhibits cytochrome C oxidase and is cytotoxic to *Leishmania* parasites.

1.2 REGULATORY HISTORY

Paladin Therapeutics submitted an application April 19, 2013 to the FDA for miltefosine, an antileishmanial agent, for the following proposed indications in adult and adolescent patients:

- Visceral leishmaniasis due to *Leishmania donovani*.
- Cutaneous leishmaniasis due to members of the *Leishmania* (*L*) *viannia* (*v*) subgenus (*L.v. braziliensis*, *L.v. guyanensis*, *L.v. panamensis*).
- Mucosal leishmaniasis due to *L.v. braziliensis*, *L.v. guyanensis*, and *L.v. panamensis*.

The following are regulatory milestones pertinent to the application:

- September 26, 2012—New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Impavido (miltefosine) Capsule, 50 mg.
- November 28, 2012—Refuse to file letter sent to sponsor citing numerous deficiencies in the datasets submitted in the application.
- April 19, 2013—Paladin Therapeutics submitted an application to the FDA for miltefosine.
- May 28, 2013—FDA determined that the application should receive priority review and that the sponsor is eligible to receive a tropical disease voucher.
- June 18, 2013—Filing communication sent to sponsor accepting the application for review, and granting priority review for the application.

Miltefosine was first approved in India in 2002. Since then, miltefosine has received marketing authorization in 13 additional countries¹. The sponsor estimates that, based on sales, about (b) (4) patients have received miltefosine worldwide from 2002 to November 2011.

2 MATERIALS REVIEWED

We reviewed the following:

- Application submitted April 19, 2013.
- FDA’s May 28, 2013 determination that the application should receive priority review and that the sponsor is eligible to receive a tropical disease voucher.
- July 17, 2013 teleconference with Dr. Peter Weina, Army infectious disease leishmaniasis specialist who operates the Army’s diagnostic laboratory for leishmaniasis.
- July 18, 2013 teleconference with Nancy Maisel, Air Force officer who operates the Air Force Specialty Pharmacy Program at Wright-Patterson Air Force Base.
- Discipline handouts from mid-cycle meeting for NDA 204684, meeting held July 19, 2013.
- Sponsor’s July 29, 2013 response to DRISK’s Information Request regarding expected usage, pregnancy exposure data, and rationale for not proposing a REMS to mitigate the risk of teratogenicity.
- Sponsor’s August 19, 2013 response to DAIP’s Information Request regarding women of childbearing potential enrolled in the clinical trials, pregnancy exposure data, and pregnancy outcomes in clinical use in other countries.
- Periodic Safety Update Reports (PSURs) 1-8 reporting on safety during marketing 2004-2011 (reporting on marketing since European birth date, November 19, 2004).

¹ Miltefosine has been approved for marketing in Argentina, Bangladesh, Bolivia, Columbia, Ecuador, Germany, Guatemala, Honduras, Mexico, Nepal, Pakistan, Paraguay, and Peru.

- Summary of Product Characteristics containing the Company Core Safety Data.
- Draft clinical review by Hala Shamsuddin, M.D., Medical Officer for the application.
- Consult clinical review of reproductive toxicities of miltefosine by Caren Kieswetter, M.D., Medical Officer in Division of Bone, Reproductive, and Urologic Products (DSRUP), September 5, 2013.
- Centers for Disease Control and Prevention online information about leishmaniasis, URL <http://www.cdc.gov/parasites/leishmaniasis>; accessed July 1, 2013.
- Centers for Disease Control and Prevention online information about amebic meningoencephalitis, URL <http://www.cdc.gov/parasites/naegleria>; accessed July 25, 2013.
- Visvesvara GS, Free-living amebae as opportunistic agents of human disease. *Journal of Neuroparasitology*; Vol 1 (2010).

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM²

Visceral leishmaniasis

The data submitted in support of the visceral leishmaniasis indication were derived from two trials; one trial was conducted in India, and the other trial was conducted in Ethiopia. The trial in India was a 3-center, Phase 3, randomized, open-label trial in 398 patients with visceral leishmaniasis. Patients were treated either with intravenous amphotericin 15 mg/kg every other day for 30 days (99 patients) or oral miltefosine 2.5 mg/kg/day for 28 days (299 patients). Efficacy was assessed at end of therapy and 1 and 6 months after the end of therapy. The primary efficacy endpoint was the cure rate 6 months after end of therapy. There were similar cure rates in the amphotericin and miltefosine groups at the end of therapy (98% each). There were two deaths (one due to bacterial meningitis and one from unknown cause) in the miltefosine-treated patients, and no deaths in the amphotericin-treated patients. The FDA review of the data showed more treatment failures in the miltefosine-treated patients, compared to the amphotericin-treated patients.

The trial in Ethiopia was a single-center, Phase 2/3, open-label trial in 580 male patients with visceral leishmaniasis. Patients were treated either with intramuscular sodium stibogluconate 20mg/kg daily for 30 days (290 patients) or oral miltefosine 100 mg daily for 28 days (290 patients). Efficacy was assessed at 6 months from the institution of therapy. There were similar cure rates in the sodium stibogluconate and miltefosine groups at the end of therapy (82.2% and 79.5%, respectively). There were 15 deaths in the miltefosine-treated patients, and 34 deaths in the sodium stibogluconate-treated patients. The difference in deaths was statistically significant.

² Efficacy summary presented here is adapted from the statistics discipline mid-cycle handout, July 19, 2013.

Cutaneous leishmaniasis

The data submitted in support of the cutaneous leishmaniasis indication were derived from a randomized, double-blind, placebo-controlled, 2-center trial in 133 patients with cutaneous leishmaniasis. Patients received placebo (44 patients) or miltefosine 2.5 mg/kg/day (89 patients). Most of the patients (90%) were male. The patients receiving miltefosine were more likely to be cured of cutaneous leishmaniasis compared to patients who received placebo (greater than 2-fold improvement in cure rate).

Three other trials compared miltefosine to sodium stibogluconate for cutaneous leishmaniasis. Two of the trials showed statistically insignificant improvement in the cure rate in patients who received miltefosine, and one trial showed statistically significant improvement in the cure rate in patients who received miltefosine.

Mucosal leishmaniasis

The data submitted in support of the mucosal leishmaniasis indication were derived from a non-comparative single-center trial in 79 patients, 73% of whom were male. The sponsor reported a 62% cure-rate with miltefosine treatment.

3.2 SAFETY CONCERNS³

The most frequently reported and/or most significant adverse events summarized by the review team at the mid-cycle meeting for the application included gastrointestinal effects (nausea, vomiting, diarrhea, dyspepsia), neurological effects (dizziness, headache, somnolence), skin effects (pruritus, one case of Stevens Johnson Syndrome), renal function impairment (by laboratory report), and probable teratogenicity, including craniofacial abnormalities, based on animal (rat) evidence.

Mean serum creatinine increased in patients receiving miltefosine, but increased creatinine did not result in discontinuation of therapy. Miltefosine caused a smaller increase in serum creatinine compared to amphotericin. Because miltefosine has a long half-life, increased serum creatinine occurred after therapy had been completed in some patients.

Post marketing reports from the 15 countries where miltefosine is approved include reports of renal impairment, diarrhea, vomiting, decreased platelets, epididymitis, and testicular pain. A post marketing labeling change to incorporate rare instances of thrombocytopenia was made in 2007. The labeling change was made based on a literature report of three cases of thrombocytopenia. The third PSUR covering November 2005 to May 2006 reported a labeling change to change the frequency of nausea from “common” to “very common”. Wording was also incorporated into labeling to instruct providers that in case of prolonged vomiting, sufficient fluid intake must be ensured to avoid dehydration and consequently the risk of an impaired renal function.

Three pregnancies have been reported in the post marketing setting. The conceptions occurred 2 weeks after the start of therapy, 2 weeks after the end of therapy, and 3

³ Safety summary presented here is adapted from the presentation of data by H.Shamsuddin at the mid-cycle meeting for the application July 19, 2013, and from postmarketing data reported in PSURs 2004-2011.

months after the end of therapy. All three pregnancies resulted in apparently healthy babies.

3.3 ANTICIPATED USE OF MILTEFOSINE

The sponsor was asked to estimate the US use of miltefosine for leishmaniasis. The sponsor estimated that the total US use of miltefosine is likely to be about 75 patients yearly, with one-half of the patients being civilians and one-half of the patients being in the military. The sponsor estimates that one-half of the civilians would likely be female, and 75% of the female civilians (~13 patients yearly) would likely be women of childbearing potential.

Reviewer comment: The sponsor's estimate of use of miltefosine in fewer than 100 US patients yearly for leishmaniasis is consistent with the information provided by Dr. Peter Weina, Army infectious disease leishmaniasis specialist who operates the Army's diagnostic laboratory for leishmaniasis. Based on the specimens submitted to the diagnostic laboratory, Dr. Weina estimated that about 40 to 60 cases occur in the US yearly, with 11% of the positive cases being submitted for female patients.

In addition to the use of miltefosine for leishmaniasis, miltefosine would likely be used off-label to treat amebic meningoencephalitis.⁴ Since 1962, 0 to 8 cases of amebic meningoencephalitis have been reported each year. Most (76) of the 128 cases of amebic meningoencephalitis reported since 1962 have occurred in boys 5 to 19 years of age. Since 1962, only 14 cases have been reported for females 10 to 54 years of age.⁵ Therefore, the anticipated use of miltefosine to treat women of childbearing potential with amebic meningoencephalitis would likely be less than 1 patient yearly.

3.4 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The sponsor did not propose risk management measures beyond routine measures, that is, labeling and routine pharmacovigilance. There are no risk mitigation plans in place for miltefosine in other regulatory jurisdictions. The Summary of Product Characteristics containing the Company Core Safety Data contains a contraindication for use during pregnancy and for use in women of childbearing potential who do not use reliable contraception during and up to ⁶₄ months after treatment.

Draft proposed labeling submitted with the application contains contraindications for use in pregnancy, and in patients with Sjögren-Larsson syndrome, pre-existing severe or life-threatening liver or kidney dysfunction, or hypersensitivity to miltefosine or any of its excipients. The draft proposed labeling includes warnings and precautions for vomiting, diarrhea and for liver function and kidney function impairment.

4 DISCUSSION OF A REMS FOR MILTEFOSINE

RISK to be Considered for Mitigation

⁴ CDC information on treatment of amebic meningoencephalitis. URL: <http://www.cdc.gov/parasites/naegleria/treatment-hcp.html>. Accessed July 25, 2013.

⁵ CDC online information about amebic meningoencephalitis, URL <http://www.cdc.gov/parasites/naegleria/>; accessed July 25, 2013.

Most of the adverse events reported with miltefosine are appropriate for routine (i.e., labeling and pharmacovigilance) risk management. The only risk under consideration for a REMS is the potential fetotoxic and teratogenic effect of miltefosine. The evidence for potential harm is present in rabbits, and rats. In rats and rabbits, miltefosine was fetotoxic and miltefosine was teratogenic in rats. Malformed rat fetuses had craniofacial abnormalities including cleft palate, and misshapen eyes. Teratogenic effects were not found in rabbits. There are no human data, beyond the three apparently normal babies born to mothers who received miltefosine during pregnancy. The cases were reported in the post marketing setting.

REMS Elements to be Considered for Miltefosine

A REMS can include a communication plan to communicate risk to prescribers, a Medication Guide to communicate risk to patients, and/or elements to assure safe use. Elements to assure safe use can include education, training, and/or certification of prescribers, dispensing through certified pharmacies, administration of the drug only in certain healthcare settings (e.g., hospitals), dispensing to patients only after demonstration that safe-use conditions have been met, monitoring of patients, or enrollment of patients in a registry. Elements to assure safe use are usually restrictive; that is, a system must be put into place to ensure that the REMS requirements are met. The system put into place to ensure that the REMS requirements are met usually enforces REMS requirements at the point of dispensing. In this case, elements to assure safe use could be put into place to be sure that women of childbearing potential are not pregnant at the time the prescription is filled. This would require, at a minimum, education and certification of prescribers, certification of pharmacies, and a required negative pregnancy test prior to dispensing.

A Medication Guide could be used to communicate risk to patients. A Medication Guide can be a part of a REMS, but can be instituted as part of labeling in the absence of a REMS. The only difference with including a Medication Guide within a REMS is that the sponsor generally must demonstrate in the REMS Assessment reports that patients understand the risk message contained in the Medication Guide.

Considerations for Miltefosine

A REMS for miltefosine must take into account the rarity of occurrence of leishmaniasis in the US, resulting in inexperience of US infectious disease specialists with leishmaniasis, the varied healthcare delivery systems that will administer treatment, and the long half-life of miltefosine, a half-life that extends the period of teratogenic risk past the period of treatment.

Rarity of Leishmaniasis and Healthcare Delivery Systems for Treatment

Leishmaniasis occurs rarely in US residents. There are fewer than 100 cases yearly, with about one-half of the cases occurring in US military personnel. We asked Dr. Weina about the protocol for treating leishmaniasis in military personnel; that is, whether an infected person in the military would be transferred from the field to an in-patient non-combat theater setting for treatment. Dr. Weina stated that an infected person in the military likely would not be transferred for treatment, but would more likely be treated

where diagnosed. Any risk mitigation protocol would need to encompass military patients, including those patients who would be treated in a combat theater.

The rarity of leishmaniasis would make it difficult to conduct an assessment of the success of the Medication Guide in communicating risk. The sponsor would need to survey a sufficient number of patients to establish whether or not patients understand the risk. This would be hard to accomplish with very few patients using miltefosine (only a subset of the fewer than 100 patients who contract leishmaniasis yearly would be treated with miltefosine), half of whom are likely to be in the military.

We discussed the interface of the Department of Defense healthcare services and REMS with Nancy Maisel, an Air Force officer who operates the Air Force Specialty Pharmacy Program at Wright-Patterson Air Force Base. The Department of Defense interfaces with REMS in different ways, depending on the location. Dr. Maisel assists healthcare providers who work at Wright-Patterson Air Force Base, and those outlying bases who receive support services from Wright-Patterson Air Force Base. Dr. Maisel helps the providers navigate the logistics of REMS to obtain pharmaceuticals that have restrictive REMS. However, not all Air Force bases staff a position like Dr. Maisel's. Furthermore, the other service branches do not have a position equivalent to Dr. Maisel's position. Therefore, any risk mitigation protocol would need to encompass the differences within the Department of Defense in delivering healthcare, and interfacing with REMS.

Leishmaniasis could also occur in State Department personnel or their families while stationed in endemic countries. State Department personnel and their families receive healthcare, including pharmaceuticals, both from domestic providers, and from non-US providers in the country of the State Department facility. Some jurisdictions do not permit shipment of pharmaceuticals from the US to the State Department personnel. A risk mitigation protocol mandated by the FDA would not apply to foreign providers. Any risk mitigation protocol would need to encompass State Department personnel and their families receiving their healthcare services from domestic providers, but must also consider that not all healthcare services required by State Department personnel and their families are provided by domestic providers.

Leishmaniasis can also occur in US residents who travel for vacation to endemic countries, and who are then diagnosed after the travelers return to the US. Infectious disease specialists in the US do not manage cases of leishmaniasis frequently; Dr. Weina noted in our conversation with him that an infectious disease specialist might never treat a case of leishmaniasis over the course of a career in infectious disease medicine.

Communication of Risk and REMS Procedures to Providers

Communication of risk and communication of REMS procedures to infectious disease specialists would be difficult because of the rarity of leishmaniasis in the US. The information about risk and REMS procedures would not likely be retained by infectious disease specialists who rarely treat a case of leishmaniasis. It is likely that in many instances, an infectious disease specialist will prescribe miltefosine only once, if at all. Obtaining miltefosine for the rare prescriptions will be out of the ordinary for the patients and providers. A restrictive REMS that increases the complexity of obtaining miltefosine would increase the burden to stakeholders. The restriction could cause the specialist to

use a product that is not restricted, rather than miltefosine.⁶ With amphotericin and fluconazole⁷ readily available without restriction, the feedback we received was that these products might be used preferentially to treat leishmaniasis.

Increasing the complexity of obtaining miltefosine could cause occasional delays in treatment. This would be unacceptable in instances in which a patient must receive miltefosine urgently (e.g., for treatment of amebic meningoencephalitis).

Long Half-life for Miltefosine

Besides the rarity of leishmaniasis, the varied settings of treatment for leishmaniasis, and the difficulty in communicating with infectious disease specialists who seldom treat a case of leishmaniasis, any risk mitigation protocol must deal with the long half-life of miltefosine. The initial elimination half-life of miltefosine is 6-7 days, and the second elimination half-life is 30 days. Because of the long half-life, the proposed labeling cautions that a woman of childbearing potential should use effective contraception for (b) (4) months following the completion of the 28-day therapy. A restricted distribution REMS could ensure that a woman who is already pregnant does not receive miltefosine. However, the period of risk exceeds the period of treatment by several months, and with treatment completed, there would be no incentive for a woman to remain in contact or comply with a REMS program. Therefore, even the most restrictive program could not ensure continued contraceptive use in a woman who has completed treatment, but who is potentially at risk for the teratogenic effects of miltefosine.

5 CONCLUSION/RECOMMENDATION

Because of the difficulty in communicating with infectious disease specialists regarding treatment of a rarely occurring disease, because miltefosine is likely to be used in varied non-traditional healthcare settings in which a REMS could create an undue burden for patients and prescribers, and because even the most restrictive REMS would be unable to mitigate risk beyond the 28-day treatment period, we do not believe a REMS should be put into place for miltefosine. DRISK believes that information about the potential risk of teratogenicity for miltefosine should be detailed in the labeling, including, if appropriate, placing the information in a boxed warning. Additionally, because patients should be informed about the risk of teratogenicity and the importance of pregnancy prevention, it would be useful to include this information in a Medication Guide for patients.

⁶ We have anecdotal information that a restrictive REMS would likely drive use to other unrestricted pharmaceuticals. One infectious disease specialist we talked to stated that he would be unlikely to prescribe a drug with a restrictive REMS, if other options were available for the treatment of leishmaniasis.

⁷ High-dose fluconazole is believed to be teratogenic.

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/s/

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09/16/2013

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