Deputy Office Director Decisional Memo

<table>
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<tr>
<th>Date</th>
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<tr>
<td>From</td>
<td>John Farley, M.D., M.P.H.</td>
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<tr>
<td>Subject</td>
<td>Deputy Office Director Decisional Memo</td>
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<tr>
<td>NDA #</td>
<td>NDA 204,684</td>
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<tr>
<td>Applicant Name</td>
<td>Paladin Therapeutics, Inc.</td>
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<tr>
<td>Date of Submission</td>
<td>April 19, 2013</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>March 19, 2014</td>
</tr>
<tr>
<td>Proprietary Name / Established (USAN) Name</td>
<td>IMPAVIDO/ Miltefosine</td>
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<tr>
<td>Dosage Forms / Strength</td>
<td>50 mg capsules for oral use</td>
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</table>
| Proposed Indication(s) | 1. Visceral leishmaniasis  
2. Cutaneous leishmaniasis  
3. Mucosal leishmaniasis |
| Action: | Approval |

Material Reviewed/Consulted

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<thead>
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<th>Action Package, including:</th>
<th>Names of discipline reviewers</th>
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<td>Medical Officer Review</td>
<td>Hala Shamsuddin, M.D.</td>
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<td>Statistical Review</td>
<td>Lan Zeng, M.S.</td>
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<td>Pharmacology Toxicology Review</td>
<td>James Wild, Ph.D.</td>
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<td>CMC Review</td>
<td>Maotang Zhou, Ph.D., Anamitro Banerjee, Ph.D., Mark Seggel, Ph.D., Bryan Riley, Ph.D.</td>
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<td>Microbiology Review</td>
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<td>Clinical Pharmacology Review</td>
<td>Seong Jang, Ph.D.</td>
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<td>Labeling Reviews</td>
<td>Adimbola Adebowale, Ph.D., Twanda Scales, R.N., M.S.N./Ed., Christine Corser, Pharm.D., Aleksander Winiarski, Pharm. D.</td>
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<tr>
<td>DRISK</td>
<td>Joyce Weaver, Pharm.D.</td>
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<td>Sumathi Nambari, M.D., M.P.H.</td>
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<td>PMHS Consult</td>
<td>Miriam Dinatale, D.O.</td>
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<td>DDBRUP Consult</td>
<td>Guodong Fang, M.D.</td>
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OND=Office of New Drugs  
DRISK=Division of Risk Management  
DMEPA=Division of Medication Error Prevention and Analysis  
OSI=Office of Scientific Investigations  
CDTL=Cross-Discipline Team Leader  
DDBRUP=Division of Bone, Reproductive, and Urologic Products  
PMHS=Pediatric and Maternal Health Staff
1. Introduction

*Leishmania* organisms are intracellular protozoan parasites that are transmitted to a mammalian host by the bite of the female phlebotomine sandfly. The main clinical syndromes are visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML). VL is the result of systemic infection and is progressive over months or years. Clinical manifestations include fever, hepatomegaly, splenomegaly, and bone marrow involvement with pancytopenia. VL is fatal if untreated. Liposomal amphotericin B (AmBisome®) was FDA approved in 1997 for the treatment of VL. CL usually presents as one or more skin ulcers at the site of the sandfly bite. In most cases, the ulcer spontaneously resolves within several months, leaving a scar. The goals of therapy are to accelerate healing, decrease morbidity and decrease the risk of relapse, local dissemination, or mucosal dissemination. There are no FDA approved drugs for the treatment of CL. Rarely, CL disseminates from the skin to the naso-oropharyngeal mucosa, resulting in ML. ML can also develop some time after CL spontaneous ulcer healing. The risk of ML is thought to be highest with CL caused by the subgenus *Viannia*. ML is characterized in the medical literature as progressive with destruction of nasal and pharyngeal structures, and death may occur due to complicating aspiration pneumonia. There are no FDA approved drugs for the treatment of ML.

Paladin Therapeutics submitted NDA 204, 684 seeking approval of miltefosine for the treatment of VL caused by *L. donovani* and for the treatment of CL and ML caused by members of the subgenus *Viannia*. The dosage form is a 50 mg capsule for oral use. The proposed dosing regimen is daily for 28 days with food for patients 12 years of age and weighing ≥ 30 kg. The number of 50 mg capsules per day is determined by bodyweight. For a body weight of 30-44 kg the dose proposed is: two 50 mg capsules daily; 1 capsule taken with breakfast and 1 with dinner. For a body weight of ≥ 45 kg the dose proposed is: three 50 mg capsules daily; one taken with breakfast, lunch, and dinner.

The efficacy review for this NDA relies upon the results of the following studies:

- **VL**
  - Study 3154, a randomized, open-label, noninferiority trial conducted in VL patients in India in 1999-2000.
  - Study Z025, a randomized, open-label trial conducted in Ethiopia in 2003-2005.

- **CL**
  - Study 3168, a randomized, placebo-controlled trial conducted in Colombia and Guatemala in CL patients in 2000-2002.
  - Study Z020, a randomized, open-label trial conducted in Brazil in 2007-2009.
  - Study Soto, an open-label study conducted in Bolivia in 2005-2007.

- **ML**
  - Study Z022, a single-arm study conducted at a single site in Bolivia in ML patients in 2004-2006.

The applicant submitted patient level data for each of these studies with the exception of Study Z025. The applicant did not conduct these studies.
The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of miltefosine for the indications proposed. For a detailed discussion of NDA 204,684, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background

The genus *Leishmania* is divided into two subgenera, *Leishmania* and *Viannia*. The *Leishmania* subgenus includes *L. donovani*, *L. chagasi/infantum*, *L. tropica*, *L. major*, *L. aethiopica*, *L. mexicana* and *L. amazonensis*. The subgenus *Viannia* includes *L. braziliensis*, *L. peruviana*, *L. guyanensis* and *L. panamensis*. Traditionally, *Leishmania* infections that occur in Asia, Africa, Europe and the Middle East are designated “Old World”, while infections that occur in the Americas are designated “New World”.

Miltefosine is an alkyllysophospholipid analogue with *in vitro* activity against the promastigote and amastigote stages of *Leishmania* species. *In vitro*, *L. donovani* is generally considered the most susceptible, and *L. braziliensis* and *L. major* the least susceptible. Variability in susceptibility between species and within species from different geographic areas as well as the limitations of the NDA data with respect to these issues were discussed at the Advisory Committee meeting (see Section 9) and is a review issue impacting labeling (see Section 12). The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death. Adverse drug effects are anticipated based on the mechanism of action and were observed in pre-clinical studies (see Section 4). The adverse drug effects observed in clinical trials and post-marketing in other countries are described in Section 8 and are addressed in labeling (see Section 12).

Miltefosine is registered in Germany as a topical drug to treat cutaneous cancers. As an oral dosage form, it is registered in Germany, several countries in South America and the Indian subcontinent for the treatment of VL and CL. Miltefosine was included in the WHO essential medicines list as an anti-leishmaniasis medicine in March 2011.

The FDA granted miltefosine orphan designation in October 2006 and Fast Track Designation in May 2010. The NDA was submitted on April 19, 2013 and granted a priority review with an original goal date of December 19, 2013. During the initial CMC review, validation data for the high-performance thin layer chromatography (HPTLC) method used to analyze some of the impurities was found to be inadequate. The applicant’s response to this deficiency was considered a major amendment, and the user fee goal date was extended 3 months to March 19, 2014. The applicant has requested a tropical disease priority review voucher as authorized by Section 524 of the Food, Drug, and Cosmetic Act, which lists leishmaniasis as a tropical disease for the purposes of the legislation.

References:


Reference ID: 3472914
3. CMC

I concur with the conclusions reached by the CMC reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding CMC issues precluding approval, but PMCs are recommended to develop a method for release and stability testing appropriate for life-cycle management.

Miltefosine is a new chemical entity (NCE). The specifications for miltefosine drug substance include tests for description, identity, water, impurities, heavy metals, and residual solvents. Inadequate validation data to support the HPTLC method used to analyze some of the impurities was identified as a deficiency early in the course of review. Upon review of an amendment submitted by the applicant, the CMC reviewers concluded that adequate validation data for the HPTLC method had been provided and that the method may be used as an interim method. The reviewers recommended that an HPLC method rather than an HPTLC method was more appropriate for life-cycle management. They recommended a PMC for the applicant to develop an appropriate method (such as HPLC) for release and stability testing (assay and impurities) of the drug product and the drug substance to facilitate life-cycle management of miltefosine capsules. They recommended an additional PMC in conjunction with the development and implementation of the HPLC methodology to perform testing in accordance with the 2003 FDA draft guidance for stratified testing. I concur with their recommendations.

The applicant provided 12 month stability data under long term conditions and 6 month stability data under accelerated conditions for close to commercial scale batches of the drug substance. The data support an expiration dating period of 24 months for the drug product, when stored at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F).

The proposed dissolution method and the revised dissolution acceptance criteria were deemed acceptable. The product quality microbiology reviewer has found the NDA acceptable.

The Office of Compliance has made an “Acceptable” overall recommendation for all the drug manufacturing facilities.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. Embryotoxicity and teratogenicity were observed in animal studies which impact the overall risk benefit of the drug in pregnant women. The effect on male fertility warrants further clinical evaluation.

Miltefosine is embryotoxic and teratogenic in animals at doses lower than the therapeutic human dose. Embryo-fetal toxicity, including death and teratogenicity, was observed in animals administered prior to mating, during early pregnancy, and during organogenesis at doses lower than the maximum recommended human dose (MRHD). Miltefosine caused fetal resorption.
during the period of organogenesis and fetal deaths in rats and rabbits and was a potent teratogen in rats.

Female fertility was affected in both rats and dogs. In a rat study, estrus cycle arrest in the metestrus or diestrus phases occurred at 1.0 times the MRHD based on BSA comparison. In a 52 week dog study, increased numbers of atretic follicles in the ovaries, and cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus was observed at doses below the MRHD based on BSA comparison.

There were effects on male fertility noted in rats; these effects were attenuated or absent in dogs at similar plasma exposures. In a male fertility study in rats, miltefosine produced a dose-dependent impairment of the male reproductive system in males treated for 4-weeks before mating and up to 7 days. Effects included: reduced copulation index, reduced fertility, reduced sperm number and viability, increased morphologically altered sperm, and atrophied testes, prostate, and seminal vesicles.

In 8- and 52-week toxicology studies in rats, the main target organs for toxicity were the kidney (chronic nephropathy) and GI tract (hyperplasia of stomach chief cells, hyperplasia and hypertrophy of intestinal mucosa) in addition to the reproductive system abnormalities described above. The overall results of the genetic toxicology studies suggest miltefosine has a negative potential for genetic toxicity in humans. Because the intended human exposure is less than 6 months, formal rodent carcinogenicity studies were not performed. However, in a 52-week oral toxicity study in rats, tumors were observed at the high-dose of miltefosine (21.5 mg/kg/day). Tumors included: benign basal cell adenoma of the skin, multiple histiocytic sarcoma, squamous cell carcinoma in the uterus and malignant uterine adenoacanthoma in 1 of 30 females and testicular Leydig cell adenoma observed in 3 of 30 males.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Of note, the terminal elimination phase half-life is estimated to be 30 days, which has implications for duration of contraception recommendations in labeling to mitigate the teratogenicity risk.

Due to concerns regarding toxicity, no clinical pharmacology / pharmacokinetic (PK) studies were conducted in healthy volunteers. All clinical studies were conducted in patients. PK parameters were available from two studies. PK parameters were obtained on Day 23 in a study of 4 different doses in adult/adolescent (>12 years) patients with VL. PK parameters were also obtained in a study of adult patients (Dutch soldiers) with CL dosed with 50 mg TID (150 mg/day) for 28 days. In both studies, it was noted that plasma concentrations did not reach a steady state at the end treatment (28 days). Based upon modeling, the terminal elimination phase half-life was estimated to be 30 days. Due to the limited data, no exposure-response analyses were conducted.
Based primarily upon the results of study 3168 (see Section 7 for study details) demonstrating safety and efficacy for the regimen proposed by the applicant, the reviewer agreed with the applicant’s proposed dosing regimen, 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 dose of 2.5 mg/kg/day.

Miltefosine is metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol, which is oxidized to palmitic acid. Miltefosine is not a substrate or a significant inhibitor or inducer of hepatic cytochrome P450 (CYP) enzymes. Drug interaction studies have not been conducted. Due to the absence of significant P450 inhibition or induction, the clinical pharmacology reviewer considered a drug interaction study with oral contraceptives not to be necessary, and I concur with this assessment.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology issues that preclude approval.

*In vitro* activity of miltefosine has been demonstrated against the promastigote and amastigote forms of a small number of strains of a variety of *Leishmania* species. Some *in vitro* studies have reported that sensitivity to miltefosine varied between species. The reviewer noted that such differences could be due to inter-laboratory variability or a lack of methods standardization.

Studies in murine models of VL and CL support activity against *L. donovani, L. infantum, L. mexicana,* and *L. major.* In one study, the activity of miltefosine was about 3-fold higher against the Indian strain of *L. donovani* compared to the Ethiopian strain of *L. donovani.*

The different *Leishmania* species are morphologically indistinguishable. Species may be differentiated by isoenzyme analysis, molecular methods such as polymerase chain reaction, or fluorescent antibody tests using monoclonal antibodies; however, these assays are not FDA cleared tests. In some of the clinical trials for CL, efforts were made to identify the *Leishmania* species by one of these tests for research purposes. However, the details of the methods and performance characteristics of the assays in the laboratories where testing was performed were not available for an independent review. Therefore, the reviewer recommended that the summary of the clinical trial findings (cure rates) in the labeling should be based on *Leishmania* species known to be prevalent in the endemic areas based on epidemiological findings in different geographic regions and not on *Leishmania* species identified by experimental methods.

7. Clinical/Statistical-Efficacy

I concur with the conclusions of the clinical reviewer, statistical reviewer, the CDTL, and the Division Director that substantial evidence of efficacy has been provided. For VL, study 3154 demonstrated that miltefosine is non-inferior to amphotericin B. Study 3154 is supported by Study Z025. For CL, Study 3168 demonstrated the superiority of miltefosine over placebo.
Study 3168 is supported by Study Soto and Study Z020. For ML, I find the evidence of efficacy from the single arm, historically-controlled study Z022 to be persuasive, supported by study 3154 and study 3168. Lower efficacy in patients treated with a lower mg/kg dose, particularly in CL, was observed. This will be further evaluated post-marketing. I discuss the study findings and evidence of efficacy in more detail below.

**VL**

**Study 3154:** Study 3154 was a randomized, open label, non-inferiority design comparative study conducted in 1999-2000 at 3 study sites in India where epidemiologically *L. donovani* is known to be the infecting pathogen. Patient level data was submitted for review. Subjects ≥ 12 years of age with clinical signs and symptoms compatible with VL parasitologically confirmed by spleen or bone marrow aspirate were randomized in a 3:1 ratio to receive oral miltefosine 50 mg twice a day if weight ≥ 25 kg or once a day if weight < 25 kg for 28 days or IV amphotericin B deoxycholate 1 mg/kg every other day for 15 doses.

Treatment response was classified as Initial Cure, Final Cure, Relapse or Failure. Initial Cure was defined as absence of parasites at the end of therapy (parasite score 0 on spleen or bone marrow aspirates). Treatment failure was defined as spleen or marrow aspirate score > 1 at EOT or score > 0 any time one month after EOT. Final Cure was defined as Initial Cure plus no relapse and absence of clinical signs and symptoms attributable to leishmaniasis during the 6 months follow up. Subjects who had experienced initial cure but who did not have absence of clinical signs and symptoms of VL at the 6 months follow up visit were to undergo a repeat spleen or marrow aspirate. The primary efficacy endpoint was Final Cure.

For the NI margin justification, the Division reviewed literature submitted by the applicant comparing the cure rates in VL of amphotericin B with sodium stibogluconate as a pseudo-placebo. M1 was conservatively estimated at 40.1%. While the pre-specified NI margin for study 3154 was 15%, the Division recommended a 10% NI margin as clinically acceptable.

299 subjects received miltefosine and 99 subjects received amphotericin B. There was a gender imbalance noted at baseline. A statistically significant higher percentage of males were randomized to miltefosine (p=0.035). The gender imbalance varied by site and raised concerns regarding the randomization process. Inspection of the source data from one of the sites with a gender imbalance did not identify an explanation. The final cure rate in both arms was similar for males and females. The statistical reviewer conducted an analysis of gender, center, and final cure and found no apparent relationship.

The final cure according to the applicant’s ITT analysis was 94.3% in the miltefosine arm vs. 97.0% in the amphotericin arm. The difference was 2.7% (95% CI -3.0%, 6.8%), indicating that miltefosine is non-inferior to amphotericin. There were 100 subjects without absence of signs and symptoms at 6 months. Of these 100 subjects, 27 underwent an aspirate at 6 months for parasitologic confirmation of cure or relapse per protocol, and this was quite variable among sites. The FDA clinical reviewer evaluated the clinical data for these 100 subjects, blinded as to which subject underwent a follow up aspirate. She identified 14 subjects who had not undergone a biopsy but she assessed clinically as warranting further evaluation. If
these 14 subjects are conservatively considered failures, the final cure rates are estimated at 90.4% in the miltefosine arm and 94.9% in the amphotericin arm. The difference is 4.6% (95% CI -2.0%, 9.8%).

Study Z025: Study Z025 was conducted in 2003-2005 by Medicins Sans Frontieres in a semi-nomadic population in Ethiopia, where epidemiologically L. donovani is known to be the infecting species. There was a high prevalence of HIV co-infection (approximately 30% of those tested). An important limitation is that the applicant did not submit patient level data for this study. Medicins Sans Frontieres (MSF)-Holland, who conducted the study, could not accommodate the request because data sharing with industry was not included in the patient consent at the time of the original Ethics Review Board approval. MSF-Holland agreed to share the case report forms of patients with serious adverse events as that may contribute to the pharmacovigilance database. The applicant’s study report and the FDA analyses both used the published article that reported the findings of this study.

Study Z025 was a randomized, open-label study comparing oral miltefosine 100 mg daily for 28 days to IM sodium stibogluconate (SSG) 20 mg/kg daily for 30 days. Only male subjects at least 15 years of age were enrolled, because birth control in women could not be assured. VL was diagnosed based on clinical symptoms and a high Leishmania direct agglutination test titer. Subjects with an indeterminate titer and subjects previously treated for VL underwent spleen or lymph node aspiration for parasitologic diagnosis. Spleen or lymph node aspirates were performed at end of therapy. The primary endpoint was final cure, defined as initial cure and no symptoms of relapse at 6 months. Initial cure was defined as a negative aspirate at EOT with clinical improvement, or if an aspirate could not be obtained, as clinical cure.

290 subjects received miltefosine and 290 subjects received SSG. Approximately 88% experienced initial cure at end of therapy in each arm. Although initial cure was similar, SSG recipients were significantly more likely to die by EOT (9.6% vs. 2.1%, p=0.0001), while miltefosine subjects were significantly more likely to experience initial failure (7.9% vs. 0.7%, p<0.0001). Initial failures were retreated with another drug (SSG if randomized to miltefosine, amphotericin B if randomized to SSG). Final cure rates in the ITT population were 60% for miltefosine and 65.2% for SSG, difference -5.2% (95% CI -2.8%, 13.1%). There were substantial losses to follow-up in study Z025. In the PP population, which excludes retreated initial failures, final cure rates were 79.5% for miltefosine and 82.2% for SSG, difference -2.7% (95% CI -4.6%, 10.1%).

Other Supportive Data: The applicant submitted study report summaries for dose ranging studies conducted in India. The dose ranging trials indicated that doses lower than 2.5 mg/kg/day were less effective than higher doses, and that durations of less than 4 weeks were less effective than longer durations. Doses higher than 2.5 mg/kg/day were poorly tolerated due to vomiting and renal and hepatic toxicities.

The applicant also submitted study report summaries or published literature describing 6 single arm post-marketing studies in VL patients treated with miltefosine conducted in India (3), Nepal (2), and Bangladesh (1). Final cure rates in the ITT population in these 6 studies ranged from 71.8% to 94.3%.
Study 3168: Study 3168 was a randomized, placebo-controlled study conducted in Colombia and Guatemala in 2000-2002 enrolling subjects ≥ 12 years of age with parasitologically confirmed CL lesions. Subjects with ≥ 45 kg body weight received miltefosine 50 mg or matching placebo three times a day, while subjects < 45 kg body weight received miltefosine 50 mg or matching placebo twice a day. The primary endpoint was apparent or partial cure at 2 weeks followed by definite cure at 6 months.

89 subjects received miltefosine and 44 subjects received placebo. The statistical and clinical reviewers raised concerns regarding the randomization methodology as treatments were marked with “A” or “B”, ID numbers were not assigned sequentially at one site, and randomization dates were not provided. The reviewers noted that the robust results lessened the concerns. Miltefosine was superior to placebo for definite cure (66.3% vs. 29.5%, p value <0.0001). The treatment difference was 36.8% (95% CI 20.1%, 53.4%).

Cure rates were higher in Colombia than Guatemala in both arms. A possible explanation raised by the clinical reviewer was the difference in the prevalent epidemiologic species in each country. Epidemiologically, *L. panamensis* and *L. braziliensis* respectively cause approximately 54% and 30% of CL lesions in Colombia, while *L. braziliensis* causes approximately 75% of CL lesions in Guatemala. *L. braziliensis* is known to cause more protracted disease compared to other species.

Study Soto: Study Soto was an investigator-initiated, open-label comparative study conducted in 2005-2007 in Bolivia where *L. braziliensis* is epidemiologically expected to be the predominant species. The applicant did not have access to the original protocol. The clinical and statistical reviewers questioned the randomization process, and there was no pre-specified statistical hypothesis of superiority or non-inferiority. Subjects ≥ 12 years of age were assigned 2:1 to receive oral miltefosine 2.5 mg/kg/day for 28 days or IM meglumine for 20mg/kg/d for 20 days. The primary efficacy endpoint was definite cure, defined as complete re-epithelialization of all lesions at 6 months after EOT. Based on the FDA analyses, definite cure occurred in 32 of 40 miltefosine subjects (80%), and 13 of 18 subjects who received meglumine (72.2%).

Study Z020: Study Z020 was conducted in 2007-2009 and was split into two studies, Z020a and Z020b. Study Z020a was conducted in an area of Brazil where *L. guyanensis* is epidemiologically the predominant pathogen and Z020b was conducted in an area of Brazil where *L. braziliensis* is epidemiologically the predominant pathogen. Both studies were randomized, open-label, comparative trials that enrolled children 2-11 years of age and adults ≥ 12 years of age. Subjects with parasitologically confirmed CL received either miltefosine at a target dose of 2.5 mg/kg/day for 28 days or meglumine IM at 20 mg/kg/day for 21 days. The primary endpoint was definite cure, defined as complete re-epithelialization all initial ulcers at 2 months and at 6 months and no new lesions and no residual lesions with parasites or ≥ 50%
enlargement of a lesion prior to 6 months. There was no pre-specified statistical hypothesis, but the original protocol and other materials submitted indicate the intent was for the primary analysis to be for the study as a whole. The overall ITT analysis for study Z020 showed definite cure rates of 88 of 120 (73.3%) among miltefosine treated subjects and 36 of 60 (60.0%) among meglumine treated subjects.

ML

Study Z022: The sponsor submitted one single arm study, Study Z022, conducted in 2004-2006 in Bolivia, where _L. braziliensis_ is epidemiologically the predominant pathogen. Study Z022 was originally designed with an Amphotericin B comparator arm which was discontinued. The study report states that there were issues with patient acceptability after the initial subjects treated with oral miltefosine were noted to improve. 79 adult subjects received a target miltefosine dose of 2.5 mg/kg/day (150 mg/day) for 28 days. The primary efficacy endpoint was cure at 12 months, defined as ≥ 90% improvement in mucosal severity score at 12 months compared to baseline. 49 of 79 subjects (62%) were classified as cured. The mean mucosal severity score at baseline was 10, indicating involvement of at least 2 of 5 anatomic sites (nasal skin, nasal mucosa, palate, pharynx, and larynx). In a published manuscript describing this study², a subgroup analysis including 36 patients with extensive disease at baseline (defined as involvement of the palate, pharynx, and larynx) was presented. The cure rate at 12 months in the extensive disease subgroup was 58%. A published article reports on 2-year follow up for the subjects enrolled in Study Z022 and on the efficacy of extended duration of miltefosine treatment³. 41 of the cured subjects were located and re-examined by an ENT physician at 2 years after the end of therapy. 39 were still cured, and 2 had relapsed with infiltration of the palate and vocal cords respectively.

ML is a rare sequelae of CL, occurring in 2-5% of persons infected with _L. braziliensis_, and less commonly in persons infected with other species of the subgenus _Viannia_ ⁴. ML is described as relentlessly progressive with destruction of normal nasal and pharyngeal anatomy, and a risk of death due airway obstruction or aspiration pneumonia.⁵,⁶,⁷ I reviewed the sole literature report describing spontaneous resolution in two cases of ML⁸. In these two cases, the patients experienced significant nasopharyngeal tissue destruction which then stopped progressing during an unspecified length of follow-up. I conclude that ML is a rare disease

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which is known to invariably progress to significant nasopharyngeal tissue destruction that can be life-threatening. This natural history of disease is acceptable as a historical control for Study Z022\(^9\). There is no approved treatment for ML. The patients enrolled in Study Z022 had an overall cure rate of 62%, with a 58% cure rate in the extensive disease subgroup. While Study Z022 is a single arm historically-controlled study with limitations, I find the evidence of the efficacy of miltefosine for ML persuasive. Although Study 3154 was conducted in an area where *L. donovani* is prevalent, I find the demonstration of the efficacy of miltefosine in the treatment of VL, a more serious manifestation of the disease, to be supportive. In addition, Study 3168 demonstrated the efficacy of miltefosine in the treatment of CL in a region where the subgenus *Viannia* is prevalent. This subgenus is responsible for most cases of ML.

**Miltefosine Dose by Weight and Cure Rates**

In each of the CL studies and in all studies combined, miltefosine subjects who received less than 2 mg/kg/day had a lower 6 month cure rate compared to subjects who received higher doses. (See Table 1). In a logistic regression analysis limited to patients \( \geq 45 \) kg who were treated with 150 mg/day, patients with lower baseline weight (and therefore a higher mg/kg daily dose) were more likely to achieve definite cure at 6 months \((p=0.0112)\). A trend was also noted in Study 3154 in VL. The number of subjects in the lowest mg/kg dose strata is limited.

**Table 1: Definite Cure Rates by Miltefosine Dose and Study Site for CL Studies**

*Source: Table 2, Statistical Review Addendum 1, NDA 204,684*

<table>
<thead>
<tr>
<th>MLT Dose (mg/kg)</th>
<th>Study 3168 Columbia</th>
<th>Study 3168 Guatemala</th>
<th>Study Z020a Manaus, Brazil</th>
<th>Study Z020b Bahia, Brazil</th>
<th>All</th>
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<tbody>
<tr>
<td>1.4 -&lt; 2</td>
<td>2/4 (50%)</td>
<td>0/1 (0.0%)</td>
<td>4/10 (40%)</td>
<td>2/2 (100%)</td>
<td>8/17 (47.1%)</td>
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<tr>
<td>2 -&lt; 2.5</td>
<td>18/25 (72%)</td>
<td>7/14 (50%)</td>
<td>13/18 (72.2%)</td>
<td>6/9 (66.7%)</td>
<td>44/66 (66.7%)</td>
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<td>2.5 -&lt; 3</td>
<td>16/16 (100%)</td>
<td>11/22 (50%)</td>
<td>8/10 (80%)</td>
<td>21/24 (87.5%)</td>
<td>56/72 (77.8%)</td>
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<tr>
<td>( \geq 3 )</td>
<td>4/4 (100%)</td>
<td>1/3 (33.3%)</td>
<td>2/2 (100%)</td>
<td>5/5 (100%)</td>
<td>12/14 (85.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40/49 (81.6%)</td>
<td>19/40 (47.5%)</td>
<td>27/40 (67.5%)</td>
<td>34/40 (85%)</td>
<td>120/169 (71.0%)</td>
</tr>
</tbody>
</table>

This finding is consistent with published literature. In a published dose finding study\(^10\), subjects who received 0.75-1.5 mg/kg/day had lower responses compared to subjects who received approximately 2.3 mg/kg/day.

In Study 3154 (VL), the mean weights were 38.6 kg in the miltefosine arm and 38.3 kg in the amphotericin B arm. Miltefosine per kg dose ranged from 1.5-4.0 mg/kg. In Study 3168 (CL), the mean weights were 59.5 kg in the miltefosine arm and 58.4 kg in the placebo arm. Miltefosine per kg dose ranged from 1.8-3.4 mg/kg. In the most recent U.S. population survey, the 50\(^{th}\) percentile weight of U.S. adults 20 years and older is 86.1 kg (5\(^{th}\) percentile 61.5 kg, 95\(^{th}\) percentile 124.1 kg) for males and 71.3 kg (5\(^{th}\) percentile 50.2 kg, 95\(^{th}\) percentile 113.8 kg) for females\(^11\).

\(^9\) 21CFR§314.126(b)(2)(v) describes circumstances, such as diseases with high and predictable mortality, in which a historical control is acceptable in an adequate and well-controlled study.

\(^10\) Soto J et al. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. CID 2001;33:e57-e61

Because of the lower cure rates observed in patients receiving a lower mg/kg daily dose and the expectation that U.S. adults treated with miltefosine are likely to receive less than the target dose of 2.5 mg/kg daily, the applicant has agreed to a postmarketing commitment (PMC). A descriptive study regarding efficacy and adverse reactions in patients with leishmaniasis who weigh more than 75 kg will be conducted.

8. Safety

I concur with the clinical reviewer, CDTL, and Division Director that there are no safety issues which preclude approval. There are safety concerns which will be addressed in labeling. There is a risk of fetal death and teratogenicity based on animal studies. A Boxed Warning, Contraindication, Medication Guide, and pregnancy registry postmarketing requirement (PMR) are planned. In comparative clinical studies, creatinine elevation, transaminase elevation, gastrointestinal adverse events, and thrombocytopenia were observed. Male reproductive toxicities and the effect of miltefosine on the QT interval will be further evaluated as PMRs.

Safety Data Base: The efficacy studies summarized in Section 7 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 period from September, 2004, to November, 2011.

Comparative Studies: In Study 3154 (VL), there were 2 deaths among the 299 miltefosine recipients and no patient who received amphotericin B died. These deaths were assessed by the clinical reviewer as not likely to be related to miltefosine. Serious adverse reactions were reported in 6 of the miltefosine recipients and 1 of the amphotericin B recipients. Approximately 3% of patients discontinued treatment in each treatment arm due to an adverse reaction. Diarrhea was more common among miltefosine recipients (20.4% vs. 6.1%) as was vomiting (37.8% vs. 20.0%). Creatinine (Cr) elevations ≥ 1.5 times above baseline occurred in approximately 10% of miltefosine recipients and in 40% of amphotericin B recipients at the end of therapy. Elevations of transaminases during therapy occurred in up to half of miltefosine recipients and up to a third of amphotericin B recipients. The elevations were < 3x ULN in 94% of those who experienced transaminase elevation. Platelet count < 150,000 at the end of therapy was common in both arms (62% of miltefosine recipients and 54% of amphotericin B recipients). Platelet count < 50,000 at the end of therapy was uncommon (2.4% of miltefosine recipients and 2.0% of amphotericin B recipients).

In Study 3168 (placebo controlled, CL), 12/89 (13.4%) miltefosine recipients had Cr increases of 1.5-3 times above baseline, compared to 2/44 (4.5%) placebo subjects at end of therapy. The frequency of AST and ALT increases above upper limit of normal at end of therapy was similar in miltefosine and placebo recipients (approximately 5%).
In Studies Soto and Z020 (meglumine comparator, CL) approximately 25% of miltefosine recipients and 11% of meglumine recipients had Cr elevations 1.5-3 times above baseline at the end of therapy. The frequency of AST and ALT increase above upper limit of normal at end of therapy was similar in miltefosine and meglumine recipients (approximately 5-10% and all but 1 subject < 3xULN).

Post-marketing Reports: Post-marketing, 3 cases of thrombocytopenia during miltefosine therapy were reported in HIV positive patients co-infected with VL. The German product labeling was updated in 2008 to include thrombocytopenia as an adverse event.

Female Reproductive Toxicities: As described in Section 4, miltefosine is embryotoxic and teratogenic in animals and impacted female fertility. A total of 143 women at least 12 years of age were enrolled in the premarketing clinical trials (Studies 3168, Soto, Z020, Z022 and 3154). All were required to use some form of birth control for the duration of treatment and for 2-3 months post therapy. No pregnancies were reported. Only 3 pregnancies have been reported in Phase 4 studies, without congenital abnormalities. Pregnancy labeling is further discussed in Section 12. A pregnancy registry will be required as a PMR.

Male Reproductive Toxicities: As described in Section 4, there were effects on male fertility noted in rats. Spermiograms were obtained at screening, 2 weeks and 6 months in 15 men (11 miltefosine recipients) who participated in Study 3168 (CL). There were large variations in sperm counts and motility. Post treatment spermiograms were also obtained in 12 miltefosine subjects enrolled in Study 3154 (VL). Two of these had oligospermia. 220 male subjects (197 miltefosine recipients) who previously participated in Phase 2 VL studies and in Study 3154 (VL) in India and who had a female sexual partner were retrospectively tracked and queried regarding fertility documented by at least one delivery or ongoing pregnancy. 69% of miltefosine male recipients (136/197) reported at least one delivery or ongoing pregnancy. A published literature article reported on 34 Dutch military personnel with CL returning from Afghanistan treated with miltefosine. The dose administered was 150 mg/day (range 1.3 to 2.1 mg/kg/day) for 28 days. Five (14.7%) subjects spontaneously reported decreased ejaculate volume and 16 (47.1%) additional subjects reported the same after specific questioning. Two of these subjects reported complete absence of ejaculation. Four (11.8%) subjects complained of scrotal tenderness, and epididymitis was diagnosed in one (3.0%). All adverse events resolved after completion of treatment.

The Division of Bone, Reproductive and Urology Products (DBRUP) considered the evaluations submitted by the applicant inconclusive, opined that the male reproductive signal in animals may be clinically relevant, and recommended an observational post-marketing study evaluating semen parameters (semen volume, sperm count, sperm concentration, sperm motility). This will be required as a PMR.

QT Interval: The effects of miltefosine on the QT interval have not been rigorously evaluated. A thorough QT study was waived because the need for lengthy exposures to achieve steady

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state and the toxicities of miltefosine precluded conducting such a study in healthy volunteers, and ethical considerations precluded conducting a placebo-controlled QT study in patients with leishmaniasis. A dedicated QT study will be required as a PMR.

Visual Assessment: Retinal degeneration that was dose and duration dependent was noted in the 8 week and 52 week rat toxicity studies, but was not noted in the dog toxicity studies. All Phase 1 and 2 studies and Study 3154 in India included weekly visual assessment (total 548 subjects). One subject in Study 3154 was noted as having “central retinosis”. Study 3168 in CL subjects also included weekly visual assessment. One subject had abnormal fundoscopy in one eye that was not specified and that returned to normal at 6 months. Visual findings were otherwise unremarkable, and no visual AEs were reported in any of the clinical studies, published literature, or reported to the German regulatory authorities post-marketing.

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? The committee voted 15 Yes and 1 No. The panel member who voted “No” was concerned about the phrasing of the question and discussed the data regarding variability in sensitivity between species and within the same species from different geographic areas. The dissenting member stated that if the question had been about using miltefosine for *Leishmania donovani* from the Indian subcontinent, then he would have voted ‘Yes’.

2. Has the applicant demonstrated the safety and efficacy of miltefosine for the treatment of cutaneous leishmaniasis? The committee voted 14 Yes and 2 No. Dissenting members stated that CL is often self-limited, and the risks of therapy may outweigh the benefits.

3. Has the applicant demonstrated the safety and efficacy of miltefosine for the treatment of mucosal leishmaniasis? The committee voted 13 Yes and 3 No. The committee members that voted ‘No’, stated that there may be selection bias in this single-arm study. They also stated that they would like to see more data from another study site, preferably in another country.

10. Pediatrics

Miltefosine was granted orphan designation and is therefore exempt from PREA. The applicant sought a treatment indication for children ≥ 12 years of age and adults.
11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

*Ethics Committee Oversight:* All submitted clinical trials were conducted in accordance with the national laws of the countries where the studies were conducted, the Declaration of Helsinki, and Good Clinical Practice. All submitted clinical trials were approved by an Independent Ethics Committee relevant to the centers involved. An Ethics Committee-approved written informed consent document was obtained from all participating subjects or legal guardians.

*Clinical Site Inspections:* In lieu of inspecting the clinical sites, some of which were closed in the interim, the FDA’s Office of Scientific Investigation inspected certified copies of the original source data for one of the clinical sites for the pivotal VL study 3154 (India) and one of the sites for the pivotal CL study 3168 (Guatemala) that were held at Paladin’s headquarters in Montreal, Canada. No data integrity issues were identified, and the inspection was classified as NAI (no action indicated).

*REMS:* DRISK was consulted regarding a risk mitigation strategy for teratogenicity. 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 for this long half-life drug, DRISK did not recommend that a REMS be put into place for miltefosine.

12. Labeling

*Indications and Usage:* A limitation of the clinical trials is that the *Leishmania* species were based on epidemiologic data regarding the species known to be prevalent in the area where the study was conducted. As noted in Sections 6 and 9 of this review, there are concerns regarding variability in sensitivity to miltefosine between species and within the same species from different geographic areas. The Division and applicant agreed to address this issue through a “Limitations of Use” statement in the PI.

*Mitigation of the Embryo-Fetal Toxicity Risk:* The risk of fetal death and teratogenicity, which occurred in animals administered miltefosine at doses lower than the recommended human dose, will be described in a Boxed Warning. The Boxed Warning will recommend obtaining a serum or urine pregnancy test in females of reproductive potential prior to prescribing miltefosine and advising females of reproductive potential to use effective contraception during therapy and for 5 months after therapy. The recommendation regarding use of
contraception for 5 months after therapy is based upon the long half-life of the drug with 5 months approximating 5 half-lives. In addition, the drug is contraindicated in pregnancy. The reviewers acknowledged that in some international settings, the risk benefit for use during pregnancy may favor treatment in certain circumstances as VL is a fatal disease and there may be no alternative treatment available. However, in the U.S., liposomal amphotericin B is available and approved for treatment of VL and can be administered to pregnant women.

In addition, a Medication Guide for patients will be provided which focuses on the embryo-fetal toxicity risk and the need for effective contraception.

Regarding the pregnancy category, the Pediatric and Maternal Health Staff recommended pregnancy category I. I concur with the Division conclusion that pregnancy category D was more appropriate based on the based on the known cytotoxicity of the drug and may communicate the potential risks more effectively.

Proprietary Name: DMEPA reviewed the proposed proprietary name, Impavido, and concluded the name was acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

I concur with the review team that the overall benefit risk is favorable and the appropriate regulatory action is Approval. Miltefosine will provide an effective oral treatment option for a serious tropical infectious disease. The only FDA-approved drug for VL is liposomal amphotericin B (AmBisome®). There are no approved drugs for CL or ML. Substantial evidence of efficacy has been provided for VL, CL, and ML. A limitation of the data is that the response rate may differ from that observed in the clinical trials when the drug is used in a different geographic setting due to possible differences in sensitivity to miltefosine between species and within species. This is addressed in a Limitation of Use statement in the PI. The major safety concern is embryo-fetal toxicity. Mitigation strategies for this risk include a Boxed Warning, Contraindication, and Medication Guide. A pregnancy registry will be required as a PMR. Male reproductive toxicities and the effect of miltefosine on the QT interval warrant further evaluation. These evaluations can take place post-marketing as a PMR.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None

- Recommendation for Postmarketing Requirements

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.

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.

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.

- Recommendations for Postmarketing Commitments

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

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).

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

Upon approval, the applicant will be issued a tropical disease priority review voucher as authorized by Section 524 of the Food, Drug, and Cosmetic Act.
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