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APPLICATION NUMBER:

204684Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 18, 2014
From	Thomas Smith, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 204684
Applicant	Paladin Therapeutics, Inc.
Date of Submission	April 19, 2013
PDUFA Goal Date	March 19, 2014
Proprietary Name / Established (USAN) names	Impavido [®] /Miltefosine
Dosage forms / Strength	50 mg capsules for oral use
Proposed Indications	<ol style="list-style-type: none"> 1. Visceral leishmaniasis 2. Cutaneous leishmaniasis 3. Mucosal leishmaniasis
Recommended:	Approval

1. Introduction

NDA 204684 is submitted by Paladin Therapeutics, Inc., for the use of miltefosine for the treatment of visceral, cutaneous, and mucosal leishmaniasis in adults and adolescents. The NDA was originally submitted September 27, 2012. A Refuse to File letter was issued November 26, 2012, because of dataset deficiencies which did not allow a meaningful review of the efficacy and safety data. The application was resubmitted April 19, 2013. It received a priority review designation because miltefosine may provide a significant improvement compared to marketed products for the treatment of visceral leishmaniasis and there are no approved drug products for the treatment of cutaneous or mucosal leishmaniasis.

The proposed indication for treatment of visceral leishmaniasis due to *Leishmania donovani* is supported by Study 3154, a randomized, open-label, noninferiority trial conducted in India in 1999-2000 which compared miltefosine with intravenous amphotericin B deoxycholate. Additional supportive information included Study Z025, a randomized, open-label trial conducted in Ethiopia in 2003-2005 by Medicins Sans Frontieres which compared miltefosine with intramuscular sodium stibogluconate; postmarketing studies conducted in India, Nepal, and Bangladesh; and published reports of studies in India and Nepal.

The proposed indication for treatment of cutaneous leishmaniasis due to members of the *Leishmania Viannia* subgenus (*L. (V.) braziliensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis*) is supported by Study 3168, a randomized, placebo-controlled trial conducted in Colombia and Guatemala in 2000-2002. Additional supportive information included Study Z020, a randomized, open-label trial conducted in Brazil in 2007-2009 which compared miltefosine with intramuscular meglumine, and Study Soto, an open-label study conducted in Brazil in 2005-2007 which also compared miltefosine with intramuscular meglumine.

The proposed indication for the treatment of mucosal leishmaniasis due to *L. (V.) braziliensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis* is supported by a single-arm study conducted at a single site in Bolivia in 2004-2006.

This review will summarize the findings of the review team and highlight notable issues.

2. Background

Leishmania species are obligate intracellular protozoan parasites that are transmitted by the bite of infected female phlebotomine sandflies. *Leishmania* spp. infect mononuclear phagocytes in humans and cause three major clinical syndromes: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML).

The genus *Leishmania* has two subgenera: *Leishmania* and *Viannia*. The subgenus *Leishmania* includes the *L. donovani* complex (*L. donovani*, *L. infantum*, and *L. chagasi*); the *L. mexicana* complex (*L. mexicana*, *L. amazonensis*, and *L. venezuelensis*); *L. tropica*; *L. major*; and *L. aethiopica*. The subgenus *Viannia* includes *L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana*.

VL has an estimated incidence of 0.5 million cases annually worldwide. Most cases are in the Indian subcontinent, East Africa, and Brazil and are caused by *L. donovani* complex (India and Africa) and *L. chagasi/infantum* (Brazil). VL results from dissemination of infection throughout the reticuloendothelial system. Most infections are asymptomatic; clinical manifestations of symptomatic disease include fever, hepatosplenomegaly, and pancytopenia. Fully symptomatic infection is fatal if untreated. Treatment options include pentavalent antimonials (sodium stibogluconate, meglumine antimoniate), amphotericin B deoxycholate, liposomal amphotericin B, paromomycin, and miltefosine; amphotericin B liposome for injection (AmBisome[®]) is the only therapy approved by FDA. Resistance to antimonials is a concern with VL on the Indian subcontinent.

CL has an estimated incidence of 1.5 million cases annually worldwide. Most cases are in the Middle East and Afghanistan (“Old World CL”) and Brazil and Peru (“New World CL”). Old World CL is most commonly caused by *L. major*, *L. tropica*, and *L. aethiopica*; New World CL is most commonly caused by *L. (V.) braziliensis*, *L. (V.) panamensis*, *L. (V.) guyanensis*, and *L. mexicana*. Cases of CL have occurred in troops stationed in the Middle East. CL results from local infection at or near the site of a sandfly bite. Lesions originate as papules which progress to nodule and then ulcer formation over a period of weeks to months. CL is not life-threatening but may result in scarring. Most cases resolve, and treatment is not always indicated. New World CL is often more severe and has a longer healing time compared with Old World CL. Options for treatment of Old World CL include observation, paromomycin plus methyl benzethonium chloride ointment, intralesional antimonials, thermotherapy, and cryotherapy. Systemic therapies include fluconazole and itraconazole. Options for treatment of New World CL include observation in selected cases; local therapies as for Old World CL; and systemic therapies, including ketoconazole, miltefosine, pentamidine, pentavalent antimonials, amphotericin B deoxycholate, and liposomal amphotericin B. There are no FDA-approved therapies for CL.

ML develops in approximately 2-5% of patients with *L. (V.) braziliensis* infection and more rarely with other *Viannia* subspecies infections. Most cases of ML are in South America. ML usually occurs following resolution of a primary cutaneous ulcer, with development of ulceration and destruction of tissues of the nasopharynx. Spontaneous resolution is rare. Treatment options include pentavalent antimonials, amphotericin B deoxycholate, liposomal amphotericin B, pentamidine, and miltefosine. There are no FDA-approved therapies for ML.

Miltefosine is an alkyl phospholipid analog with *in vitro* activity against the promastigote and amastigote stages of *Leishmania spp.* The presumed mechanism of action is inhibition of phosphocholine synthesis. Miltefosine was originally developed for leishmaniasis by ASTA Medica/Zentaris in collaboration with the World Health Organization (WHO). Miltefosine is marketed in 14 countries for the treatment of visceral leishmaniasis and cutaneous leishmaniasis and is included on WHO's 18th Essential Medicines List (April, 2013).

Miltefosine was granted orphan designation in October, 2006, for the treatment of leishmaniasis. Paladin Laboratories acquired miltefosine from ASTA Medica/Zentaris in 2008. A pre-IND meeting was held in July, 2009, between Paladin and the former Division of Special Pathogens and Transplant Products (DSPTP). Paladin initially sought advice on requirements for an NDA submission for CL and ML and was advised by DSPTP to consider pursuing the VL indication as well. In October, 2009, Paladin submitted a proposal for the use of several completed clinical studies to support approval of miltefosine for the treatment of VL, CL, and ML. For VL, Paladin proposed to use Study 3154, a randomized, open-label, noninferiority trial conducted in India in 1999-2000 that compared miltefosine with amphotericin B deoxycholate; and Study 3206, an open-label noncomparative study conducted in children 2 to 11 years of age in India in 2001-2002. For CL, Paladin proposed to use Study 3168, a randomized, placebo-controlled trial conducted in Colombia and Guatemala in 2000-2002. For ML, Paladin proposed to use Study Z022, a single-arm study conducted at a single site in Bolivia in 2004-2006. In April, 2010, DSPTP advised that Studies 3154 and 3168 were potentially adequate but not sufficient to support the VL and CL indications. DSPTP identified additional studies summarized in the pre-IND package that might provide additional support: for VL, Study Z025, a randomized, open-label trial conducted in Ethiopia in 2003-2005 by Medicins Sans Frontieres that compared miltefosine with sodium stibogluconate; and for CL, Studies Z020a or Z020b, components of a randomized, open-label trial conducted in Brazil in 2007-2009 that compared miltefosine with meglumine antimoniate; or Study Soto, an open-label study conducted in Bolivia in 2005-2007 that compared miltefosine with meglumine antimoniate. For the ML indication, DSPTP recommended that Paladin submit additional documentation to support the use of a single, uncontrolled study, including a discussion of the spectrum of clinical presentations of leishmaniasis and the evidence of effectiveness of miltefosine in forms of leishmaniasis other than ML.

IND 105,430 was submitted in March, 2010. Fast track designation was granted in May, 2010. The NDA was originally submitted September 27, 2012. A Refuse to File letter was issued November 26, 2012, because of dataset deficiencies which did not allow a meaningful review of the efficacy and safety data. The application was resubmitted April 19, 2013. It received a priority review designation because miltefosine may provide a significant improvement

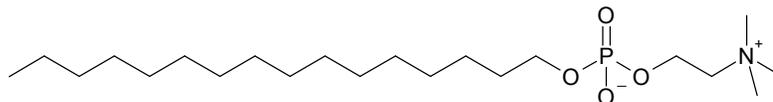
compared to marketed products for the treatment of visceral leishmaniasis and there are no approved drug products for the treatment of cutaneous or mucosal leishmaniasis. The applicant has requested a tropical disease priority review voucher as authorized by Section 524 of the Food, Drug, and Cosmetic Act; leishmaniasis is listed as a qualifying tropical disease.

During the initial CMC review, the high-performance thin layer chromatography (HPTLC) method used to analyze some of the impurities was found to be deficient. The applicant's complete response was considered a major amendment, and the user fee goal date was extended 3 months to March 19, 2014.

3. CMC/Device

The CMC reviewers were Maotang Zhou, Ph.D., and Anamitro Banerjee, Ph.D. The biopharmaceutics reviewer was Mark Seggel, Ph.D., and the product quality microbiology reviewer was Bryan Riley, Ph.D. Their findings are summarized below.

Miltefosine is a new molecular entity. The chemical name of miltefosine is 2-[[[(hexadecyloxy)hydroxyphosphenyl]oxy]-N,N,N-trimethylethylammonium inner salt. Miltefosine is a white powder that is freely soluble in water, 0.1 N HCl or NaOH, methanol, and ethanol. It has the empirical formula $C_{21}H_{46}NO_4P$ with a molecular weight of 407.6 and the following structural formula:



Specifications for the drug substance include tests for description, identity, water, assay, impurities, (b) (4) heavy metals, and residual solvents. Initial CMC review found that the HPTLC method used to analyze some of the impurities was deficient. The applicant was requested to repeat stress studies using appropriate conditions and to validate the HPTLC method using appropriately stressed samples. The applicant's response was considered sufficient to permit use of the HPTLC method as an interim method that will be replaced with a high-performance liquid chromatography (HPLC) method developed postapproval. The applicant's complete response was considered a major amendment, and the user fee goal date was extended 3 months to March 19, 2014.

For the drug substance, the applicant provided 12 month stability data under long-term conditions and 6 month stability data under accelerated conditions. The applicant proposed a (b) (4) retest period, which was considered acceptable by the CMC reviewers.

The drug product, Impavido, is an oral capsule containing 50 mg of miltefosine. The inactive ingredients are colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water. The capsules are packaged in blister cards and a (b) (4) outer carton. Release testing includes tests for description, identity, water content, assay, degradants, weight variation, dissolution, and microbial limits. The applicant submitted up to 18 month long-term and 6 month accelerated stability data for three primary stability batches. Testing is to continue

to (b) (4) Supportive stability data from previous batches produced with a slightly different manufacturing process were submitted for up to 48 months long-term. The stability data support a 24 month expiration date for the drug product when stored at 20-25°C.

The biopharmaceutics review recommended approval of this application with an acceptance criterion of not less than (b) (4) dissolution of miltefosine in 15 minutes. The product quality microbiology review found that the microbial limits specification for the drug product was acceptable and recommended approval.

All facilities inspections have been completed and the Office of Compliance has determined these facilities to be acceptable.

The final CMC review concluded that there was sufficient information on the drug substance and drug product to assure the strength, purity, and quality of the drug product through the expiration dating period and recommended approval provided that the facilities inspections by the Office of Compliance were acceptable.

The applicant has agreed to the following postmarketing commitments:

1. Develop an appropriate HPLC method for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules.
2. In conjunction with the development and implementation of the HPLC methodology, perform (b) (4) testing in accordance with the 2003 FDA draft guidance for stratified testing.

4. Nonclinical Pharmacology/Toxicology

James Wild, Ph.D., was the pharmacology/toxicology reviewer for this application. Dr. Wild's findings and recommendations are summarized or excerpted below.

Oral miltefosine is 82% bioavailable in rats and 93% in dogs and 95% bound to plasma proteins in rats, dogs, and humans. In rats, miltefosine accumulates with repeated dosing with greater accumulation in nervous tissue and reproductive organs. Miltefosine has a plasma half-life ($t_{1/2}$) of approximately 80 hours in rats and 160 hours in dogs. It is excreted primarily in urine and feces.

The major target organs in 8- and 52-week toxicology studies in rats were kidney (chronic nephropathy), the gastrointestinal tract (hyperplasia of stomach chief cells, hyperplasia and hypertrophy of intestinal mucosa), male reproductive organs (atrophy of testes; Leydig cell hyperplasia and adenomas; atrophy of prostate, epididymides, and seminal vesicles; spermatogenic granulomas in epididymides), female reproductive organs (ovarian cysts; hydrometra, mucometra, and pyometra of the uterus; hyperplasia of cervical and vaginal mucosa), and the eye (corneal inflammatory changes, homogenization of the nucleus of the lens, swelling and vacuolization of lens fibers, and retinal degeneration). Toxicities were dose-dependent. Chronic nephropathy, testicular atrophy, and retinal degeneration were not fully reversible during recovery in the high-dose group in the 52-week study. The No Observed

Adverse Effect Level (NOAEL) in both studies was ≤ 4.64 mg/kg/day, which corresponds to a human equivalent dose of 0.74 mg/kg/day based on body surface area (BSA) comparisons and is 0.2 times the maximum recommended human dose (MHRD) of 3.33 mg/kg/day. Juvenile rats were more sensitive than adults to toxic effects of miltefosine.

Target organs in dogs included the gastrointestinal tract (vomiting, diarrhea, reduced food consumption, and hyperemia of intestinal mucosa), female reproductive organs (increased number of atretic ovarian follicles and cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus), and male reproductive organs (multifocal atrophy and degeneration of seminiferous tubules in the high-dose group in the 52-week study and prostate atrophy in the mid- and high-dose groups in a 13-week study). These toxicities were reversible during recovery; however, in the 52-week study, 2/2 recovery males had reduced testicular weight and testicular atrophy that were not observed in the main study animals. The male reproductive organ toxicity was generally of more limited scope and less severe in dogs than in rats. Retinal degeneration was not noted in dogs.

Genotoxicity studies included negative results in the Ames-Salmonella test, DNA-amplification test, chromosomal aberration test *in vitro*, unscheduled DNA synthesis test *in vivo/in vitro*, and oral mouse micronucleus test *in vivo*. The V 79 mammalian cell HPRT gene mutation test showed an increase in mutant frequency without dose dependency. In view of all mutagenicity test results, the single positive finding in the V 79 HPRT test is considered to be not of toxicological relevance with respect to a mutagenic risk to humans.

Carcinogenicity studies were not performed. In a 52-week oral rat toxicity study, testicular Leydig cell adenoma was observed in 3 of 30 male rats with daily administration of 21.5 mg/kg/day miltefosine (1.0 times the MRHD based on BSA comparison). The carcinogenic potential of miltefosine in humans is unknown.

In a fertility study in male rats, testicular atrophy and impaired fertility were observed following oral doses of ≥ 8.25 mg/kg/day (0.4 times the MRHD based on BSA comparison). These findings were reversible within a recovery period of 10 weeks except at the highest dose tested, 21.5 mg/kg/day (1.0 times the MHRD based on BSA comparison), where effects were not fully reversible.

In a fertility study in female rats, estrus cycle arrest in the metestrus or diestrus phases occurred with the high dose of 21.5 mg/kg/day. Reproductive performance was affected in a dose-dependent manner at doses of 6.81 and 21.5 mg/kg/day in the form of increased numbers of embryonic and fetal resorptions and the proportion of dead fetuses. Fetal visceral and skeletal malformations were observed at these doses.

In rat embryo-fetal toxicity studies during early embryonic development (up to day 7 of pregnancy), embryonic, fetotoxic, and teratogenic effects were observed with dosages of ≥ 1.2 mg/kg/day (0.06 times the MRHD based on BSA comparison). Teratogenic effects included undeveloped cerebrum, hemorrhagic fluid in the luminal skull, cleft palate, and generalized edema. Embryotoxic and fetotoxic effects were also observed in rabbits after oral administration of dosages of > 2.4 mg/kg/day (0.2 times the MRHD based on BSA

comparison). No live fetuses were obtained in rats or rabbits following doses of ≥ 6.0 mg/kg/day (0.3 or 0.6 times the MRHD based on BSA comparison for rats and rabbits, respectively).

Dr. Wild concluded that this application was approvable and that the label should include information about the major toxicities observed in rats and dogs: retinal effects in rats, male and female reproductive and developmental toxicities, and the Leydig cell carcinogenicity finding in rats.

5. Clinical Pharmacology/Biopharmaceutics

Seong Jang, Ph.D., was the clinical pharmacology reviewer for this application. Dr. Jang's findings and recommendations are summarized below.

The proposed dose of miltefosine is one 50 mg capsule twice daily with food for patients weighing 30-44 kg and one 50 mg capsule three times daily with food for patients weighing ≥ 45 kg, based on a target regimen of 2.5 mg/kg/day. The duration of treatment is 28 days. The proposed dosing regimen was chosen on the basis of phase 2 dose-finding studies.

Miltefosine causes hemolysis in vitro. Clinical pharmacology studies have not been conducted in healthy volunteers. All studies have been conducted in patients with VL or CL, and clinical pharmacology information is limited.

Absolute bioavailability of miltefosine has not been determined because miltefosine cannot be administered intravenously. In patients with VL, the observed concentrations following oral administration suggest that absorption may proceed throughout the dosing interval. The effect of food on the bioavailability of miltefosine has not been evaluated; it is administered with food to reduce gastrointestinal adverse reactions. The distribution of miltefosine has not been studied in humans. Human plasma protein binding was 98% over the drug concentration range of 0.1-10 $\mu\text{g/mL}$. Plasma $t_{1/2}$ is greater than 6 days, and plasma steady state is not reached at the end of a 28-day course of therapy. Miltefosine is metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol, which is oxidized to palmitic acid. In patients with VL, $<0.2\%$ of the administered dose was excreted into the urine.

Pharmacokinetic parameters are listed in Table 1 below.

Table 1. Mean (%CV) Pharmacokinetic Parameters for Miltefosine Following Oral Capsule Administration to Adult Patients with Visceral and Cutaneous Leishmaniasis

	Dose	C_{\max} ($\mu\text{g/mL}$)	T_{\max}^c (hr)	AUC_{τ}^d ($\mu\text{g}\cdot\text{hr/mL}$)	$t_{1/2,\alpha}^e$ (day)	$t_{1/2,\beta}^e$ (day)
Visceral Leishmaniasis ^a (on Day 23)	50 mg BID (4 wks)	66.2 (28.5)	7(2-12)	636 (26.7)	6.4 (31.1)	
	50 mg BID (1 wk)/ 50 mg TID (3 wks)	75.9 (17.6)	4 (2-8)	486 (18.1)	8.5 (28.9)	
Cutaneous Leishmaniasis ^b (on Day 27)	50 mg TID (4 wks)	37.3 (22) ^f		295 (22) ^f	6.8 (5.8) ^{f,g}	30.7 (18.3) ^{f,g}

a: Adolescent (>12 years)/Adults, mean dose per kg was 3.1 mg/kg/day

b: Adults, mean dose per kg was 1.8 mg/kg/day

c: median (range)

d: AUC_{0-12h} for BID, AUC_{0-8h} for TID

e: $t_{1/2,\alpha}$ = distribution phase half-life; $t_{1/2,\beta}$ = terminal elimination phase half-life

f: Estimates based on a population PK model

g: mean (% standard error)

Source: Clinical pharmacology review draft labeling recommendation for Section 12.3

Miltefosine is not a substrate or a significant inhibitor or inducer of hepatic cytochrome P450 (CYP) enzymes. Drug interaction studies have not been conducted.

The effects of intrinsic factors on miltefosine pharmacokinetics were not evaluated.

DAIP requested consultation from the QT Interdisciplinary Review Team (QT-IRT) from the Division of Cardiovascular and Renal Products. QT-IRT waived a formal thorough QT study because of safety and tolerability issues and noted that the clinical study data were insufficient to rule out a clinically relevant effect of miltefosine on the QT interval. They recommended that a dedicated QT study be considered as a postmarketing requirement.

Dr. Jang concluded that this NDA was acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology

Shukal Bala, Ph.D., was the clinical microbiology reviewer for this application. Dr. Bala's findings and recommendations are summarized below.

The specific mechanism of action of miltefosine against *Leishmania* species is unknown. It is likely related to interaction with lipids, including membrane lipids, inhibition of cytochrome c oxidase, and apoptosis-like cell death.

Miltefosine is active *in vitro* against the promastigotes and amastigotes of several *Leishmania* species. Methods for testing are not standardized, and a limited number of strains have been tested. The highest 50% inhibitory concentrations (IC₅₀) reported were 10.2 µg/mL for promastigotes of *L. donovani* and 15.2 µg/mL for amastigotes of *L. major*. One study comparing activity of miltefosine against promastigotes and amastigotes of a single strain of six different species of *Leishmania* suggested that *L. donovani* was the most sensitive species and *L. major* the least sensitive. Clinical isolates of *L. donovani* have been tested, with IC₅₀ values ranging from 0.6-7.4 µg/mL for the promastigotes and 0.01-10.9 µg/mL for the amastigotes. One study reported a trend toward higher 90% inhibitory concentrations (IC₉₀) for isolates from highly endemic areas compared with isolates from areas of lower endemicity.

In models of acute and chronic VL, miltefosine reduced parasite burden in liver and spleen in immunocompetent mice infected with *L. donovani* or *L. infantum*. The activity of miltefosine was three times greater against a strain of *L. donovani* from India than against one from Ethiopia in one study. In a model of CL, topical miltefosine reduced parasite burden and lesion

size in mice infected with *L. mexicana* or *L. major*. Oral treatment with miltefosine was not evaluated in the CL model.

In vitro studies show the potential for development of resistance to miltefosine. Drug resistance could result from a decrease in miltefosine concentration in *Leishmania* parasites due to an increase in drug efflux mediated by overexpression of the ABC transporter P-glycoprotein or a decrease in drug uptake by inactivation of miltefosine transport machinery. Some strains of *L. braziliensis* with intrinsic resistance to miltefosine have been identified.

Leishmania species cannot be distinguished morphologically. Species are differentiated by isoenzyme analysis or molecular methods such as polymerase chain reaction (PCR). These tests are not FDA cleared. In the clinical studies, parasitological diagnosis was based primarily on microscopy of tissue aspirates or smears. Some of the CL and ML studies attempted to identify *Leishmania* species, but details of the methods and performance characteristics of the assays were not available for review. The identification of *Leishmania* species in most of the clinical trials was based on epidemiologic patterns rather than on methods that are considered experimental.

Dr. Bala concluded that this NDA was approvable from a clinical microbiology perspective. Because of the lack of definitive speciation in most of the studies, she recommended that the indications be written to reflect that the clinical trial findings were based on cure rates in different geographic regions.

7. Clinical/Statistical- Efficacy

Hala Shamsuddin, MD, was the clinical reviewer, and Lan Zeng, MS, was the statistical reviewer for this submission. As recommended by DSPTP in April, 2010, Paladin submitted the following studies to support the leishmaniasis indications:

- Visceral leishmaniasis
 - Study 3154, a randomized, open-label, noninferiority trial conducted in India in 1999-2000 that compared miltefosine with amphotericin B deoxycholate
 - Study Z025, a randomized, open-label trial conducted in Ethiopia in 2003-2005 by Medicins Sans Frontieres - Holland that compared miltefosine with sodium stibogluconate
- Cutaneous leishmaniasis
 - Study 3168, a randomized, placebo-controlled trial conducted in Colombia and Guatemala in 2000-2002
 - Studies Z020a and Z020b, identical randomized, open-label trials conducted in different regions of Brazil in 2007-2009 that compared miltefosine with meglumine antimoniate
 - Study Soto, an open-label study conducted in Bolivia in 2005-2007 that compared miltefosine with meglumine antimoniate
- Mucosal leishmaniasis
 - Study Z022, a single-arm study conducted at a single site in Bolivia in 2004-2006

Visceral leishmaniasis**Study 3154**

Study 3154 was conducted at three sites in India in 1999-2000 by ASTA Medica in collaboration with the WHO. *L. donovani* is the most common cause of VL in this region. Patients 12 years of age and above with VL were randomized 3:1 to receive miltefosine, 2.5 mg/kg/day orally for 28 days (50 mg daily for patients <25 kg or 100 mg daily for patients \geq 25 kg), or amphotericin B deoxycholate, 1 mg/kg/day intravenously every other day for 15 doses. Amphotericin B was chosen as the comparator because of increasing rates of resistance to pentavalent antimonials in the region. VL was confirmed by splenic or bone marrow aspiration demonstrating presence of *Leishmania* amastigotes. All patients were hospitalized during treatment, and splenic or bone marrow aspiration was performed at the end of therapy. The primary endpoint was final cure, which was defined as initial cure followed by 6 months without relapse and absence of clinical signs or symptoms attributable to VL (fever, splenomegaly, and hematologic indices). Patients with clinical signs or symptoms attributable to VL were to undergo splenic or bone marrow aspiration; if the aspirate was negative, the patient was considered to be cured. Initial cure was defined as eradication of parasites (based on splenic or bone marrow aspiration) at the end of treatment or within 4 weeks thereafter. The trial was designed with a noninferiority margin of 15%, but DAIP informed Paladin that a margin of 10% for the final analysis was more appropriate for this potentially fatal disease.

There were 400 patients randomized, with 398 receiving at least one dose of study medication: 299 received miltefosine, and 99 received amphotericin B. Approximately one-third (32.6%) of the patients were female; females were disproportionately enrolled in the amphotericin B arm (41.4% of amphotericin B patients). The median weight of study patients was 40 kg, with a maximum of 67 kg.

In each treatment arm, 98.0% of patients had initial cures. There were 100 patients who had clinical signs or symptoms compatible with VL at the 6-month follow-up visit: 88 (29.4%) in the miltefosine arm and 12 (12.1%) in the amphotericin B arm. Investigators identified an alternative explanation for 73 patients, and 27 patients underwent splenic or bone marrow aspiration; all were in the miltefosine arm. Nine aspirates were positive. Final cure rates in the applicant's analysis were 94.3% for miltefosine and 97.0% for amphotericin B (Table 2). Miltefosine was noninferior to amphotericin B.

Table 2. Study 3154 Final Cure Rates (ITT)

	Miltefosine (N = 299)		Amphotericin B (N = 99)		Difference	
	n	(%)	n	(%)	%	(95% CI)
Final cure	282	(94.3)	96	(97.0)	2.7	(-3.0, 6.8)
Relapse	9	(3.0)	0	-		
Deaths	2	(0.7)	0	-		
Not assessable	6	(2.0)	3	(3.0)		

CI = confidence interval

Adapted from FDA AIDAC presentation, 10/18/13

The 100 patients with signs or symptoms compatible with VL at the 6-month follow-up visit were approximately evenly distributed among the three study sites. Splenic or bone marrow aspirates were performed in the majority of cases at study site 1 (23/27; 85%) and infrequently at study sites 2 (2/35; 5.7%) and 3 (2/38; 5.3%). This discrepancy prompted Dr. Shamsuddin to perform a review, blinded to aspiration status, of patients with signs or symptoms compatible with VL at the 6-month follow-up visit. She determined that 27 of these patients should have undergone aspiration. Aspiration was performed in 13 patients and was positive in 9. The remaining 14 patients (12 miltefosine and 2 amphotericin B) who did not undergo aspiration were considered to be treatment failures or relapses. In this analysis, final cure rates were 90.3% (270/299) for miltefosine and 94.9% (94/99) for amphotericin B (treatment difference 4.6%; 95% confidence interval, -2.0, 9.8).

Although a gender imbalance was noted in treatment assignment, final cure rates for each drug were similar in males and females. Final cure rates varied with miltefosine dose; 92.3% (120/130) for doses of less than 2.5 mg/kg/day, 94.2% (114/121) for 2.5 to less than 3 mg/kg/day, and 100% (48/48) for 3 or more mg/kg/day. The proposed maximum dose of miltefosine is 150 mg/day; appropriate dosing of patients weighing more than 60 kg must be determined.

Study Z025

Study Z025 was conducted in Ethiopia in 2003-2005 by Medicins Sans Frontieres - Holland. VL due to *L. donovani* is endemic in this region. Paladin was unable to obtain patient level data from this study; only case report forms for patients with serious adverse events were available. The Paladin study report was derived from a publication¹ and from the case report forms.

Male patients 15 years of age and above with VL were randomized to receive oral miltefosine, 100 mg/day for 28 days, or intramuscular sodium stibogluconate (SSG), 20 mg/kg/day for 30 days; SSG is the standard of care in Ethiopia. Female patients were excluded because of the potential teratogenicity of miltefosine. The diagnosis of VL was confirmed serologically and/or by splenic or lymph node aspiration. Splenic or lymph node aspiration was to be performed at the end of therapy. Patients who did not respond to miltefosine or who had therapy discontinued because of adverse events were treated with SSG; patients who did not respond to SSG or who had therapy discontinued because of adverse events were treated with amphotericin B deoxycholate. The primary endpoint was final cure at the 6-month follow-up visit.

There were 580 patients randomized: 290 to miltefosine and 290 to SSG. HIV testing was performed in 63.6% of those enrolled, and 28.5% of those tested were seropositive.

Initial cure rates were 88.3% in the miltefosine arm and 87.6% in the SSG arm. Twenty-eight patients in the SSG arm died during initial therapy, compared with 6 patients in the miltefosine

¹ Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis 2006; 43:357-64.

arm. In contrast, patients treated with miltefosine were more likely to have treatment failure or relapse than those treated with SSG. Final cure rates were 60.0% for miltefosine and 65.2% for SSG (Table 3).

Table 3. Study Z025 Final Cure Rates (ITT)

	Miltefosine (N = 290)		Sodium stibogluconate (N = 290)		Difference	
	n	(%)	n	(%)	%	(95% CI)
Final cure	174	(60.0)	189	(65.2)	5.2	(-2.8, 13.1)
Relapse	30	(10.3)	7	(2.4)		
Deaths	17	(5.9)	34	(11.7)		
Lost to follow-up	69	(23.8)	60	(20.7)		

From Ritmeijer et al.¹ and FDA AIDAC presentation 10/18/13

Final cure rates include patients who had initial treatment failure and had a successful second course of therapy with another drug. In the miltefosine arm, there were 23 patients who were initial failures who were then treated with SSG. Inclusion of these patients as final cures confounds the evaluation of the effect of the initial miltefosine therapy. Without source data, it cannot be determined how many of these patients are included as final cures. The lack of source data also precludes alternative analyses.

Study 3154 demonstrates that miltefosine is noninferior to amphotericin B in the treatment of VL. The major issues with this trial are the gender imbalance in treatment assignment and the inconsistencies among study sites in performing diagnostic aspirations in patients who had clinical signs or symptoms compatible with VL at the 6-month follow-up visit. Study Z025 provides supportive evidence of the efficacy of miltefosine but has serious limitations: lack of patient level data; confounding in the determination of the final cure rates, particularly in the miltefosine arm; substantial losses to follow-up; and the high prevalence of HIV co-infection, which limits generalizability. The clinical and statistical reviewers concluded that miltefosine is effective in the treatment of VL.

Cutaneous leishmaniasis

Study 3168

Study 3168 was conducted at two sites in Colombia and Guatemala in 2000-2002. *L. (V.) panamensis* is the most common cause of CL in Colombia, and *L. (V.) braziliensis* and *L. mexicana* are the most common causes in Guatemala. Patients 12 years of age and above with CL were randomized 2:1 to receive miltefosine, 100 mg daily for patients <45 kg or 150 mg daily for patients ≥45 kg, or placebo for 28 days. CL was confirmed by parasitologic examination of slit skin smears, aspirates, or biopsies demonstrating presence of *Leishmania* amastigotes or promastigotes or identification by PCR. The primary endpoint was definite cure, defined as complete epithelialization of all ulcers and complete disappearance of inflammatory induration from all lesions at the end of the 6-month post-therapy follow-up period. In the study report, classification as definite cure also required that there be no 50% or more enlargement of previously documented lesions, no new lesions, and the absence of parasites (if tested) for the period between two weeks after the end of therapy and the 6-month follow-up.

There were 133 patients randomized: 89 to miltefosine and 44 to placebo. Definite cure rates were 66.3% in the miltefosine arm and 29.6% in the placebo arm (Table 4).

Table 4. Study 3168 Definite Cure Rates (ITT)

	Miltefosine		Placebo		Difference	
	n/N	(%)	n/N	(%)	%	(95% CI)
Overall	59/89	(66.3)	13/44	(29.6)	36.7	(18.5, 52.4)
By study site						
Colombia	40/49	(81.6)	9/24	(37.5)	44.1	
Guatemala	19/40	(47.5)	4/20	(20.0)	27.5	

Adapted from FDA briefing document for 10/18/13 AIDAC meeting

Cure rates were higher in Colombian patients than in Guatemalan patients for both miltefosine and placebo. At each site, cure rates were higher in patients receiving miltefosine. Differences in cure rates between sites may be due to differences in the natural history or response to therapy of CL that relate to the predominant *Leishmania* species in each country.

Definite cure rates varied with miltefosine dose: 59.1% (26/44) for doses of less than 2.5 mg/kg/day and 73.3% (33/45) for doses of 2.5 or more mg/kg/day.

Studies Z020a and Z020b

Studies Z020a and Z020b are identical investigator-initiated trials conducted in Brazil in 2007-2009. Study Z020a was conducted in an area in which *L. (V.) guyanensis* is the most common cause of CL, and Study Z020b was conducted in an area in which *L. (V.) braziliensis* is the most common cause. Paladin submitted separate reports of these trials, but they are discussed together because they used the same protocol and case report forms, were performed simultaneously, had a pooled planned sample size, and had the same coordinator.

Patients 2 to 65 years of age with CL were randomized 2:1 to receive miltefosine at a target dose of 2.5 mg/kg/day for 28 days or parenteral meglumine antimoniate, 20 mg Sb⁺⁵/kg/day for 20 days. CL was confirmed parasitologically, and speciation was performed. The primary endpoint was definitive cure, defined as complete epithelialization of all ulcers by the end of the 6-month follow-up period. In the study report, definitive cure was defined as 100% re-epithelialization and loss of induration of all initial lesions at 2 months and at 6 months, and no new lesions, residual lesions with parasites, or ≥50% enlargement of a lesion prior to 6 months. Enrollment for the combined studies was planned to be a total of 180 patients (90 per site), with 60 patients (30 per site) 2 to 11 years of age and 120 patients (60 per site) 12 to 65 years of age. There was no formal statistical hypothesis.

Table 5 displays the definitive cure rates for Study Z020 and its components. In Study Z020a, 95.6% (86/90) of patients had *L. (V.) guyanensis* infection. In Study Z020b, 71% of patients (64/90) had a positive culture or PCR; *L. (V.) braziliensis* was the only species identified. For Studies Z020a and Z020b combined, definitive cure rates were 73.3% for patients treated with miltefosine and 60.0% for patients treated with meglumine.

Table 5. Study Z020 Definitive Cure Rates (ITT)

	Miltefosine		Meglumine antimoniate		Difference	
	n/N	(%)	n/N	(%)	%	(95% CI)
Z020						
All patients	88/120	(73.3)	36/60	(60.0)	13.3	(-1.4, 28.4)
≥12 years	61/80	(76.3)	21/40	(52.5)	23.8	(5.2, 41.9)
<12 years	27/40	(67.5)	15/20	(75.0)	-7.5	(-30.4, 18.7)
Z020a						
All patients	41/60	(68.3)	18/30	(60.0)	8.3	
≥12 years	27/40	(67.5)	12/20	(60.0)	7.5	(-17.9, 34.6)
<12 years	14/20	(70.0)	6/10	(60.0)	10.0	
Z020b						
All patients	47/60	(78.3)	18/30	(60.0)	18.3	
≥12 years	34/40	(85.0)	9/20	(45.0)	40.0	(8.6, 63.5)
<12 years	13/20	(65.0)	9/10	(90.0)	-25.0	

Adapted from FDA AIDAC presentation 10/18/13 and Z020a/b study reports

In Study Z020a, definitive cure rates for similar for miltefosine and meglumine in both adults and children. In Study Z020b, definitive cure rates were greater for miltefosine in adults and for meglumine in children. In these studies, cure rates did not vary by dose on a mg/kg basis.

Study Soto

Study Soto was an investigator-initiated study that was conducted at a single site in Bolivia in 2005-2007; *L. (V.) braziliensis* is the most common cause of CL in Bolivia. Patients 12 years of age and above with CL were randomized 2:1 to receive miltefosine at a target dose of 2.5 mg/kg/day for 28 days or parenteral meglumine antimoniate, 20 mg Sb⁺⁵/kg/day for 20 days. CL was confirmed parasitologically, but speciation was not performed. The primary endpoint was clinical cure, defined as complete re-epithelialization of all lesions 6 months after completion of therapy. Planned enrollment was 80 patients. There was no formal statistical hypothesis.

This study was terminated before completion of enrollment; no reason was provided. The clinical and statistical reviewers concluded that this study was likely not to have been randomized. Forty patients received miltefosine, and 18 received meglumine. Three patients in the meglumine arm were excluded from the FDA analysis because it appears that they were not followed because of closure of the study. Clinical cure rates were 80.0% (32/40) for patients treated with miltefosine and 86.7% (13/15) for patients treated with meglumine (95% confidence interval for treatment difference: -26.3, 21.4)

Study 3168 was a placebo-controlled trial that demonstrates that miltefosine is effective in the treatment of CL. Study Z020 provides supportive evidence of the efficacy of miltefosine along with parasitologic speciation. Study Soto has issues with study design and conduct, including concerns about randomization and follow-up of patients, that limit its interpretability. The clinical and statistical reviewers concluded that miltefosine is effective in the treatment of CL.

Mucosal leishmaniasis

Study Z022

Study Z022 was a single-arm study conducted in 2004-2006 at the same site in Bolivia as Study Soto; *L. (V.) braziliensis* is the most common cause of ML in Bolivia. This study was originally intended to be a comparative study of 100 patients randomized 3:1 to receive miltefosine or meglumine antimoniate, but “the study team became aware that the pentavalent antimony had been rejected as ineffective at this site” (Z022 study report, p. 15). According to the study report, the standard therapy for ML at this site was amphotericin B, 1 mg/kg every other day for a total of 45 injections, and the protocol was “conceptually modified” to include amphotericin B as the control. Patients refused to be entered into an amphotericin B arm after “the efficacy of miltefosine became apparent in initial patients” (Z022 study report, p. 16). The study therefore became a single-arm evaluation of miltefosine. The study report also states that the protocol was not formally amended during the study. Patients 18 years of age and older with ML received miltefosine at a target dose of 2.5 mg/kg/day for 28 days. ML was confirmed parasitologically by culture, histopathologic examination, or Montenegro skin test. In the original protocol, clinical cure was defined as 90% to 100% resolution of lesions at various anatomic sites in the nasopharynx. The study report states that, because of the complexity of analyzing data from five anatomic sites at six time points, a “mucosal severity score” was derived retrospectively by assigning a severity score (0 = none, 1 = mild, 2 = moderate, 3 = severe) to each sign (erythema, edema, infiltration, erosion) at each anatomic site (nasal skin, nasal mucosa, palate, pharynx, larynx); the maximum score at any time point was 60. The primary endpoint of clinical cure was re-defined as $\geq 90\%$ reduction in mucosal severity score 12 months after the end of therapy. Seventy-nine patients were treated with miltefosine, and 49 (62.0%) were considered to be cured at the 12-month follow-up visit; all cured patients had severity scores of 0. For all patients, mean severity score was 10 at screening and 2 at the 12-month follow-up visit.

The lack of a comparator severely limits the interpretability of this study. In the Z022 study report, Paladin summarized 8 published studies that reported cure rates for ML of 28% to 89% for pentavalent antimony (6 studies) and 29% and 90% for amphotericin B. Dr. Shamsuddin also reviewed published studies and reported similar response rates for pentavalent antimony and amphotericin B. She concluded that the risk-benefit assessment was favorable for miltefosine in the treatment of ML. Ms. Zeng concluded that the effect of miltefosine in the treatment of ML is unclear because of the lack of comparative studies and deferred to the clinical reviewers on the question of the support provided by the findings from the VL and CL trials.

Summary

Miltefosine is effective in the treatment of VL due to *L. donovani*, CL due to *L. braziliensis*, *L. guyanensis*, and *L. panamensis*, and ML due to *L. braziliensis*. *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 miltefosine.

One unresolved issue is dosing in patients who weigh more than 75 kg. The proposed dose of miltefosine is 150 mg daily for patients weighing 45 kg or more. In the VL trial (Study 3154), the median weight of patients was 40 kg, and no patient weighed more than 67 kg. In Study

3168 for CL, the mean weight of patients was 59.1 kg, and no patient weighed more than 84 kg. There is evidence from these trials that lower doses (based on mg/kg) are associated with decreased efficacy. Patients in the US who need treatment for leishmaniasis (e.g., military personnel or travelers) will often weigh more than 75 kg, and there is a need to determine the effectiveness of the proposed dose in these heavier patients. The review team recommends a postmarketing requirement for the applicant to conduct a descriptive study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

8. Safety

Hala Shamsuddin, MD, reviewed the safety data for this submission. The studies summarized in the Clinical/Statistical – Efficacy section above included 587 patients 12 years of age and older who were treated with miltefosine. An additional 321 patients participated in dose-ranging studies in VL and CL. The applicant also submitted postmarketing periodic safety update reports that had been filed with the German regulatory authorities for the periods from September, 2004, to November, 2011.

Visceral leishmaniasis

Two deaths were reported in Study 3154, both in the miltefosine arm. One patient developed bacterial meningitis and died on day 13 of treatment. The second patient had persistent splenomegaly and anemia following completion of miltefosine therapy and was diagnosed with malaria. She completed a course of antimalarial therapy and was considered to be well but died three weeks later. Both deaths are unlikely to be related to miltefosine. Six patients in the miltefosine arm had serious adverse events. The nonfatal serious adverse events included hemiplegia, hemiparesis, convulsions, Stevens-Johnson syndrome, and melena and thrombocytopenia. The case of Stevens-Johnson syndrome was considered related to miltefosine, and the case of melena and thrombocytopenia was considered possibly related to miltefosine. Eight patients in the miltefosine arm had adverse events leading to drug discontinuation. These events include the serious adverse events noted above, along with cases of rash and arthritis, diarrhea, and jaundice. The latter events were considered to be drug-related.

Spontaneously reported adverse events were generally similar in both treatment arms; the most common adverse events were anorexia and pyrexia. Information about body temperature, vomiting, diarrhea, and rigors was also collected each treatment day. Vomiting and diarrhea were reported more frequently in patients receiving miltefosine (38% and 20%, respectively), and rigors were reported more frequently in patients receiving amphotericin B.

Elevations of creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were common in patients receiving miltefosine. No patients discontinued miltefosine because of renal impairment. One patient discontinued miltefosine because of hyperbilirubinemia.

Cutaneous leishmaniasis

There were no deaths or serious adverse events in the CL studies. One patient discontinued miltefosine because of motion sickness. The most common adverse events in patients receiving miltefosine were headache, nausea, vomiting, pyrexia, motion sickness, and diarrhea.

Elevation of creatinine above baseline was common in patients receiving miltefosine. ALT and AST elevations above the upper limit of normal were reported in fewer than 10%.

Mucosal leishmaniasis

In the single-arm ML study, Z022, one patient died on day 16 from an illness characterized by abdominal pain, fever, and vomiting that progressed to shock and cardiopulmonary arrest. The applicant attributed the death to infection, possibly typhoid fever, but it was assessed by Dr. Shamsuddin as more compatible with septic shock and unlikely to be related to miltefosine. No other patients had serious adverse events or discontinuations due to adverse events.

The most common adverse events were headache, nausea, abdominal pain, and pruritus. Elevation of creatinine above baseline was reported commonly; no patients had elevated ALT, AST, or bilirubin.

Postmarketing reports

The applicant estimates that over 90,000 patients had been exposed to miltefosine through the last safety update report through November, 2011. In 2008, thrombocytopenia was added to the German label as an adverse event.

Special safety concerns

Male fertility

Miltefosine caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the maximum recommended human dose (MHRD). At a higher dose approximating the MHRD, it causes testicular atrophy and impaired fertility that did not fully reverse 10 weeks after drug administration ended.

The applicant submitted a retrospective analysis of the “reproductive performance” of participants in VL studies in India, including Study 3154. Of 197 miltefosine recipients who were evaluated 11 to 57 months posttherapy, 136 (69%) had “proven fertility,” as evidenced by at least one delivery or ongoing pregnancy reported in a female partner. One study center performed semen analyses in 12 patients who received miltefosine. Analyses were reported to be normal in 10, with two having oligospermia. One of the patients with oligospermia reported two post-study pregnancies in partners. Semen analyses were also performed in 11 patients with CL who received miltefosine in Study 3168. There were large variations in sperm concentration and motility.

In Study Z020a of CL, four miltefosine recipients reported testicular pain. In a study of 34 Dutch soldiers with CL, 5 (15%) reported decreased or absent ejaculation during therapy;

specific questioning identified an additional 16 (47%) with the same complaint. Postmarketing reports include cases of epididymitis, scrotal pain, and reduced ejaculate volume.

DAIP requested consultation from the Division of Bone, Reproductive, and Urology Products (DBRUP) to evaluate the reproductive toxicity in males and provide recommendations for labeling and postmarketing studies. The DBRUP consultants concluded that the toxicity signal in the animal studies was potentially clinically relevant and that the limited analyses performed in participants in the clinical studies were not sufficient to eliminate these concerns. DBRUP recommended consideration of additional premarketing studies in animals such as primates; a randomized, placebo-controlled premarketing study in healthy volunteers to evaluate the effect of miltefosine on human spermatogenesis and male sex hormones; and the inclusion of warnings in labeling about the nonclinical male reproductive toxicity findings along with a postmarketing requirement for a study of the effect of miltefosine on human spermatogenesis and male sex hormones in the target population.

Language about the nonclinical male reproductive toxicity findings will be included in the WARNINGS AND PRECAUTIONS section of the label. The review team believes that a postmarketing study in the target population is the best way to evaluate the male infertility risks.

Reproductive toxicity in women

Miltefosine caused impaired fertility in rats and dogs at doses approximately 1.0 and 0.2 times the MRHD. Also, embryo-fetal toxicity, including death and teratogenicity, was observed in studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the 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.

Adequate data are not available to support the use of miltefosine in pregnancy. Pregnant and lactating women were excluded from the clinical studies. In foreign labeling, miltefosine is contraindicated in pregnancy.

DAIP requested consultation from the DBRUP and the Pediatric and Maternal Health Staff (PMHS) to evaluate the reproductive toxicity in women and provide recommendations for labeling and postmarketing studies. DBRUP recommended that labeling contain a warning about the potential adverse fetal effects of miltefosine and about the need for effective contraception during therapy and for (b) (4) months posttherapy. DBRUP also recommended establishment of a postmarketing pregnancy and birth registry and a drug-drug interaction study to evaluate the effect of miltefosine on hormonal contraceptive exposure and efficacy. Miltefosine does not induce or inhibit CYP enzymes, however, and the clinical pharmacology team did not believe a drug-drug interaction study is necessary. PMHS recommended a classification of pregnancy category (b) (4) for all indications based on the animal data and the potential benefit to a pregnant woman. PMHS also recommended specific language for the relevant sections of the label.

The DAIP review team believes that pregnancy category D may communicate the potential risks more effectively and that miltefosine should be contraindicated in pregnancy. The label will contain a boxed warning about the embryo-fetal risks along with instructions to perform a pregnancy test before prescribing to women of reproductive potential and to advise them to use effective contraception during therapy and for 5 months after therapy.

Summary

The most significant safety issue with miltefosine is the risk of embryo-fetal toxicity, which will be highlighted in a boxed warning. Miltefosine is contraindicated in pregnancy. The label will also contain warnings and precautions about infertility risks; renal, hepatic, and gastrointestinal effects; thrombocytopenia; absorption of oral contraceptives; and Stevens-Johnson syndrome. Postmarketing requirements include establishment of a pregnancy registry, evaluation of the effect of miltefosine on human spermatogenesis and male sex hormones, and evaluation of the cardiac effects of miltefosine.

Renal function, transaminases, and bilirubin should be monitored in patients receiving miltefosine.

9. Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee met on October 18, 2013, to discuss this application. The questions for the committee and major discussion points are summarized below.

1. Has the applicant demonstrated the safety and efficacy of miltefosine for the treatment of visceral leishmaniasis? Please vote Yes or No. If yes, are there specific questions that should be addressed in labeling? If no, what additional data are needed?

The committee voted 15 to 1 in favor of approval. Comments included: Applicability of trial findings to the US population is limited by lack of data in patients weighing more than 75 kg, and a postmarketing study should be considered. Children should be studied. Consideration should be given to administration as directly observed therapy. Contraception should be recommended for (b) (4) 5 months post-therapy. The dissenting committed member stated that VL is actually several different syndromes and that data were lacking for efficacy beyond the Indian subcontinent.

2. Has the applicant demonstrated the safety and efficacy of miltefosine for the treatment of cutaneous leishmaniasis? Please vote Yes or No. If yes, are there specific questions that should be addressed in labeling? If no, what additional data are needed?

The committee voted 14 to 2 in favor of approval. Comments included: There are differences in response rates among *Leishmania* species. Children should be studied. Dissenting members stated that CL is often self-limited, and the risks of therapy may outweigh the benefits. Study results differed between adults and children.

3. Has the applicant demonstrated the safety and efficacy of miltefosine for the treatment of mucosal leishmaniasis? Please vote Yes or No. If yes, are there specific questions that should be addressed in labeling? If no, what additional data are needed?

The committee voted 13 to 3 in favor of approval. Comments included: There are differences in response rates among *Leishmania* species. Children should be studied. Dissenting members cited the poor quality of the data for this indication.

10. Pediatrics

Miltefosine was granted orphan designation for the treatment of leishmaniasis in October, 2006, and this application is exempt from the requirements of the Pediatric Research Equity Act. The applicant submitted reports of a dose-escalation study (Study 3091) and an open-label non-comparative trial of miltefosine in the treatment of VL (Study 3206) in children 2 to 11 years of age in India, and Studies Z020a and Z020b enrolled children 2 to 11 years of age with CL. Phase 4 studies of VL in India and Nepal included children 2 to 11 years of age, and a VL study in Brazil included children 2 to 12 years of age. Datasets were submitted only for the CL studies. (b) (4)

11. Other Relevant Regulatory Issues

The primary studies that support this application (Study 3154 for VL and Study 3168 for CL) were performed from 1999 to 2002, and the applicant's agent stated that the clinical sites were no longer operational. The applicant stores certified copies of source documents from these studies in Montreal, Canada. The Office of Scientific Investigations (OSI) inspected source documents for data verification and evaluated the applicant's monitoring procedures. OSI found no significant regulatory violations during the applicant inspection and concluded that the studies appear to have been conducted adequately and that the data generated may be used to support the application.

12. Labeling

The proprietary name, Impavido, is considered acceptable by the Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis.

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology concluded that a Medication Guide for patients would be useful to communicate information about the risk of teratogenicity and the importance of pregnancy prevention.

Major issues that were discussed with the applicant in labeling negotiations included the language in the WARNINGS and PRECAUTIONS, USE IN SPECIFIC POPULATIONS, and NONCLINICAL TOXICOLOGY sections to characterize the reproductive effects observed in the animal studies and the potential effects in humans. All issues were resolved. Labeling will include a boxed warning about the potential for fetal harm and language in other sections

describing the reproductive effects in animal studies in greater detail. Miltefosine will be contraindicated in pregnancy.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the recommendation of the review team that miltefosine be approved for the treatment of VL due to *L. donovani*, CL due to *L. braziliensis*, *L. guyanensis*, and *L. panamensis*, and ML due to *L. braziliensis*.

- Risk Benefit Assessment

For each of these indications, the risk benefit assessment favors miltefosine. Study 3154 demonstrated that miltefosine is noninferior to amphotericin B in the treatment of VL. Study 3168 was a placebo-controlled trial that demonstrated that miltefosine is effective in the treatment of CL. The findings of efficacy in VL and CL, along with the results of the single-arm Study Z022, support the conclusion that miltefosine is effective in the treatment of ML as well. The only therapy approved by FDA for leishmaniasis is amphotericin B liposome for injection (AmBisome®) for VL. Miltefosine is generally well-tolerated and offers an oral alternative to other therapies for leishmaniasis. The most common adverse reactions are gastrointestinal reactions. Miltefosine causes embryo-fetal toxicity and should be contraindicated in pregnancy.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

DRISK performed a risk evaluation and mitigation strategy (REMS) review and concluded that a REMS should not be put into place for miltefosine and that a Medication Guide for patients would be useful to communicate information about the risk of teratogenicity and the importance of pregnancy prevention.

- Recommendation for Other Postmarketing Requirements and Commitments

Recommendations for postmarketing requirements:

1. Conduct a dedicated QT study to evaluate the effects of Impavido on the QT interval.

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

2. Conduct a study to evaluate the effects of Impavido on spermatogenesis and male hormones.

Final Protocol Submission:	March, 2015
Study Completion:	March, 2018

Final Report Submission: March, 2019

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

Final Protocol Submission: March, 2015
Interim Report Submission: March, 2016, then annually
Study Completion: March, 2025
Final Report Submission: March, 2026

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

Final Protocol Submission: March, 2015
Interim Report Submission: March, 2016, then annually
Study Completion: March, 2020
Final Report Submission: March, 2021

Recommendations for postmarketing commitments:

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

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

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

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

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/s/

THOMAS D SMITH
02/18/2014