CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204684Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sumathi Nambiar, MD, MPH
Subject	Division Director Summary Review
NDA #	204684
Applicant Name	Paladin Therapeutics, Inc.
Date of Submission	April 19, 2013
PDUFA Goal Date	With 3 month extension due to major amendment: March 19, 2014
Proprietary Name/ Established (USAN) Name	Impavido/miltefosine
Dosage Forms/Strength	Capsules 50 mg
Proposed Indications	1. Visceral leishmaniasis due to *Leishmania donovani* 2. Cutaneous leishmaniasis due to *Leishmania braziliensis, Leishmania guyanensis,* and *Leishmania panamensis* 3. Mucosal leishmaniasis due to *Leishmania braziliensis*
Action for NDA	Approval

Material Reviewed/Consulted	**Names of Discipline Reviewers**
Action Package including:	
Medical Officer Review	Hala Shamsuddin MD
Statistical Review	Lan Zeng MS
Pharmacology Toxicology Review	James Wild PhD
Chemistry Manufacturing and Controls	Anamitro Banerjee PhD, Mark Seggel PhD, Maotang Zhou PhD, Bryan Riley PhD
Microbiology Review	Shukal Bala PhD
Clinical Pharmacology Reviews	Seong Jang PhD
Cross-Discipline Team Leader Review	Thomas Smith MD
Risk Management	Joyce Weaver Pharm D
Pediatric and Maternal Health Staff Consult	Miriam Dinatale, D.O.
Division of Bone, Reproductive, and Urologic Products Consult	Guodong Fang, M.D.
Office of Scientific Investigations	Susan Thompson, M.D.
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D
Labeling Reviews	Twanda Scales R.N.,M.S.N, Christine Corser Pharm D, Adimbola Adebowale PhD

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 patients ≥12 years of age. The proposed dosing regimen is one 50 mg capsule twice daily with food for patients weighing 30-44 kg (66-97 lbs.) and one 50 mg capsule three times daily with food for patients weighing ≥ 45 kg (≥ 99 lbs.).

Leishmaniasis is caused by obligate intracellular protozoa of the genus *Leishmania*. The clinical manifestations are divided into three syndromes of visceral leishmaniasis, cutaneous leishmaniasis, and mucosal leishmaniasis. A single species of *Leishmania* can produce more than one clinical syndrome and each of the syndromes can be caused by more than species of Leishmania.

Human infection is caused by about 21 of 30 species that infect mammals. These include the *L. donovani* complex with 2 species (*L. donovani*, *L. infantum* [also known as *L. chagasi* in the New World]); the *L. mexicana* complex with 3 main species (*L. mexicana*, *L. amazonensis*, and *L. venezuelensis*); *L. tropica*; *L. major*; *L. aethiopica*; and the subgenus *Viannia* with 4 main species (*L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana*). Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies. The promastigotes injected by the sandflies during blood meals are phagocytized by macrophages and other types of mononuclear phagocytic cells and transform into amastigotes. The amastigotes multiply by simple binary fission and lead to rupture of the infected cell and invasion of other reticuloendothelial cells.[1]

Miltefosine is an alkyl phospholipid analog with *in vitro* activity against the promastigote and amastigote stages of *Leishmania* species. The presumed mechanism of action is inhibition of phosphocholine synthesis.

Liposomal amphotericin is the only FDA approved product for the treatment of visceral leishmaniasis.[2] There are no FDA approved drug products for the treatment of cutaneous or mucosal leishmaniasis. Miltefosine is available in Germany, several countries in South America, and in the Indian subcontinent. Miltefosine is included in the WHO essential medicines list as an anti-leishmaniasis drug.[3]

2. Background

The NDA was originally submitted on September 26, 2012 and received on September 27, 2012. A Refuse-to-File letter was issued on November 26, 2012, because of dataset

[1] http://www.cdc.gov/parasites/leishmaniasis/biology html; accessed March 9, 2014
[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050740s021lbl.pdf; accessed March 16, 2014
[3] http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf; accessed March 9, 2014

deficiencies which did not allow for a meaningful review of the efficacy and safety data. The application was resubmitted on April 19, 2013 and was granted a priority review designation.

During the review, the high-performance thin layer chromatography (HPTLC) method used to analyze some of the impurities was found to be deficient. 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.

Miltefosine was granted orphan designation for the treatment of leishmaniasis on October 10, 2006. The applicant has requested a tropical disease priority review voucher as authorized by Section 524 of the Food, Drug, and Cosmetic Act.

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 204684, please refer to discipline specific reviews and the Cross-Discipline Team Leader Review.

3. Chemistry and Manufacturing (CMC)

The CMC reviewers for this application are Dr. Maotang Zhou and Dr. Anamitro Banerjee. Dr. Mark Seggel is the biopharmaceutics reviewer and Dr. Bryan Riley is the product quality microbiology reviewer.

Miltefosine is a new molecular entity. The drug substance is manufactured by (b) (4) It is a hygroscopic (b) (4) and is freely soluble in water (b) (4) The applicant provided 12-month stability data under long-term conditions and 6-month stability data under accelerated conditions for the drug substance. No drug substance degradation was identified when stored in the proposed container closure system (b) (4) . The drug product, Impavido® is an oral capsule containing 50 mg of miltefosine. The excipients are colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water. All excipients are of compendial grade (USP/NF). The capsules are packaged in blister cards (7 blisters/strip) in a (b) (4) carton (2 strips/carton). The drug product is manufactured and packaged by (b) (4) The applicant has submitted up to 18-month long term stability data and 6-month stability data under accelerated conditions for the three primary stability batches. The applicant has accepted the CMC reviewers' proposal for a 24-month expiration dating period.

The CMC reviewers found the HPTLC method used to analyze some of the impurities deficient. The applicant was requested to repeat stress studies using appropriate conditions and to validate the HPTLC method using appropriately stressed samples. The reviewers considered use of the HPTLC method as an acceptable interim method with the provision that a high-performance liquid chromatography (HPLC) method be developed as a postmarketing commitment (PMC). The applicant has agreed to two PMCs, one to develop an HPLC method

and the second to perform in-process blend uniformity testing in accordance with the 2003 FDA draft guidance for stratified testing.

The inspections at all facilities have been completed and the Office of Compliance has determined that all facilities are acceptable.

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 the microbial limits specification for the drug product acceptable and recommended approval.

The final CMC review concluded that with the agreed to PMCs, 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.

I concur with the assessment of the CMC, Biopharmaceutics, and product quality microbiology reviewers.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology toxicology reviewer for this application is Dr. James Wild. The main target organs for toxicity identified in the 8 and 52-week toxicology studies in rats were kidney (chronic nephropathy), 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), 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 lens nucleus, swelling and vacuolization of lens fibers, and retinal degeneration).

In a 52-week toxicology study in dogs, toxicities in the gastrointestinal and female reproductive organs (increased numbers of atretic follicles in the ovaries, cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus) were noted. These findings reversed during recovery. Multifocal atrophy and degeneration of seminiferous tubules in high-dose (6.19 mg/kg/day) males were seen. These effects were reversed during recovery. In general, effects in male reproductive organs were less severe in dogs compared to rats.

As miltefosine was negative in the micronucleus assay, it was considered to be of low genotoxic potential in humans. Rodent carcinogenicity studies were not performed as the duration of therapy is less than 6 months.

In a male fertility study in rats, dose-dependent effects included reduced copulation index, fertility, and sperm number and viability, increased morphologically altered sperm, and atrophy of testes, prostate, and seminal vesicles. Diffuse tubular atrophy with degenerative

spermatocytes and spermatogonia were noted on histology. The No Observed Adverse Effect Level (NOAEL) dose was 3.16 mg/kg (approximately 0.15 fold the maximum recommended human dose). After a 10-week recovery period, the effects were reversed in rats receiving 8.25 mg/kg miltefosine; most effects were not fully reversed in rats receiving 21.5 mg/kg.

In a female fertility study, estrus cycle arrest in the metestrus or diestrus phases occurred at a dose of 21.5 mg/kg. At doses of 6.81 and 21.5 mg/kg, embryonic and fetal resorptions and proportion of dead fetuses increased. Substantial fetal visceral and skeletal malformations were also noted at the higher doses.

Miltefosine was a potent teratogen in rats when administered at doses of ≥1.2 mg/kg/day. Malformations included undeveloped cerebrum, hemorrhagic fluid in lumina of the skull, cleft palate and generalized edema. Doses ≥ 6.0 mg/kg caused pronounced fetal resorption in dams treated during the period of organogenesis. In the fertility study in female rats, a dose of 6.14 mg/kg/day produced visceral and skeletal abnormalities. The visceral abnormalities included misshaped cerebral structures, cerebral ventricles filled with brown masses, misshaped spinal cord, and misshaped and malpositioned eyes, hypophysis, and absent inner ear. The skeletal abnormalities included cleft palate, dumbbell shaped ossification of thoracic vertebral centers, increased sizes for skull bones, and markedly dilated suturae.

Dr. Wild recommends approval of the NDA. I agree with Dr. Wild's recommendation.

5. Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Dr. Seong Jang. No clinical pharmacology or pharmacokinetic (PK) studies were conducted in healthy volunteers. PK data were based on the efficacy and safety observed in several dose-finding studies. No exposure-response analyses were conducted because only limited PK data were available. The proposed dose was justified based on efficacy and safety data from dose finding studies and clinical trials.

The distribution phase half-life of miltefosine ranged from 6.4-8.5 days and the terminal elimination phase half-life was 30.7 (18.3) days. Plasma concentrations do not reach a steady state at the end treatment (i.e., 28 days). Miltefosine is metabolized by phospholipase 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. No drug interaction studies were conducted.

The proposed dosing regimen is one 50 mg capsule twice daily with food for patients weighing 30-44 kg (66-97 lbs) and one 50 mg capsule three times daily with food for patients weighing ≥ 45 kg (≥ 99 lbs). Miltefosine is administered with food to ameliorate gastrointestinal adverse reactions. The effect of food on the bioavailability of miltefosine has not been evaluated. Dr. Jang considers this regimen to be safe and effective for the treatment of both visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). I concur with Dr. Jang's recommendations.

6. Clinical Microbiology

The clinical microbiology reviewer for this NDA is Dr. Shukal Bala. Miltefosine is active *in vitro* against promastigotes and amastigotes of a variety of *Leishmania* species. The exact mechanism of action of miltefosine is not clear. Miltefosine interacts with lipids (phospholipids and sterols), including membrane lipids, inhibits cytochrome c oxidase (mitochondrial function), and cause apoptosis like cell death. The susceptibility of different *Leishmania* species to miltefosine can vary by geographic regions. Studies in animal models of visceral and cutaneous leishmaniasis support the activity of miltefosine against *L. donovani, L. infantum, L .mexicana,* and *L. major*. Some strains of *L. braziliensis* are considered to be intrinsically less susceptible to miltefosine due to a low expression of miltefosine transporter and protein complex. No data are available on cross-resistance between miltefosine and other anti-leishmanial drugs.

In some of the clinical studies used to support this NDA, attempts were made to identify the *Leishmania* species using different assay methods. As the details of these tests and performance characteristics of these methods were not available for review, Dr. Bala's assessment is based primarily on the epidemiology of the disease and not the species identified in the clinical studies. Dr. Bala recommends approval of the NDA and I concur that there are no clinical microbiology issues precluding approval.

7. Clinical/Statistical

Efficacy

The clinical reviewer for this NDA is Dr. Hala Shamsuddin and the statistical reviewer Ms. Lan Zeng. The applicant submitted data from the following trials to support the safety and efficacy of miltefosine in each of the following indications:

Visceral Leishmaniasis

1. Study 3154: A randomized, open-label, noninferiority trial conducted in India that compared miltefosine with amphotericin B deoxycholate.
2. Study Z025: A randomized, open-label trial conducted in Ethiopia by Medicins Sans Frontieres that compared miltefosine with sodium stibogluconate.

Cutaneous Leishmaniasis

1. Study 3168: A randomized, placebo-controlled trial conducted in Colombia and Guatemala.
2. Studies Z020a and Z020b: Identical randomized, open-label trials conducted in different regions of Brazil that compared miltefosine with meglumine antimoniate.
3. Study Soto: An open-label trial conducted in Bolivia that compared miltefosine with meglumine antimoniate.

Mucosal Leishmaniasis

1. Study Z022: A single-arm study conducted at a single site in Bolivia.

Visceral Leishmaniasis

Study 3154

Study 3154 was a noninferiority (NI) trial conducted at three sites in India where *L. donovani* is the most common cause of VL. Patients ≥ 12 years of age 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 ≥ 25 kg), or amphotericin B deoxycholate, 1 mg/kg/day intravenously every other day for 15 doses. VL was confirmed by the presence of *Leishmania* amastigotes in splenic or bone marrow aspirate. Initial cure was defined as eradication of parasites from a splenic or bone marrow aspirate at the end of treatment (EOT). Patients with a parasite density score of 1 at EOT were reassessed one month later and classified as initial cure if the parasite density was 0. Treatment failure was defined as parasite density score of > 1 at EOT or > 0 after EOT. The primary endpoint was final cure, defined as initial cure followed by no relapse and absence of clinical signs or symptoms attributable to VL (fever, splenomegaly, and hematologic indices) at 6 months.

Of the 400 patients randomized, 299 received miltefosine, and 99 received amphotericin B. The study arms were generally similar with the exception of a male preponderance in the miltefosine arm (70.6%) compared to the amphotericin B arm (58.6%). The median weight of study patients was 40 kg (range 14-67 kg).

Final cure rates in the applicant's analysis were 94.3% (282/299) in the miltefosine arm and 97.0% (96/99) in the amphotericin B arm, treatment difference 2.7 % [95% CI, (-3.0%, 6.8%)], demonstrating that miltefosine was noninferior to amphotericin B using an NI margin of 10%.

Dr. Shamsuddin conducted a blinded review of the case reports of 100 patients who still had signs and symptoms compatible with VL at the 6-month visit and re-classified 14 patients (12 miltefosine and 2 amphotericin B-treated) as treatment failures or relapses. Based on this reclassification, final cure rates in Dr. Shamsuddin's analysis were 90.3% (270/299) in the miltefosine arm and 94.9% (94/99) in the amphotericin B arm, treatment difference 4.6% [95% CI, (-2.0%, 9.8%)]. Using either analysis, miltefosine was noninferior to amphotericin B using an NI margin of 10%.

Dr. Shamsuddin and Ms. Zeng have reviewed the literature and justified an NI margin based on reported cure rates for sodium stibogluconate (SSG) as a putative placebo and reported cure rates for amphotericin B as the active comparator. Pentavalent antimony was considered a putative placebo as resistance to antimonials is prevalent in Bihar, India where these studies were conducted. In the ITT population, final cure rate in the SSG-treated patients was estimated at 47.1% [95% CI, (38.14%, 56.03%)] and 97.8% [95% CI, (96.14%, 99.52%)] in amphotericin B-treated patients. The treatment effect (M1) was estimated as 40.11% based on the difference between the upper limit of the 95% CI in SSG-treated patients and lower bound of the 95% CI in amphotericin B-treated patients (96.14-56.03%). Although an M2 of 15% can

be supported, they considered a 10% margin to be clinically acceptable as VL is a serious systemic disease. I agree with their approach and justification for the NI margin.

The majority of patients (225/299, 75.2%) were treated with doses of 2-3 mg/kg/day. Analysis of final cure rates based on dosing by mg/kg body weight suggests that cure rates are lower at miltefosine doses <2.5 mg/kg/day. Patients treated with doses of < 2.5 mg/kg/day had a final cure rate of 92.3% (120/130) compared to 95.9% (162/169) in those treated with doses ≥ 2.5 mg/kg/day. Ms. Zeng performed a logistic regression analysis based on the 271 patients who received miltefosine 100 mg/day as their body weight was ≥ 25 kg. No significant relationship between body weight and final cure at 6 months was seen (p=0.2057).

The weight distribution of patients enrolled in this study raises concerns about the applicability of the data to the US population. Anthropometric reference data for adults in the United States (2007–2010) indicate that the 50th percentile for males > 20 years of age is 86.6 kg and for females 71.3 kg. The 5th centiles are 61.5 and 50.2 kg for males and females respectively. With a median weight of 40 kg (range 14-67 kg), most patients enrolled in this trial were below the 5th centile of weight distribution of the US population. It is thus possible that at the proposed dose of 100-150 mg/day, lower efficacy may be seen in US patients. Despite this limitation of the data, the overall benefit-risk considerations support the use of miltefosine at the proposed dosing regimen for the treatment of VL. The clinical studies and the adverse reactions sections of the product labeling describe the weight distribution of patients in the trial. The clinical studies section also includes a statement that no patient weighed more than 70kg. This issue was also discussed at the Anti-Infective Advisory Committee meeting for miltefosine held on October 18, 2013. A postmarketing commitment has been agreed to by the applicant to conduct a study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Study Z025

Study Z025 was a randomized open label trial conducted in Ethiopia by Medicins Sans Frontieres (MSF), where VL due to *L. donovani* is endemic. Male patients ≥15 years of age with VL were randomized to receive oral miltefosine, 100 mg/day for 28 days, or intramuscular SSG, 20 mg/kg/day for 30 days. Female patients were excluded as birth control could not be assured.

The applicant was unable to obtain patient level data for this trial as data sharing with industry was not included in the patient consent and the original Ethics Review Board approval did not include analysis of data beyond what was included in the study proposal. MSF agreed to share the case report forms of patients with serious adverse events as it may contribute to the pharmacovigilance database.

This trial provides supportive evidence of the efficacy of miltefosine in VL. However, the lack of patient level data limited the reviewers' ability to verify the results or perform any additional analyses.

Baseline characteristics including age, BMI, hemoglobin, spleen size and ability to walk unaided were similar between the two arms. In contrast to Study 3154, which did not enroll

HIV positive patients, HIV positive patients were enrolled in this trial. HIV serology testing was voluntary and done 2-3 weeks after providing consent to be in the study. Sixty-five percent of enrolled subjects underwent voluntary HIV testing, and approximately 30% of those tested were infected. A higher percentage of patients in the miltefosine arm were HIV infected (22% vs. 15%), while a higher percentage of patients in the SSG arm had unknown HIV status (38% vs. 33%). Another issue with interpreting the results of final cure rate was that patients who failed initial therapy with miltefosine could receive SSG while those who failed SSG could receive amphotericin B.

Twenty-three miltefosine-treated patients who were initial failures were treated with SSG, while two SSG-treated patients subjects who were initial failures were treated with amphotericin B.

A total of 290 patients received miltefosine or SSG. Final cure rates as reported by the applicant were 60% (174/290) in the miltefosine arm and 65.2% (189/290) in the SSG arm. The total number of deaths was higher in the SSG arm; 34/290 (11.7%) in the SSG arm and 17/290 (5.9%) in the miltefosine arm.

Cutaneous Leishmaniasis

Study 3168
This was a randomized placebo-controlled double-blind trial conducted at two sites, one each in Colombia and Guatemala. *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 with parasitologically confirmed 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.

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. Definite cure also required that there be no more than 50% 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.

Of the 133 patients randomized, 89 received miltefosine and 44 received placebo. The majority of patients in both arms were males. The median body weight was 60 kg (range 29-84 kg) in the miltefosine arm and 59.5 kg (range 33-82 kg) in the placebo arm. The median lesion size in the miltefosine arm was 480 mm^2 (range 48-11360 mm^2) and in the placebo arm was 779 mm^2 (36-4800 mm^2).

Definite cure rates were 66.3% (59/89) in the miltefosine arm and 29.6% (13/44) in the placebo arm, treatment difference 36.8 % [95% CI, (20.1%, 53.4%)], demonstrating superiority of miltefosine over placebo. In both arms, higher cure rates were seen in patients from Colombia compared to patients from Guatemala. One possible explanation for this difference might be the differences in the prevalent species in each country. In Guatemala, *L.*

braziliensis is a more common cause of CL than in Colombia. *L. braziliensis* is known to cause a more protracted disease compared to other species. [4, 5]

The majority of patients (79/89, 88.8%) were treated with doses of 2-3 mg/kg/day. Analysis of final cure rates based on dosing by mg/kg body weight suggests that cure rates were lower at doses < 2.5 mg/kg/day. Patients treated with doses of < 2.5 mg/kg/day had a final cure rate of 61.4% (27/44) compared to 71.1% (32/45) in those treated with doses ≥ 2.5 mg/kg/day. Ms. Zeng performed a logistic regression analysis on the 154 patients in studies 3168 and Z020 who received miltefosine 150 mg/day as their body weight was ≥ 45 kg to test the effect of baseline weight and geographic region on definite cure. There was a significant relationship between baseline weight and definite cure (p=0.0112).

While the median body weight in this study was also lower than the 50th percentile for the US population, the median weight was higher than that seen in Study 3154. Despite this limitation of the data, the overall benefit-risk considerations support the use of miltefosine at the proposed dosing regimen for treatment of CL. The clinical studies section of the product labeling describes the weight distribution of patients in the trial and a statement that no patient weighed more than 84 kg. As noted in the discussion for VL, this issue was discussed at the Anti-Infective Advisory Committee meeting held on October 18, 2013. A post marketing commitment has been agreed to by the applicant to conduct a study regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75 kg.

Studies Z020a and Z020b

This study conducted in Brazil was split into two parts. Study Z020a was conducted in an area where *L. (V.) guyanensis* is the most common cause of CL and Study Z020b was conducted in an area where *L. (V.) braziliensis* is the most common cause of CL. Patients 2 to 65 years of age with CL were randomized 2:1 to receive miltefosine 2.5 mg/kg/day for 28 days or parenteral meglumine antimoniate, 20 mg/kg/day for 20 days. CL was confirmed by parasitology 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, definite cure was defined as complete re-epithelialization of all initial ulcers at 2 months and at 6 months, and no new lesions, or residual lesions with parasites, or ≥50% enlargement of a lesion prior to 6 months. No formal statistical testing was planned.

A total of 120 patients received miltefosine and 60 received meglumine antimoniate. Definitive cure rates for studies Z020a and Z020b pooled were 73.3% (88/120) in the miltefosine-treated patients and 60.0% (36/60) in the meglumine antimoniate-treated patients. Definite cure rate in patients aged ≥12 years was 27/40 (67.5%) for Manaus, Brazil and 34/40 (85%) for Bahia, Brazil. In this study, identified organisms were speciated. In study Z020a, 99% of isolates were *L. guyanensis* and all isolates in study Z020b were *L. braziliensis.*

[4] Herwaldt B, Arana B, Navin T. The natural history of cutaneous leishmaniasis in Guatemala. JID 1992; 165:518-527

[5] Soto J, Berman J. Treatment of New World cutaneous leishmaniasis with miltefosine Trans R Soc Trop Med Hyg 2006; 100 (S1): S34-40

Study Soto
This was an investigator-initiated open-label trial that was conducted at a single site in Bolivia, where *L. (V.) braziliensis* is the most common cause of CL. Patients ≥12 years of age were randomized 2:1 to receive miltefosine 2.5 mg/kg/day for 28 days or parenteral meglumine antimoniate 20 mg/kg/day for 20 days. The primary endpoint was clinical cure, defined as complete re-epithelialization of all lesions 6 months after completion of therapy. No formal statistical testing was planned. The trial was terminated before completing enrollment. Forty three patients received miltefosine, and 18 received meglumine antimoniate. Records for three miltefosine-treated patients were missing and so outcomes were only reported for 40 patients. The reported clinical cure rates were 80.0% (32/40) in the miltefosine arm and 72.2 % (13/18) in the meglumine antimoniate arm.

Mucosal Leishmaniasis

Study Z022
This single-arm study was conducted at a single site in Bolivia. *L. (V.) braziliensis* is the most common cause of ML in Bolivia. This study was originally designed as a comparative study of miltefosine and pentavalent antimony. According to the applicant, once the study team became aware that pentavalent antimony was ineffective, the protocol was modified to include amphotericin B as the control. However, patients refused to be treated with amphotericin B once the efficacy of miltefosine became known from the initial patients who were enrolled. This study was therefore modified to a single arm study evaluating miltefosine.

Patients ≥18 years of age with ML received miltefosine 2.5 mg/kg/day for 28 days. ML was confirmed by culture, histopathologic examination, or Montenegro skin test. The applicant used a "mucosal severity score" by assigning a severity score to each sign (erythema, edema, infiltration, erosion) at each anatomic site (nasal skin, nasal mucosa, palate, pharynx, larynx). The primary endpoint of clinical cure was defined as >90% reduction in mucosal severity score 12 months after the end of therapy.

The mean number of clinical sites involved was 1.8 ± 0.9. The mean baseline severity score (SD) was 10.0 (±8.1) and the median was 6 (range 1-38). Forty patients (51%) presented with mild disease, defined as involvement only of the nasal skin and nasal mucosa and 38 patients (49%) presented with extensive disease (involving the palate, pharynx, and larynx). Of the 79 patients treated with miltefosine, 49 (62.0%) were considered to be cured (all had severity score of 0) at the follow-up visit, 12 months after EOT. The 2-year follow up for patients enrolled in Study Z022 has also been published.[6] Of the cures, 41 were re-examined 2 years after the end of therapy by the same ENT physician who had initially evaluated the patient; 39 remained cured and 2 had relapsed with infiltration of the palate and vocal cords respectively. An additional four patient were contacted by phone, three of whom were asymptomatic and hence presumed cured and one reported bleeding and pain and was presumed relapsed.

[6] Soto J, Rea J, Valderrama M et al. Short report: efficacy of extended (six weeks) treatment with miltefosine for mucosal leishmaniasis in Bolivia. Am J Trop Med Hyg 2009;81:387-389

The results of Z022 have been published.[7] Although not included in the study report, the published article reported clinical response in 19 patients treated with amphotericin B deoxycholate at the same study center. The mean mucosal severity score at baseline was 10 (range 5-23), similar to that seen in miltefosine-treated patients. Of the 19 amphotericin-treated patients, 3 discontinued due to an adverse event and 2 were lost to follow up. Of the 14 evaluable patients, seven were cured (50.0%). Among the cures, four patients had disease limited to the nares and three patients had more extensive disease. Among the failures, five had disease limited to the nares and two had extensive disease. It seems unlikely that the cases were misclassified as each patient who experienced clinical worsening or relapse had a higher score at the end of the follow-up period than at the beginning of the study. The cure rate in the ITT population was 7/19 (36.8%).

The applicant summarized eight published studies, each including 10-59 patients, for a total of 238 reported patients. The reported cure rates ranged from 28%- 89% for pentavalent antimony (6 studies) and 29%- 90% for amphotericin B. Dr. Shamsuddin also reviewed published studies and noted similar response rates for pentavalent antimony and amphotericin B.

Mucosal leishmaniasis is a progressive disease with significant morbidity that can be potentially fatal. Granulomas in the anterior nasal septum progress to septal perforation after a few days or months. The disease can progress to involve the upper lip, the palate and the pharynx, resulting in severe deformity and feeding, breathing and phonation difficulties.[8] Secondary bacterial infections can develop and inter-current pneumonia is the leading cause of death.[9] In the one publication describing spontaneous clinical resolution without specific treatment in mucosal leishmaniasis, one patient was found to have a 2 cm septal perforation but was asymptomatic and remained symptom free during an unspecified period of observation. The second patient had extensive scarring of and damage to the nose, oropharynx and vocal cords.[10]

In Study Z022, ~ 50% of patients had extensive disease (involving palate, pharynx, and larynx), suggesting a lower likelihood of spontaneous cure. Approximately, 60% of patients had a mucosal severity score of 0 at 12 months after completing therapy indicating that they had complete resolution of disease. Additionally, the cure rate seen with miltefosine in this study was comparable and in some instances higher than that reported with other antileishmanial drugs.

[7] Soto J. et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. Clin Infect Dis 2007;44:350-6
[8] Lessa MM, Lessa HA, Castro TW et al. Mucosal leishmaniasis: epidemiological and clinical aspects. Braz J Otorhinolaryngol. 2007 Nov-Dec;73(6):843-7
[9] Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010. http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf
[10] Marsden PD1, Badaró R, Netto EM, Casler JD. Spontaneous clinical resolution without specific treatment in mucosal leishmaniasis. Trans R Soc Trop Med Hyg. 1991 Mar-Apr;85(2):221.

In the published literature, the reported cure rate for ML varies by region with higher cure rates generally reported in Brazil. [11] The efficacy of miltefosine in the treatment of ML in study Z022 was numerically higher compared to the cure rates seen with amphotericin B at the same study center in Bolivia. When compared with other published studies, the efficacy of miltefosine was numerically similar to that observed in patients treated with antimony in Peru. However, the cure rates in miltefosine-treated patients in Z022 were lower compared to antimony or amphotericin-treated patients in Brazil.

Dr. Shamsuddin concluded that the benefits of miltefosine outweigh the risks for each of the three indications being sought by the applicant. Ms. Zeng noted that the efficacy of miltefosine was demonstrated in the treatment of VL based on one pivotal and one supportive study and in the treatment of CL with one pivotal and one supportive study. She noted that the overall results were not as strong as they could have been due to various issues associated with the study conduct and analysis. She concluded that the effect of miltefosine in the treatment of ML was 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.

I concur with the recommendations by Dr. Shamsuddin, Dr. Smith, and Ms. Zeng regarding the approval of miltefosine for the indications of visceral and cutaneous leishmaniasis. I also agree with the recommendations by Dr. Shamsuddin and Dr. Smith, regarding the approval of miltefosine for the indication of mucosal leishmaniasis.

Safety

The safety database comprised 587 patients ≥12 years of age treated with miltefosine in studies 3154, 3168, Z020, Study Soto, and Z022, 321 patients from dose ranging studies in VL and CL, and postmarketing safety reports submitted to the German regulatory authorities for the period from September 2004-November 2011.

There were two deaths in VL studies (Study 3154), both in the miltefosine arm and one death in the ML study. All three deaths seem unrelated to miltefosine treatment. In the VL study, one patient developed bacterial meningitis and died on day 13 and the second patient with persistent splenomegaly and anemia following completion of miltefosine therapy was diagnosed with malaria. She died three weeks after completing a course of antimalarial therapy. In the ML study, the 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. In Dr. Shamsuddin's assessment, the events were more likely related to septic shock and unlikely to be related to miltefosine.

In Study 3154, six patients in the miltefosine arm and one patient in the amphotericin B arm developed at least one SAE. The non-fatal SAEs in the miltefosine arm included hemiplegia,

[11] Amato VS, Tuon FF, Siqueira AM, Nicodemo AC, Neto VA. Treatment of mucosal leishmaniasis in Latin America: systematic review. Am J Trop Med Hyg. 2007 Aug;77(2):266-74.

hemiparesis, convulsions, and Stevens- Johnson Syndrome (SJS). SJS occurred in a 12-year old male and was assessed as related to miltefosine.

In the VL studies, vomiting and diarrhea were reported more frequently in patients receiving miltefosine and rigors were reported more frequently in patients receiving amphotericin B. Elevations of serum creatinine were more frequent in patients receiving amphotericin while elevation of alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were more common in patients receiving miltefosine. No SAEs were reported in the CL or ML studies.

The most common adverse events in CL patients receiving miltefosine were headache, nausea, vomiting, pyrexia, motion sickness, and diarrhea. Elevation of creatinine above baseline was more common in patients receiving miltefosine compared to either placebo or meglumine antimoniate. ALT and AST elevations three times above the upper limit of normal were reported in less than 10% of patients. The most common AEs reported in the ML study were headache, nausea, abdominal pain, and pruritus. In the ML study, at day 28, a third of patients had elevation of serum creatinine above baseline. There were no reports of elevated ALT, AST, or bilirubin.

Special Safety Concerns

Male Fertility

The applicant submitted an assessment of miltefosine's effect on male fertility. The applicant tracked reproductive performance in 220 male patients who had participated in Study 3154 or Phase 2 studies in VL. 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. In Study 3154, post treatment semen analyses were obtained in 12 patients who received miltefosine. Analyses were reported to be normal in 10, and two had oligospermia. One of the patients with oligospermia reported two post-study pregnancies in partners and the other patient had no offspring. 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.

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 seen in the animal studies was potentially clinically relevant and that the limited human data available were not sufficient to rule out an effect in humans. 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.

The applicant is being required to conduct a study to evaluate the effects of miltefosine on spermatogenesis and male hormones as a postmarketing requirement. The study will be

conducted in patients with leishmaniasis who are receiving miltefosine. Evaluations will include semen volume, sperm count, sperm concentration and motility as well as evaluation of total testosterone and FSH.

Female Fertility
A total of 143 females ≥ 12 years of age were enrolled in the clinical trials (Studies 3154, 3168, Soto, Z020, and Z022). They 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. Of the three pregnancies reported from postmarketing studies, no congenital abnormalities were noted.

The DBRUP consultant's recommendations included a warning in product labeling regarding fetal risks and the need for birth control during therapy and for (b)(4) months post therapy, a voluntary post-marketing pregnancy and birth registry, and a study to evaluate drug-drug interactions between miltefosine and oral contraceptives. A drug interaction study was not considered necessary by the clinical pharmacology reviewer as miltefosine is not an inducer or an inhibitor of CYP enzymes.

The Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-MHT) were consulted regarding the pregnancy category. PMHS- MHT recommends pregnancy category (b)(4) as the appropriate classification for visceral, mucosal and cutaneous leishmaniasis because there is potential benefit for the mother for these conditions despite the potential fetal risks identified in animal studies. They also recommended that the pregnancy subsection be structured in the Proposed Pregnancy and Lactation Labeling Rule (PLLR) format in order to assist prescribers with benefit/risk decision making, as well as still complying with the current pregnancy labeling regulations. As miltefosine has anti-neoplastic properties, Dr. Shamsuddin recommended a pregnancy category D based on its mechanism of action. I concur with Dr. Shamsuddin's recommendations. The labeling has been structured as recommended by the PMHS-MHT.

Effects on QT Interval
The Division had consulted the interdisciplinary review team (IRT) regarding the need for a thorough QT study. The IRT granted a waiver for a thorough QT study because of safety and tolerability issues. Due to the long half-life of miltefosine, lengthy exposures are needed to achieve steady-state. The toxicities of miltefosine preclude conducting a study in healthy volunteers. As the data from study 3154 were inadequate to rule out a clinically significant effect on QT interval, the IRT advised that a QT assessment be performed as a post marketing requirement.

The applicant is being required to conduct a dedicated QT study as a postmarketing requirement. The study will be conducted in patients with leishmaniasis who are receiving miltefosine. ECGs and PK samples will be obtained to identify potential effects of miltefosine on the QT interval or other ECG parameters.

Thrombocytopenia
In Study 3154, 48.5% of miltefosine-treated patients and 44.4% of amphotericin treated patients had platelet counts < 150,000 at EOT. At 6 months, 24.8% and 20.2% patients had thrombocytopenia in the miltefosine and amphotericin arms, respectively. No cases of thrombocytopenia were reported in the CL studies. Three cases of thrombocytopenia have been reported postmarketing in HIV positive patients with VL. The German product labeling was updated in 2008 to include thrombocytopenia as an adverse event. The product labeling includes a warning about the risk of thrombocytopenia.

Ophthalmic Effects
Dose and duration dependent retinal degeneration was noted in the rat toxicity studies, but not in the dog toxicity studies. Visual assessments were performed in the Phase 2 VL studies and Study 3154 in India (total 548 subjects) and in Study 3168 in CL patients. Two ophthalmic adverse reactions were reported; one unspecified "abnormal fundoscopy" in one eye that resolved at 6 months and one "central retinosis". No visual adverse reactions were reported in any of the other studies or in the periodic safety update reports.

8. Advisory Committee Meeting

This NDA was discussed by the Anti-Infective Drugs Advisory Committee on October 18, 2013. The following three questions and the respective votes are noted below:

Question 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?

There were 15 votes in favor and one against.

Question 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?

There were 14 votes in favor and two against.

Question 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?

There were 13 votes in favor and three against.

The advisory committee meeting minutes are available at:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM389213.pdf

9. Pediatrics

The Pediatric Research Equity Act (PREA) does not apply to any drug for an indication for which orphan designation has been granted. As miltefosine was granted orphan drug designation for leishmaniasis, submission of a pediatric assessment is not required.

10. Other Relevant Regulatory Issues

Clinical Site Inspections

Dr. Susan Thompson from the Office of Scientific Investigations provided a summary of clinical inspections. As the clinical investigator sites were closed, certified copies of the investigator's site records were inspected. An inspection of Paladin Labs Inc., Montreal, Canada was also conducted. The data maintained at Paladin for the three clinical sites that were audited were found to be acceptable. No major violations were noted during the inspection of Paladin. Dr. Thompson concluded that data from these sites are acceptable to support the NDA.

11. Labeling

Adequate provisions have been made in labeling including the Medication Guide to address the following risks associated with miltefosine.

Risk of Teratogenicity

The Boxed Warning states that "IMPAVIDO may cause fetal harm. Fetal death and teratogenicity, occurred in animals administered miltefosine at doses lower than the recommended human dose. Do not administer IMPAVIDO to pregnant women. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing IMPAVIDO. Advise females of reproductive potential to use effective contraception during therapy and for 5 months after therapy."

The Contraindications Section includes a contraindication for use in pregnant women.

The Warnings and Precautions Section describes embryo-fetal toxicity observed in animals, recommends against using miltefosine in pregnant women and a recommendation to obtain a urine or serum pregnancy test prior to prescribing miltefosine to females of reproductive potential. Effective contraception is recommended during miltefosine therapy and for 5 months after completion of therapy in females of reproductive potential.

The Use in Specific Populations Section, Pregnancy subsection describes the embryo-fetal toxicity findings in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the maximum recommended human dose

(MRHD), based on body surface area (BSA) comparison. A pregnancy category D was considered appropriate based on its antineoplastic activity.

Reproductive Effects

Male and female reproductive effects noted in nonclinical studies are described in the Warnings and Precautions Section.

Other Safety Concerns

Renal effects including elevation of serum creatinine, hepatic effects including elevation of serum transaminases, thrombocytopenia and gastrointestinal adverse reactions of vomiting and/or diarrhea are described in the Warnings and Precautions section. Recommendations for appropriate monitoring are also provided.

All the above safety concerns are also addressed in appropriate sections of the Medication Guide.

Limitations of Use

The Indications and Usage Section includes a subsection on limitations of use noting that the *Leishmania* species studied in clinical trials evaluating IMPAVIDO were based on epidemiologic data, geographic variation in clinical response of the same *Leishmania* species to IMPAVIDO may be seen, and that the efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

Labeling reviews were also completed by Dr. Aleksander Winiarski (DMEPA), Twanda Scales (Division of Medical Policy Programs), Dr. Christine Corser (Office of Prescription Drug Promotion), and Dr. Adimbola Adebowale (Safety Endpoints and Labeling Development) and recommendations have been incorporated as appropriate.

12. Risk Mitigation

A review by Dr. Joyce Weaver from the Division of Risk Management concluded that a REMS was not needed for miltefosine. As most adverse reactions could be addressed in labeling and routine pharmacovigilance, the need for a REMS for the risk of fetal toxicity and teratogenicity was considered. Dr. Weaver's recommendation that a REMS for the risk of fetal toxicity and teratogenicity was not needed for miltefosine was based on the difficulty in risk communication and communication of REMS procedures to infectious diseases specialists regarding the treatment of a rare disease, the likely use of miltefosine in non-traditional healthcare settings in which a REMS could create an undue burden on patients and providers, and that even the most restrictive REMS would be unable to mitigate risk beyond the 28-day treatment period. Dr. Weaver recommended a boxed warning to convey the risk of teratogenicity and also to include a Medication Guide. I concur with these recommendations.

The applicant is required to conduct the following studies as postmarketing requirements under Section 505(o)(3) of the FDCA according to the timelines noted below:

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.

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

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.

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

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.

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

The applicant has agreed to the following postmarketing commitments and their respective timelines as noted below:

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

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

2. 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

3. In conjunction with the development and implementation of the HPLC methodology, perform in-process blend uniformity 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

13. Decision/Action/Risk Benefit Assessment

The applicant has provided adequate data to support the safety and effectiveness of miltefosine for the treatment of adults and adolescents ≥ 12 years of age for the following indications:

- Visceral leishmaniasis caused by *L. donovani*
- Cutaneous leishmaniasis caused by *L. braziliensis*, *L. guyanensis,* and *L. panamensis,* and
- Mucosal leishmaniasis caused by *L. braziliensis*

As the specific species of *Leishmania* was not identified in most of the trials, the inclusion of the specific species in the indication is based on epidemiologic data regarding the likely causative pathogen in any given geographic region. A limitation of use is included in product labeling to convey this information.

The effectiveness of miltefosine in the treatment of visceral leishmaniasis was demonstrated in an adequate and well-controlled clinical trial (Study 3154) in which miltefosine was shown to be noninferior to amphotericin B. Additional supportive information is provided by Study Z025.

The effectiveness of miltefosine in the treatment of cutaneous leishmaniasis was demonstrated in an adequate and well-controlled clinical trial (Study 3168) in which miltefosine was shown to be superior to placebo. Additional supportive information is provided by Study Z020 and Study Soto.

A single adequate and well-controlled trial was conducted in each of the indications-visceral and cutaneous leishmaniasis. The findings of efficacy in each of the indications provide

independent substantiation of effectiveness for the other indication. In addition, supportive data were provided from other clinical trials in each of these indications to support the effectiveness of miltefosine in visceral and cutaneous leishmaniasis. As provided in Section 115(a) of the Modernization Act, Section 505(d) of the Act was amended to allow data from one adequate and well-controlled clinical investigation to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.[12]

Mucosal leishmaniasis was studied in a single arm trial; the effectiveness of miltefosine in mucosal leishmaniasis can be determined by the cure rates seen in this trial in comparison to historical controls. 21 CFR 314.126 (b) recognizes historical controls as acceptable. When historical controls are used, results of treatment with the test drug are compared with experience historically derived from adequately documented natural history of the disease or condition.

Mucosal leishmaniasis is a progressive disease with significant morbidity that can also lead to fatal outcomes if left untreated. Most of the evidence in the literature point to a very low likelihood of spontaneous resolution. Multiple mucosal lesions progress if treatment is not instituted and single nasal lesions may remain stationary for years.[13] No natural history studies of a cohort of patients with mucosal leishmaniasis could be identified in the literature. In study Z022, ~ 50% of patients had extensive disease (involving palate, pharynx, and larynx), suggesting a lower likelihood of spontaneous cure. Approximately, 60% of patients had a mucosal severity score of 0 at 12 months after completing therapy indicating that they had complete resolution of disease. Additionally, the cure rate seen with miltefosine in this study was comparable and in some instances higher than that reported with other antileishmanial drugs. As miltefosine is an orally administered drug, and other available therapies need to be administered parenterally, miltefosine provides another option for patients in areas of the world that have limited access to healthcare.

In summary, the applicant has provided adequate data in the NDA to support the safety and effectiveness of miltefosine for the treatment of visceral, cutaneous, and mucosal leishmaniasis. I recommend approval of the NDA.

[12] Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products http://www fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf

[13] Marsden PD. Mucosal leishmaniasis ("espundia" Escomel, 1911).Trans R Soc Trop Med Hyg. 1986;80(6):859-76.

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/s/

SUMATHI NAMBIAR
03/19/2014