CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204684Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 204-684	Submission Date(s): 04/19/2013
Drug	Miltefosine
Trade Name	Impavido®
OCP Reviewers	Seong H. Jang, Ph.D.
OCP Team Leader	Phil Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Paladin Therapeutics, Inc
Relevant IND(s)	IND 118,459; IND 105,430
Submission Type; Code **Standard or Priority**	Original, 1S (NME) Priority
Formulation; Strength(s)	50 mg Oral Capsules
Indications	Treatment of visceral leishmaniasis due to *Leishmania (L) donovani*; cutaneous leishmaniasis due to members of the *L viannia (v) subgenus (L.v. braziliensis, L.v. guyanenesis, L.v. panamensis)*; and mucosal leishmaniasis due to *L.v. braziliensis, L.v. guyanenesis, L.v. panamensis* in adolescent and adults ≥12 years of age weighing ≥30 kg (66 lbs).
Dosage and Administration	• 30-44 kg (66-97 lbs): one 50 mg capsule twice daily with food for 28 days • ≥45 kg (99 lbs): one 50 capsule three times daily with food for 28 days

Table of Contents

1. Executive Summary

This NDA was submitted for Impavido® (miltefosine) 50 mg oral capsules for the treatment of visceral leishmaniasis (VL) due to *Leishmania (L) donovani*; cutaneous leishmaniasis (CL) due to members of the *L viannia (v)* subgenus (*L.v. braziliensis, L.v. guyanenesis, L.v. panamensis*); and mucosal leishmaniasis (ML) due to *L.v. braziliensis, L.v. guyanenesis, L.v. panamensis* in adolescent and adults ≥12 years of age weighing ≥30 kg (66 lbs). The original NDA was submitted on September 27, 2012. The FDA issued a Refusal to File (RTF) letter mainly because clinical datasets were not adequate for review. Thus, the sponsor resubmitted the NDA at this time with information requested in the RTF letter. The FDA granted miltefosine orphan designation in October 2006 and Fast Track Designation in May 2010. The NDA was granted a 6 month priority review.

Miltefosine is an alkyllysophospholipid analogue with *in vitro* activity against *Leishmania* species. Miltefosine is registered in Germany as a topical drug to treat cutaneous cancers. As an oral agent, 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.

As miltefosine has been shown to cause hemolysis in vitro, no clinical pharmacology / pharmacokinetic (PK) studies were conducted in healthy volunteers. All clinical studies were conducted in patients and clinical pharmacology information is very limited to determine an effective and safe dosing regimen of miltefosine. The proposed recommended dose (see Table below) was justified based on the safety and efficacy data obtained from dose finding studies and pivotal clinical trials. It is recommended to take miltefosine with food because administration with food ameliorates gastrointestinal adverse reactions.

Weight	**Dosage and Administration**	**Treatment Duration**
30-44 kg (66-97 lbs)	One 50 mg capsule daily twice daily with food (breakfast and dinner)	28 days
≥45 kg (≥99 lbs)	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)	

The half-life of miltefosine is >6 days and, thus, plasma concentrations do not reach a steady state at the end treatment (i.e., 28 days). 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.

1.1. Recommendation

The NDA 204-684 for Impavido® (miltefosine) 50 mg Capsules for the treatment of VL, CL, and ML in adolescent and adults ≥12 years of age weighing ≥30 kg (66 lbs) is acceptable from the Clinical Pharmacology perspective.

1.2. Phase 4 Commitments

No Phase 4 commitments are recommended

1.3. Summary of Important Clinical Pharmacology findings

As miltefosine has been shown to cause hemolysis in vitro, no pharmacokinetic (PK) studies were conducted in healthy subjects. There also were no disease-oriented studies in patients with cancer or in patients with leishmaniasis that had human pharmacology variables as a primary endpoint. The PK information for miltefosine was obtained from adult patients with VL and CL.

PK of miltefosine in adult/adolescent (>12 years) patients with VL (Study 3109):
The PK parameters of miltefosine on Day 23 following administration of 4 different doses in adult/adolescent (>12 years) patients with VL are summarized in Table 1 below. Due to the long half-life of miltefosine (> 6 days), trough plasma concentrations did not appear to reach a steady state at the end of treatment on Day 23 (Figure 1)

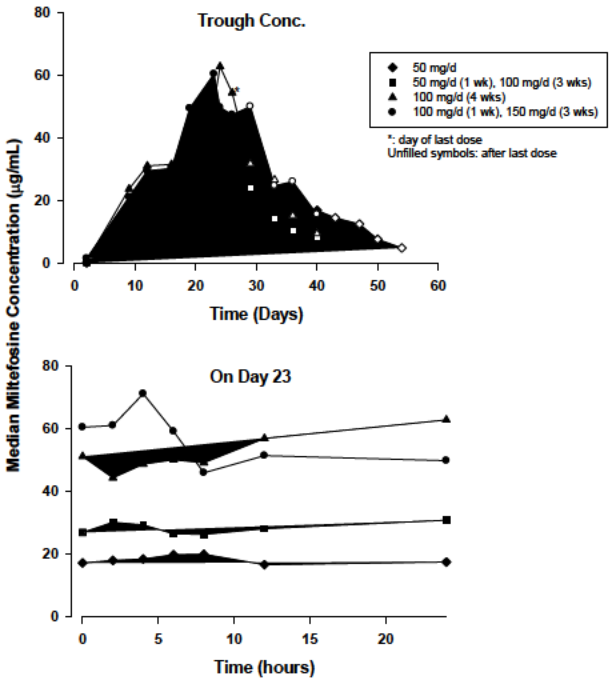


Figure 1. Median plasma concentrations of miltefosine following multiple oral administrations in patients with VL (Dose Groups 1 to 4, Study 3109). The upper panel shows drug concentrations before the first dose on each day and the lower panel shows drug concentrations on Day 23

Table 1. Mean (%CV) pharmacokinetic parameters for miltefosine following oral capsule administration to adult/adolescent (>12 years) patients with visceral leishmaniasis

	On Day 23			After last dose
	C_{max} (µg/mL)	T_{max}[a] (hr)	AUC_{tau}[b] (µg·hr/mL)	$t_{1/2}$ (hr)
50 mg/d (6 wks) (Group 1, N=9)	23.5 (30.8)	8 (2 - 24)	445 (28.1)	166.7 (34)
50 mg/d (1 wk) / 100 mg/d (3 wks) (Group 2, N=10)	39.2 (47.6)	5 (2-12)	378 (37.4)	199.8 (65.4)
100 mg/d (4 wks) (Group 3, N=10)	66.2 (28.5)	7 (2-12)	636 (26.7)	154 (31.1)
100 mg/d (1 wk) / 150 mg/d (3 wks) (Group 4, N=10)	75.9 (17.6)	4 (2-8)	486 (18.1)	202.8 (28.9)

[a]: Median (range)
[b]: AUC from time 0 h to 24 h, 12 h, 12 h, and 8 h for Groups 1, 2, 3, and 4, respectively

PK of miltefosine in adult patients with CL (Dutch PK Study):
A population PK analysis was conducted with plasma concentrations obtained following administration of 50 mg TID (150 mg/day) for 28 days to adult patients with CL. Miltefosine PK during multiple dosing was best described by a 2-compartment population model with first-order absorption. The $t_{1/2\alpha}$ was 6.75 days from bootstrapping. C_{max} and AUC_{tau} were 37 µg/mL and 295 µg·hr/mL, respectively, based on simulated plasma concentrations after the last dosing on day 27. The apparent terminal $t_{1/2}$ was approximately 30 days and explains the fact that steady-state plasma concentrations were not achieved by 28 days of dosing.

Absorption: Absolute bioavailability has not been determined because intravenous administration of miltefosine is not feasible. In Study 3019, maximum concentrations following oral tablet administration were observed right before the next dose in many patients, indicating that the absorption of miltefosine may proceed throughout the dosing interval.

Distribution: No clinical studies provided the distribution characteristics of miltefosine. In rats, radioactivity of [^{14}C]miltefosine and derived material is widely distributed after both single and repeated oral administration. Human plasma protein binding of miltefosine, evaluated by an ultracentrifugation method, was 98% over the drug concentration range from 0.1 to 10 µg/mL.

Metabolism: Miltefosine is metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol, which is oxidized to palmitic acid. No oxidative metabolism of miltefosine was observed with any of the reconstituted hepatic CYP monooxygenase systems, comprising the following CYP enzymes: 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, 4A1.

Excretion: The urinary excretion of the unchanged drug on Day 23 after repeated oral administration of miltefosine to adult patients was below 0.2% of the daily dose.

Drug-Drug Interactions: Miltefosine is not a substrate, inhibitor, or inducer of hepatic CYP enzymes. Drug interaction studies have not been conducted.

Proposed dose and justification: The target regimen is 2.5 mg/kg/day for 28 consecutive days. Administration with food ameliorates gastrointestinal adverse reactions. The number of 50 mg capsules per day is determined by bodyweight as described in Table 2.

Table 2. Proposed dosage and administration as a function of body weight

Weight	**Dosage and Administration**
30-44 kg (66-97 lbs)	One 50 mg capsule daily twice daily with food (breakfast and dinner)
≥45 kg (≥99 lbs)	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)

No exposure-response analyses were conducted in this NDA because there were limited PK data obtained in most of the clinical trials. Instead, the appropriate doses to be evaluated in the Phase 3 studies were determined based on the efficacy and safety observed in several dose-finding studies conducted by the sponsor. The recommended dose regimen in Table 2 above is based on the results of Study 3168 (Placebo-Controlled Pivotal CL Trial), which showed this regimen to be adequately safe and efficacious for the treatment of CL. For the treatment of VL, a miltefosine dose regimen of 100 mg/day for patients weighing ≥25 kg (a lower or equal dose compared to the effective and safe dose for the treatment of CL) was determined to be safe and effective in Study 3154 and was based on several dose-finding studies. The proposed dosage regimen in Table 2 above is considered by the Clinical Pharmacology reviewer to be safe and effective for the treatment of both VL and CL.

_____.

Seong H. Jang, Ph.D.
Clinical Pharmacology Reviewer

OTS/OCP/DCP 4

Concurrence _____.

Phil Colangelo, Pharm.D., Ph.D
Clinical Pharmacology Team Leader

OTS/OCP/DCP 4

2. Question-Based Review

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

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

The inactive ingredients are colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The specific mode of action of miltefosine in leishmaniasis is unknown. The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids.

The proposed indications of miltefosine are treatment of visceral leishmaniasis (VL) due to *Leishmania (L) donovani*; cutaneous leishmaniasis (CL) due to members of the *L viannia (v)* subgenus (*L.v. braziliensis, L.v. guyanenesis, L.v. panamensis*); and mucosal leishmaniasis (ML) due to *L.v. braziliensis, L.v. guyanenesis, L.v. panamensis* in adolescent and adults ≥12 years of age weighing ≥30 kg (66 lbs).

Impavido has not been sufficiently evaluated for other species of *Leishmania* causing visceral, cutaneous, and mucosal leishmaniasis. Impavido has not been sufficiently evaluated in patients 3–11 years of age or >65 years of age.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The target regimen is 2.5 mg/kg/day for 28 consecutive days. Administration with food ameliorates gastrointestinal adverse reactions. The number of 50 mg capsules per day is determined by bodyweight as described in Table 3.

Table 3. Proposed dosage and administration as a function of body weight

Weight	Dosage and Administration
30-44 kg (66-97 lbs)	One 50 mg capsule daily twice daily with food (breakfast and dinner)
≥45 kg (99 lbs)	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical pharmacology / PK studies were conducted in healthy subjects, and there were no disease-oriented studies, neither in patients with cancer nor in patients with leishmaniasis, that had human pharmacology variables as a primary endpoint.

As miltefosine has been shown to cause hemolysis in vitro, no clinical studies were conducted with intravenous administration, which would be a prerequisite for assessing absolute bioavailability. Because of the cytostatic/cytotoxic potential of the drug substance, PK studies in healthy subjects were considered non-feasible at times when miltefosine was under development as an anticancer agent. Later, when clinical development of oral miltefosine for VL was started, it could not be excluded that use of miltefosine could be associated with adverse reactions which are mediated by the cytostatic/cytotoxic mode of action. Therefore, studies in healthy volunteers were considered not feasible still.

Two dose-finding studies in patients with VL included repeated blood sampling to assess PK parameters of orally administered miltefosine, both in adult patients (study 3109) and in children (study 3091). Both studies used a sensitive high performance liquid chromatograph tandem mass spectroscopy (HPLC-MS/MS) assay. (b) (4) Study 3091 was not reviewed at this time. Subsequently, an academic pharmacokinetic study was performed with sparse sampling in the CL population (study "Dutch PK Study"). Key pharmacokinetic parameters were comparable in the VL and CL populations.

Treatment of VL:
Efficacy and safety of miltefosine in the treatment of VL have been investigated in prospective clinical trials involving 766 patients, of whom 667 patients (out of 669 randomized patients), including 119 children younger than 12 years, were treated with miltefosine. Additionally 99 patients received amphotericin B as the active control drug in a randomized controlled Phase 3 trial (study 3154) that is to be considered as an adequate and well-controlled study to prove the efficacy of miltefosine in the target indication.

Table 4 shows the final cure rates and the numbers of patients with missing data as well as with documented treatment failure, including data from patients treated at dosages that were subsequently identified as non-sufficient for the pooled study population.

Table 4. Pooled efficacy rate in Phase 1 to 3 trials for treatment of VL

	Final parasitological cure, ITT population						**all**
	Missing/not assessable		**no**		**yes**		
	n	**%**	**n**	**%**	**n**	**%**	**n**
All patients treated with miltefosine (any age)	12	1.8	32	4.8	623	93.4	667
Study 3154 (patients allocated to treatment with amphotericin B	3	3.0	0	0	96	97.0	99
All patients (any treatment)	15	2.0	32	4.2	719	93.9	766

In accordance with the current state-of-the-art in the evaluation of drugs in VL, patients were accepted as being cured ("definite" or "final" cure) only after a 6-month period had elapsed without signs or symptoms indicative of treatment failure. Therefore it is important to note that the percentage of patients with missing data or patients whom the investigators classified as not assessable was very low, i.e., 12 of 667 cases (1.8%). According to intention-to-treat (ITT) principles, these patients were added to the documented treatment failures in the calculated overall cure rate across all studies (623 of 667 = 93.4%).

Treatment of CL:

The endpoint for CL trials was complete re-epithelialization of the ulcer at 6 months after therapy. This endpoint is synonymous with clinical cure.

Efficacy of miltefosine for the treatment of CL was evaluated in one industry-sponsored placebo-controlled trial (Study 3168), where 59 of 89 patients with miltefosine were cured compared with 13 of 44 patients who received placebo (Table 5).

Table 5. Efficacy of miltefosine for the treatment of CL in placebo-controlled CL trial (Study 3168)

Definite cure (ITT)	**Placebo**	**Miltefosine**
Center 1 (Columbia)	9/24 (37.5%)	40/49 (81.6%)
Center 2 (Guatemala)	4/20 (20.0%)	19/40 (47.5%)
Total	13/44 (29.5%)	59/89 (66.3%)

In addition to comparing miltefosine to placebo in the industry-sponsored trial, the FDA suggested, and the sponsor was able to gain access to the primary data from 3 investigator-sponsored trials.

The primary efficacy endpoint in the 3 investigator studies was initial cure (complete re-epithelialization of the ulcer 2 months after the end of therapy (studies Z020a and Z020b) or at least 50% diminution in ulcer size at 3 months after therapy (Soto study), followed

by final cure (100% reepithelialization at 6 months after the end of therapy) in all studies. The results of the 3 studies are summarized in Table 6.

Table 6. Integrated analysis of investigator-sponsored pivotal studies

Parameter	**Soto Study**	**Study Z020a**	**Study Z020b**
Age range for adolescents/adults	≥ 12 years	≥ 12 years	≥ 12 years
Miltefosine target dose	miltefosine target 2.5 mg/kg/day x 28 days	miltefosine target 2.5 mg/kg/day x 28 days	miltefosine target 2.5 mg/kg/day x 28 days
Comparator target dose	meglumine antimonate (Glucantime) 20 mg/kg/day x 20 days	meglumine antimonate (Glucantime) 20 mg/kg/day x 20 days	meglumine antimonate (Glucantime) 20 mg/kg/day x 20 days
Randomization	2:1	2:1	2:1
Entrance data			
Gender	78 % male	82% male	70% male
Weight (mean)	58 kg	66 kg	58 kg
lesion area (mean)	285 mm^2	209 mm^2	419 mm^2
% pts with 1 lesion	59%	45%	80%
Primary endpoint	100% re-epithelialization of all ulcers at 6 months after therapy	100% re-epithelialization (and loss of induration) of all ulcers at 6 months after therapy	100% re-epithelialization (and loss of induration) of all ulcers at 6 months after therapy
ITT cure rate miltefosine group	32/ 40 = 80%[a]	27/40 = 67%	34/40 = 85%
ITT cure rate antimony group	13/18 = 72 %	12/20 = 60%	9/20 = 45%

[a]: 30/40=75% if criteria for initial cure used in Brazil had been used in Bolivia.

Treatment of Mucosal Leishmaniasis:

Miltefosine was evaluated in a single group study against mucosal leishmaniasis due to L. (v) braziliensis in Bolivia. Of the 79 total patients, 76 were evaluable. Forty nine (49) of the patients cured with 12 months of follow up, which equates to a 62% ITT cure rate and a 64% per protocol cure rate. The cure rate for proximal disease of the nose was 27 of 37 (73%) evaluable patients, a value that tended to be higher than the cure rate for patients with distal disease (involvement of the palate, pharynx, and larynx): 22 of 39 (56%) evaluable patients. The cure rates for historic controls are 28% - 89% for antimony and 29% - 90% for amphotericin B.

No clinical pharmacology information was obtained from patients with mucosal leishmaniasis and no dose-finding studies were conducted in patients with mucosal leishmaniasis. Thus, the Clinical Pharmacology review of this NDA was focused on the results of the studies conducted in patients with VL and CL.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

See **2.2.1.**

2.2.3. Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Miltefosine was the active moiety measured in human plasma in and the clinical studies. There is no evidence that any metabolites of miltefosine have activity.

2.2.4. Exposure-response

No exposure-response analyses were conducted in this NDA because there were limited PK data in most clinical trials. Instead, several dose-finding studies were conducted and the appropriate doses to be evaluated in the Phase 3 studies were determined based on the efficacy and safety data observed in the dose-finding studies. The results of the dose-finding studies are summarized below.

2.2.4.1. Summary of Clinical Efficacy for the treatment of VL

Based on experience in cancer patients, a dosage of 50 mg every second day was expected to be tolerable and possibly effective in the treatment of patients with leishmaniasis and chosen as starting dose for a pilot trial (study 0033). Treatment duration of 28 days was chosen in analogy to the treatment duration of standard agents used in this indication. Table 7 shows the ranges in dosage that were evaluated in the different dose finding studies.

Table 7. Miltefosine doses that were evaluated in dose ranging trials

Study	Group: Dosage ranges tested	No. of Patients
0033	1: 50 mg q2d x14 6: 250 mg/day x28	30 (6 x 5)
3089	1: 100 mg/day x 28 3: 200 mg/day x 28	46 (2 x 18 + 10)
3109	1: 50 mg/day x 42 4: 100 mg /day x7+150 mg /day x 21	120 (4 x 30)
3127	1 :100 mg/day x 14 3: 100 mg/day x 28	54

A pilot study (study 0033) served as a preliminary evaluation of the maximum tolerated dose in adult patients with VL. The dose range of interest in the pilot study was evaluated in a larger number of patients (study 3089). In that study, the dosage of 200 mg/day was found to be not sufficiently tolerable and excluded from further evaluation. Study 3109,

that was planned and conducted in co-operation with the WHO, included a prolonged treatment duration at the starting dose level as well as two dosage schemes with a one week run-in period at a lower dose and a three week follow-up treatment at a higher dosage. A scheme with lower dosage in a run-in period had been used in cancer patients. The run-in period was not found to be needed to ensure tolerability of miltefosine in patients with leishmaniasis and, therefore, was not included in subsequent studies. The last dose finding study (study 3127) assessed the effect of shortening the dosing period on the safety and efficacy of the treatment.

VL Pilot Study 0033: Treatment for 28 days; dosages 50 mg/q2day - 250 mg/day
This was an open, non-controlled, single institution, sequential group, dose ranging study to determine the safety and efficacy of escalating doses of miltefosine in male patients with mild to moderate VL. The planned duration of treatment per subject was 4 weeks and the protocol included a 5-month post-treatment follow-up for assessment of final cure. Male patients with signs and symptoms of mild to moderate VL (e.g. fever, enlarged spleen, loss of appetite) confirmed by demonstrating amastigotes in Giemsa-stained splenic aspirate smear were allowed to enter the trial. Anti-leishmanial treatment within 3 months before study entry was excluded. Sequential groups with 5 patients each used the following dosages: 50 mg every other day, 100 mg every other day; 100, 150, 200, and 250 mg/day for 28 days. Drug was taken after meals; in the highest two dose groups (i.e., 200 and 250 mg/day), with 4 and 5 capsules per day, the last 1 or 2 capsules, respectively, were taken in the evening. In total, 30 patients entered the study.

Table 8 summarizes the results by dose group. Oral use of miltefosine showed positive results in the treatment of patients with VL; at dosages of 100 mg/day for 4 weeks and higher, patients were cured from the disease. This included patients who were not cured by standard treatment with antimony based drugs. Only 1 of 19 patients treated at 100 mg/day or above relapsed during long-term follow-up. Cure from the infections was accompanied by recovery of disease related abnormalities and improvement in general condition. Dose-limiting adverse reactions were observed at 200 and particularly at 250 mg/day. These included vomiting and diarrhea as well as, in one patient each, an increase in AST and creatinine. Because of the early onset of dose-limiting adverse reactions, a dosage of 250 mg/day, even if used in shorter course only, did not seem to warrant further investigation. Dosages ranging between 100 and 200 mg/day were concluded to deserve further clinical studies.

Table 8. Efficacy results of Study 0033

Dose Group(mg/day)	**50(q2d)**	**100(q2d)**	**100**	**150**	**200**	**250**
Patients treated	5	5	5	5	5	5
Treatment duration(days)	27	27	28	28	28(4x), 7(1x)	7, 8, 10, 15[a] .28
Apparent cure by day 14	3	5	2	2	5	4
Apparent cure by day 28	5	5	5	5	5	4
Relapses	3	3[b]	0	1	0	0
Definite cure at 6 months	2	2[b]	5	4	5	4

[a]: Patient No. 30 died on day 22 with dehydration, shock, renal and heart failure.
[b]: One patient relapsed after 7.5 months.

VL Phase 2 Study 3089: Treatment for 28 days: dosages 100 - 200 mg/day

This was an open label, randomized dose ranging study, with 3 parallel groups, to assess the efficacy of miltefosine in patients with Indian VL (endpoint: cure rate, definite and apparent) and to characterize the safety of the proposed treatment schedules. The planned duration of treatment per subject was 4 weeks in all groups. Male and female patients with newly diagnosed or resistant/relapsing VL (confirmed by splenic aspirate), with signs and symptoms from leishmaniasis, such as hepato-splenomegaly, anemia, thrombocytopenia, leukocytopenia, and fever and with a Karnofsky performance status above 30%, entered the trial.

Eligible patients were randomly allocated to one of three dosage groups:
Group 1: 100 mg/day x 4 weeks (2 capsules/day: 1 capsule each in the morning and evening)
Group 2: 150 mg/day x 4 weeks (3 capsules/day: 1 capsule each in the morning, at lunch time, and in the evening)
Group 3: 200 mg/day x 4 weeks (4 capsules/day: 1 capsule each in the morning, at lunch time, and 2 capsules in the evening). The dose group 3 (200 mg/day) was prematurely closed for recruitment, after inclusion of 10 patients, due to the observed intolerability.

Forty-six of a planned total of 54 patients were randomized. One patient did not receive trial medication. The remaining 45 patients (100 mg/day: 17 patients, 150 mg/day: 18 patients, 200 mg/day: 10 patients) were evaluable according to ITT and safety. Thirty eight patients were evaluable per-protocol. Seven patients discontinued the treatment prematurely, due to intolerability in 6 cases (100 mg/day: 1 patient, 150 mg/day: 2 patients, 200 mg/day: 3 patients) and due to withdrawn consent in one case.

The primary efficacy endpoint of the study was the rate of patients with definite parasitological cure 6 months after end of treatment. In two patients, the respective examination was done after 5 instead of 6 months. These patients were re-assessed 7 months later to confirm the response. Table 9 summarizes the results. A 100% per protocol rate of definitive cure at 6 months was achieved in all dosage groups. The 100 mg and 150 mg regimens were well tolerated.

Table 9. Efficacy results of Study 3089

	ITT Population		**Per Protocol Population**	
Treatment	**Cure Rate**	**Lower bound of 95% CL[a]**	**Cure Rate**	**Lower bound of 95% CL[a]**
100 mg/d	16/17[b] (94.1%)	75.0%	15/15 (100%)	81.9%
150 mg/d	18/18 (100%)	84.7%	16/16 (100%)	82.9
200 mg/d	10/10 (100%)	74.1%	7/7 (100%)	65.2%

[a]: Confidence limit

VL Phase 2 Study 3109: Treatment at dosages from 50 mg/day x 42 days to 100/150 mg/d x 28 days

This was a multicenter, open-label, sequential group dose escalating trial to identify a dosage regimen of miltefosine with a good therapeutic index (determination of initial

cure rate, final cure rate and adverse events) and to assess the pharmacokinetics of miltefosine (e.g., C_{max}, $t_{1/2}$, T_{max}, AUC in plasma). Male and female patients with VL, confirmed by spleen aspirate, and with signs and symptoms compatible with VL, like fever and splenomegaly, entered the trial. A total of 120 patients were randomly allocated to one of 4 groups:

- Group 1: 50 mg/day x 6 weeks (1 capsule/day: in the morning);
- Group 2: 50 mg/day x 1 week, then 100 mg/day x 3 weeks (1 or 2 capsules/day: 1 capsule in the morning or 1 capsule each in the morning and evening);
- Group 3: 100 mg/day x 4 weeks (2 capsules/day: 1 capsule each in the morning and evening); and
- Group 4: 100 mg/day x 1 week, then 150 mg/day x 3 weeks (2 or 3 capsules/day: 1 capsule each in the morning and evening or 1 capsule each in the morning, at lunch time, and in the evening).

One-hundred-and-twenty patients were recruited. All patients received trial medication and were evaluable for safety and efficacy according to ITT. Two patients were excluded from the per protocol analysis due to premature discontinuation. These two patients discontinued the treatment prematurely due to intolerability.

The primary parameter of the study was the rate of patients with final cure. Table 10 summarizes the results. The trial demonstrated that orally administered miltefosine has the potential to cure patients with Indian VL. A marked clinical improvement started shortly after institution of therapy and 116 (of 120) patients were initially cured and returned to normal life at the end of therapy. Final cure rates (six months after end of treatment) when treated per protocol were: group 1 and 2: 93%; group 3: 97%; group 4: 100%.

Table 10. Final cure rate of patients in Study 3109

	Final Cure			
	ITT Population		**PP Population**	
Group	**Rate**	**Lower bound of 95% CL[a]**	**Rate**	**Lower bound of 95% CL[a]**
1	28/30 (93.3%)	80.5%	27/29 (93.1%)	79.8%
2	28/30 (93.3%)	80.5%	28/30 (93.3%)	80.5%
3	29/30 (96.7%)	85.1%	29/30 (96.7%)	85.1%
4	29/30 (96.7%)	85.1%	29/29 (100%)	90.2%

[a]: Confidence limit

VL Phase II Study 3127: Treatment for 14 vs. 21 vs. 28 days: dosage 100 mg/day

This was a single-center, open label, randomized trial with 3 parallel groups to assess the apparent and 6-months definite cure rates as well as the adverse events in relation to treatment duration, either 2, 3 or 4 weeks. Male and female patients with newly diagnosed or resistant/relapsing VL, confirmed by spleen or bone marrow aspirate, and with clinical symptoms (hepato-splenomegaly, anemia, thrombocytopenia, leukocytopenia, fever) and with a Karnofsky performance status above 30% entered the trial.

Fifty-four patients were randomly allocated to one of 3 dose groups:

- Group 1: 100 mg/day (two capsules/day: 1 capsule each in the morning and evening), 2 weeks treatment
- Group 2: 100 mg/day (two capsules/day: 1 capsule each in the morning and evening), 3 weeks treatment
- Group 3: 100 mg/day (two capsules/day: 1 capsule each in the morning and evening), 4 weeks treatment

No premature discontinuation of treatment occurred due to adverse reactions, no serious adverse event was reported, and none of the patients died during the course of study. The primary efficacy endpoint was the rate of patients with definite parasitological cure 6 months after end of treatment. Definite cure rates with oral miltefosine were: 89% after 2 weeks treatment and 100% after a 3 or 4 weeks therapy (Table 11), indicating that a shorter treatment duration than 3 weeks seems less effective.

Table 11. Six month cure rates in patients in Study 3127

	Definite Cure at 6 months	
Treatment	**Rate**	**Lower bound of 95% CL[a]**
2 weeks	16/18 (88.9%)	69.0% (73.1%)
3 weeks	18/18 (100%)	84.7 (88.0%)
4 weeks	18/18 (100%)	84.7 (88.0%)

[a]: Confidence limit

Dose Adaptation for Light-weight Patients with VL

Studies 0033 and 3089 included "adult" patients with a lower age of 14 years, while studies 3109 and 3127 also allowed "adolescent" patients with a lower age of 12 years. Dosages in all these studies did not take into account the individual patient's body weight. After dose ranging studies had shown a dosage of 100 mg/day in these approximately 40 kg adults (approximately 2.5 mg/kg/day) to be effective, a reduction in dosage was decided upon for patients with a body weight below 25 kg in order to avoid relative overdosing of such patients. Therefore, the confirmatory study 3154 for these lighter body weight patients included a dosage scheme with 50 mg/day. For patients of 25 kg or less who received 50 mg per day, the daily dose would be 2.0 mg/kg/day or more. Thus in study 3154, the target dose for patients of all weight was approximately 2.5 mg/kg/day.

VL Phase III Study 3154: Treatment for 28 days: dosage 100 mg/day as follows to achieve a target of 2.5 mg/kg/day; comparator amphotericin B.

This was a randomized controlled Phase 3 trial to show that miltefosine is not or only moderately inferior to amphotericin B regarding final cure rates. Patients were randomly allocated to treatment with miltefosine or amphotericin B. Patients with initial cure at end of treatment were re-evaluated 6 months later for final cure. Secondary endpoints of this trial included the assessment of initial (parasitological) cure and clinical response at end of treatment, as well as the characterization of the safety of the proposed miltefosine schedule. Male and female, adolescent and adult patients (12 years and older) with newly diagnosed or resistant/relapsing VL, confirmed by splenic/bone marrow aspiration, and

with clinical signs and symptoms compatible with VL, like fever, splenomegaly, and anemia, entered the trial.

Treatment duration was 4 weeks; patients had a 6 month post treatment follow-up for assessment of final cure.
Treatments to be compared were as follows:

- Group A (MIL): miltefosine capsule 50 mg; administered orally for 28 days
  − Patients > 25 kg body weight: 100 mg/day
  − Patients < 25 kg body weight: 50 mg/day
- Group B (amphotericin B): amphotericin B powder 50 mg; administered as 15 i.v. infusions over 30 days. 1 mg/kg as 6 hours continuous i.v. infusion every-other-day

In total, 400 patients entered the study; 398 received at least one dose of study drug (1 failure of central randomization). In the miltefosine group, 271 patients had a body weight of 25 kg or higher and received the drug at a dosage of 100 mg/day while the remaining 28 patients were treated at 50 mg/day due to their lower body weight.

Table 12 summarizes the efficacy results of the for the ITT population. The upper 97.5%-confidence bounds (6.6%) are below the protocol pre-defined non-inferiority margin of 15%, indicating that the dose evaluated in this Phase 3 study is effective to treat VL.

Table 12. Summary of efficacy – Study 3154 (ITT population)

ITT Analysis	**Miltefosine (N=299)**	**Amphotericin B (N=99)**
Final cure Treatment failure Not accessible	282 (94.3%) 9 (3.0%) 8 (2.7%)	96 (97.0%) ---- 3 (3.0%)
Difference amphotericin B-miltefosine of final cure rates **(upper 97.5%-confidence bound)** center adjusted not center adjusted	2.6% (**6.2%)** 2.7% **(6.6%)**	

2.2.4.2. Summary of Clinical Efficacy for the treatment of CL

Dose finding study for the treatment of CL – Study 3092
This was a clinical trial to assess the efficacy and safety of different dosages of oral miltefosine in patients with South-American CL, in order to define a dosage regimen for a subsequent confirmatory trial. The study was conducted in male patients aged 16 years and older, who had newly diagnosed or resistant/relapsing CL, confirmed by aspirate and parasitological examination of each lesion, and with typical cutaneous ulceration. In pretreated patients, end of prior therapy had to be longer than 4 weeks ago and cutaneous lesions had to be equal or worse than at the end of the prior therapy. Groups of 18 patients were treated at escalating doses for 20 days (Groups 1-3) or 28 days (Group 4). Two weeks after end of treatment with oral miltefosine, response was determined. Patients with apparent or partial cure were followed (3- and 6-month follow-up visits) to

verify definite cure or relapse. Initially, 54 patients (3 cohorts of 18 each) were planned; as per-protocol amendment 3, a fourth dose group of 18 patients was added. A total of 72 patients (all males) entered the study. Miltefosine; 50 mg capsules, were given orally with meals and at the following dosage regimens:

- Group 1: 50 mg/day on day 1-20
- Group 2: 50 mg/day on day 1-7, followed by 100 mg/day on day 8-20
- Group 3: 100 mg/day on day 1-7, followed by 150 mg/day on day 8-20
- Group 4: 150 mg/day on day 1-28

In intention-to-treat (ITT) population, the definite cure rate 81.1% (30 of 37 patients) observed for the combined two higher dose group (Table 13) was considerably greater than the cure rate 60.0% (21 of 35 patients) observed for the combined two lower dose groups. The corresponding p-value of the Fisher's exact test was 0.070. Accordingly, in the absence of clinically relevant intolerability, the dosage regimen with the highest dose intensity was chosen for a confirmatory trial.

Table 13. Cure Rates in Study 3092---ITT Population

ITT Population	**Group 1**	**Group 2**	**Group 3**	**Group 4**
Rate of definite cure	9/16 (56.3%)	12/19 (63.2%)	14/17 (82.4%)	16/20 (80.0%)
95% (90%) lower confidence bound	33.3% (37.5%)	41.8% (45.9%)	60.4% (64.8%)	59.9% (63.9%)

Placebo-controlled Pivotal CL Trial Study 3168

This was a placebo-controlled clinical trial to assess the efficacy and safety of oral miltefosine in patients with South-American CL, in order to confirm the dosage recommendation that was established in the preceding trial (Study 3092). The study involved centers in two countries, Colombia (Consorcio de Investigaciones Bioclinicas (CIBIC), Santafe de Bogota) and Guatemala (Universidad del Valle de Guatemala). The primary objective of this study was to demonstrate that miltefosine is superior to placebo in CL when assessed 2 weeks and 6 months after end of treatment (apparent/definite cure). The study included male and female patients aged older than 12 years, who had newly diagnosed or resistant/relapsing CL without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer or inflammatory induration with positive parasitology (minimum area: 50 mm^2). The patients were otherwise well: exclusion criteria were aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase >2 times upper limit of normal range; total bilirubin >1.5 times upper limit of normal range; serum creatinine or blood urea nitrogen (BUN) >1.5 times upper limit of normal range. A total of 133 patients entered the study. Study treatment comprised miltefosine (50 mg) or matching placebo capsules, given orally for 28 days according to the following dosages:

- Patients ≥ 45 kg body weight: 3 capsules per day (1 capsule in the morning, 1 capsule at lunch, and 1 capsule in the evening, following meals)
- Patients < 45 kg body weight: 2 capsules per day (1 capsule in the morning and 1 capsule in the evening, following meals)

Overall, 76 of 133 patients were cured, i.e. they had cure verified after a 6-month follow-up based on an ITT analysis (Table 14).

Table 14. Cure rates in Study 3168

Definite Cure (ITT)	**Placebo**	**Miltefosine**
Center 1 (Colombia)	9/24 (37.5%)	40/49 (81.6%)
Center 2 (Guatemala)	5/20 (25.0%)	22/40 (55.0%)
Total	14/44 (31.8%)	62/89 (69.7%)

In this study, miltefosine was safe and effective in the treatment of patients with CL with a mean cure rate of 70% (ITT) compared with a placebo cure rate of 32% ($p < 0.0001$, two-sided Chochran- Mantel-Haenszel test). Definite cure rates were higher in Colombia (82%) than in Guatemala (55%), but in both countries 2.2-fold higher than in patients on placebo: $p = 0.004$ in Colombia; $p = 0.03$, two-sided Chochran-Mantel-Haenszel test in Guatemala.

2.2.4.3. Does this drug prolong the QT or QTc interval?

The effect of miltefosine on the QT or QTc intervals was not evaluated in this NDA. The FDA will request the sponsor evaluate the QT prolongation effects as a post-marketing study if this NDA is approved.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration response, and are there any unresolved dosing or administration issues?

As discussed above, the dosing regimens to be tested in the pivotal Phase 3 studies were determined based on the results of dose-finding phase 2 studies. The recommended dosing regimen is proposed based on the results of Study 3168 (Placebo-controlled Pivotal CL Trial). The dose regimen of 50 mg BID for patients weighing 30-44 kg and 50 mg TID for patients weighing ≥45 was determined based on a dose-finding study was proved effective and safe for the treatment of CL in Study 3168. For the treatment of VL, 100 mg/day for patients weighing ≥25 kg (a lower or equal dose compared to the effective and safe dose for the treatment of CL) was determined based on the efficacy and safety data from several dose-finding studies, and proved to be effective in Study 3154. Accordingly, the proposed doses are considered by the Clinical Pharmacology reviewer to be safe and effective dosing regimen for the treatment of VL and CL.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

As mentioned above, no clinical studies were conducted that had human clinical pharmacology variables as a primary endpoint. All PK information of miltefosine were obtained from patients in the Phase 2 dose finding studies and were very limited for the purpose of determining the optimal clinical use of miltefosine. As discussed in **2.2.4**, the proposed recommended dose of miltefosine was justified based on efficacy and safety data from Phase 2 dose-finding studies and pivotal Phase 3 studies. Thus, PK information

of miltefosine in this NDA is used only to provide the PK parameters of miltefosine in the labeling.

PK in patients with VL aged 12 years and Older (Study 3109)
Study 3109 was a multicenter, open-label, sequential group dose escalating trial to identify a dosage regimen of miltefosine with a good therapeutic index (determination of initial cure rate, final cure rate and adverse events) and to assess the PK of miltefosine (e.g., C_{max}, $t_{1/2}$, T_{max}, AUC in plasma).

Male and female patients with visceral leishmaniasis, confirmed by spleen aspirate, and with signs and symptoms compatible with visceral leishmaniasis, like fever and splenomegaly, entered the trial. A total of 120 patients aged 12 years and older were randomly allocated to one of 4 groups:

Group 1: 50 mg/day x 6 weeks (1 capsule/day: in the morning)
Group 2: 50 mg/day x 1 week, then 100 mg/day x 3 weeks (1 or 2 capsules/day: 1 capsule in the morning or 1 capsule each in the morning and evening)
Group 3: 100 mg/day x 4 weeks (2 capsules/day: 1 capsule each in the morning and evening)
Group 4: 100 mg/day x 1 week, then 150 mg/day x 3 weeks (2 or 3 capsules/day: 1 capsule each in the morning and evening or 1 capsule each in the morning, at lunch time, and in the evening)

The primary efficacy endpoint of the study was the rate of patients with final cure. Final cure rates in dose groups 1 and 2 were both 28/30 (93.3%) and in dose groups 3 and 4 both were 29/30 (96.7%) (see Table 7 in **2.2.4.1**).

PK investigations were performed in 10 patients from each dose group. Blood sampling was done as follows:

- Several pre-dose blood samples were collected.
- Repeated blood sampling was performed on Day 23 to determine the plasma concentration-time course over one treatment day [C_{max}, T_{max}, AUC_{0-24}, peak trough fluctuation (PTF)].
- After end of treatment blood was sampled in order to determine the terminal plasma half-life ($t_{1/2}$).

Urine was sampled for a period of 24 hours on Day 23 to study the excretion of the drug into urine.

Figure 2 shows the miltefosine plasma concentrations determined in the different groups: the upper panel shows drug concentrations before the first dose on each day and the lower panel shows drug concentrations on Day 23. Due to the long half-life of miltefosine (> 6 days), plasma concentration does not appear to reach steady state at the end of treatment on Day 23. Thus, the PK parameters obtained from the concentration-time profiles on Day 23 do not represent the PK characteristics of miltefosine adequately.

In addition, AUC_{0-24} on Day 23 could not be estimated adequately because plasma samples were not collected after the first dose on Day 23 in Groups 2, 3, and 4. Accordingly, it is appropriate to report AUC_{0-tau} (AUC_{0-12} for Groups 2 and 3 and AUC_{0-8} for Group 4 on Day 23) rather than to report (b) (4) in the labeling. In addition, dose-proportionality could not be evaluated with these data because (a) plasma concentration did not reach a steady state on Day 23, (b) the changes in dose were not consistent among group (i.e., dose was increased after the first week in Groups 2 and 4, but not in Groups 1 and 3), and (c) dosing intervals were not consistent (i.e., QD for Group 1, BID for Groups 2 and 3, and TID for Group 4). Based on the plasma concentration-time profiles on Day 23, the absorption of miltefosine appears to proceed throughout the dosing interval because maximum concentrations were observed right before next dose in many patients. Table 15 summarizes the PK parameters that can be reported in the labeling based on the available plasma concentration data.

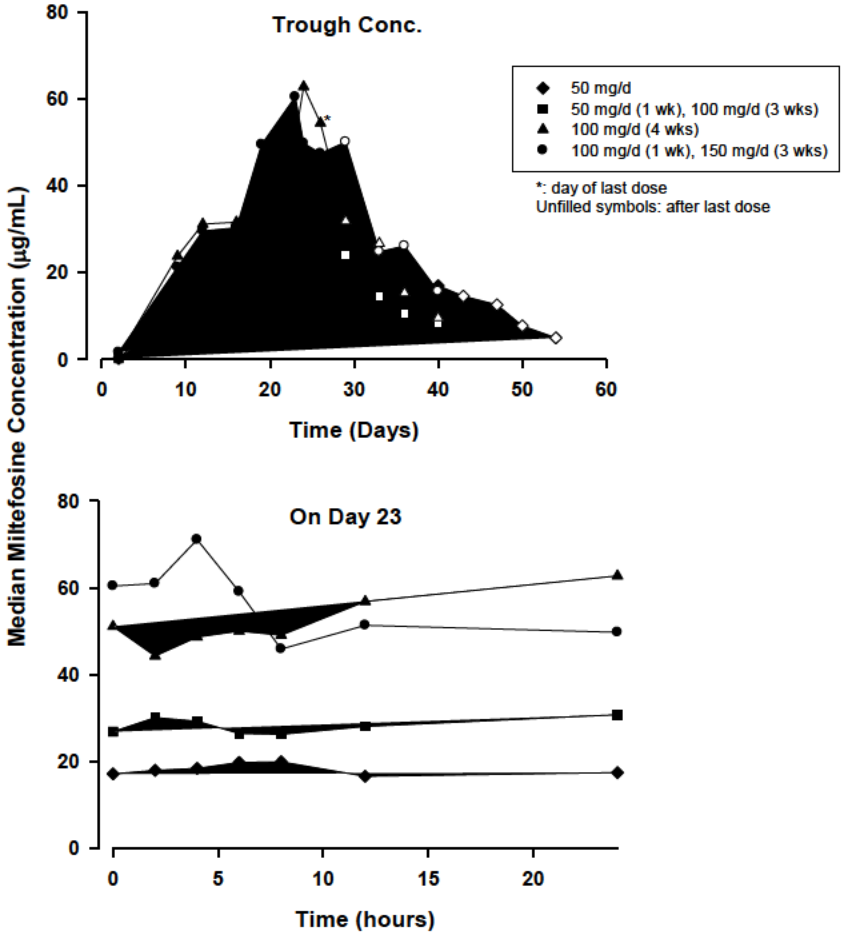


Figure 2. Median plasma concentrations of miltefosine following multiple oral administrations in patients with VL (Dose Groups 1 to 4, Study 3109). The upper panel shows drug concentrations before the first dose on each day and the lower panel shows drug concentrations on Day 23

Table 15. PK parameters [Mean (CV%)] of miltefosine on Day 23 following multiple oral administrations in patients with VL (Study 3109)

	On Day 23			After last dose
	Cmax (µg/mL)	Tmax[a] (hr)	AUCtau[b] (µg·hr/mL)	$t_{1/2}$ (hr)
50 mg/d (6 wks) (Group 1, N=9)	23.5 (30.8)	8 (2 - 24)	445 (28.1)	166.7 (34)
50 mg/d (1 wk) / 100 mg/d (3 wks) (Group 2, N=10)	39.2 (47.6)	5 (2-12)	378 (37.4)	199.8 (65.4)
100 mg/d (4 wks) (Group 3, N=10)	66.2 (28.5)	7 (2-12)	636 (26.7)	154 (31.1)
100 mg/d (1 wk) / 150 mg/d (3 wks) (Group 4, N=10)	75.9 (17.6)	4 (2-8)	486 (18.1)	202.8 (28.9)

[a]: Median (range)
[b]: AUC from time 0 h to 24 h, 12 h, 12 h, and 8 h for Groups 1, 2, 3, and 4, respectively

PK in patients with CL aged 12 years and Older (Dutch PK Study)

PK of miltefosine in patients with CL was evaluated in Dutch soldiers who acquired CL in Afghanistan. The patients were treated with miltefosine at a dose of 50 mg three times a day for 28 days. Blood samples were intended to be taken on Day 1 after the first dose of drug at 2, 4, and 6 hours; on an outpatient basis at several further time points during treatment; and irregularly until 5 months post-treatment, with the intention to take a blood sample every 2 to 4 weeks. There were 9 to 20 sample concentrations per subject with a median number of samples of 12.

A population PK analysis was performed for miltefosine plasma concentration results using the nonlinear mixed effects modeling software, NONMEM Version VII (ICON Development Solutions, Ellicott City, MD) with 384 plasma concentrations obtained from 31 (1 female) subjects. NONMEM models selected for comparisons and model building included a first-order absorption 1-compartment and 2-compartment models. Inter-individual variation in PK parameters was described by an exponential error model. Selection of models was guided by goodness of fit criteria including precision of parameter estimates, scatter plots, correlations between parameter estimates, convergence, improvement in the objective function, and the condition number. The final model and its estimates were evaluated by non-parametric bootstrapping methods to obtain standard errors and 95% confidence intervals (CI) for population parameters. Covariance between PK parameters and weight (WT, kg), body surface area (BSA, m^2), body mass index (BMI), and age (years) were investigated.

The 2-compartment model with first-order absorption, parameterized as Cl/F, Vc/F, Q/F, Vp/F, and Ka, was selected for the population modeling. The basic model included inter-individual variation terms for Cl/F, Vc/F, and Ka. Natural log (ln)-transformation of plasma concentration data for NONMEM modeling improved the scatter plots, convergence, and standard error estimates. Adding covariance between Vc/F and Cl/F improved the objective function.

For this basic model, the parameter estimates (% SE) were Cl/F = 3.85 (5.7%) L/day, Vc/F = 38.4 (4.5%) L, Q/F = 0.0408 (24.8%) L/day, Vp/F = 1.80 (11.4%) L, and Ka = 6.79 (16.6%) day-1. Inter-individual variability parameters as CV% for Cl/F, Vc/F, and Ka were 24.3%, 17.8%, and 87.0%.

To investigate the importance of demographic factors such as WT, BSA, BMI, and age in characterizing miltefosine population PK, correlations of Bayesian predicted Cl/F and Vc/F values versus these factors were examined. No apparent relationships of Cl/F or Vc/F as a function of WT, BSA, BMI, or age were noted. To further examine WT, BSA, BMI, and age influences on miltefosine PK, population models with allometric scaling of Cl/F and Vc/F based on these demographic factors were examined. Models that included WT, BSA, BMI, and age did not improve the basic population model.

The basic model was evaluated with a visual predictive check and non-parametric bootstrapping procedures. Bootstrapping methods were used to obtain mean, SE, and 95% CI estimates for parameters based on 2000 datasets (62,000 subjects). Overall, the PK parameters and their measures of variability were in good agreement between NONMEM estimates and bootstrapping approaches. Utilizing bootstrapping methods, the terminal $t_{1/2\beta}$ was 30.7 (18.3%) days, the distribution $t_{1/2\alpha}$ was 6.75 (5.8%) days, and Vss/F was 40.2 (4.7%) L. Over the 28 days of dosing, it appears that a steady state is not reached which is consistent with an estimated $t_{1/2\beta}$ of approximate 30 days (Table 16).

Table 16. Miltefosine Population PK Parameter Estimates

		Final Model		**Bootstrap**		
		Estimate	**%SE**	**Estimate**	**%SE**	**95% CI**
Cl/F	(L/day)	3.85	5.7	3.88	6.4	3.36 - 4.34
Vc/F	(L)	38.4	4.5	38.3	5.0	34.7 - 42.1
Q/F	(L/day)	0.0408	24.8	0.0500	76.1	-0.0338 -0.1154
Vp/F	(L)	1.80	11.4	1.97	32.3	0.554 - 3.05
Ka	(day-1)	6.79	16.6	6.86	16.6	4.56 - 9.02
IIV Cl/F	(%)	24.3	29.7	23.8	30.5	
IIV Vc/F	(%)	17.8	59.7	17.7	57.7	
IIV Ka/F	(%)	87.0	32.1	85.0	34.6	
IRVa	additive LN	0.215	24.9	0.209	25.1	
COV Vc/F:Cl/F		0.0420	44.3	0.0403	44.6	
Cor Vc/F:Cl/F		0.809				
Secondary Parameters						
A	(day-1)			0.1032	7.2	0.0886 - 0.1177
B	(day-1)			0.0234	22.2	0.0133 - 0.0336
t1/2α	(days)			6.75	5.8	5.98 - 7.51
t1/2β	(days)			30.7	18.3	19.7 - 41.8
Vss/F	(L)			40.2	4.7	36.5 - 43.9
Varea/F	(L)			171	16.0	117 - 224
MRT	(days)			10.5	3.7	9.78 - 11.3

SE% = standard error of estimate as %; IIV = inter-individual variability as %; IRV = intra-individual residual variability for additive error model based upon LNC; COV = covariance; Cor = correlation.

Miltefosine plasma concentrations from days 60 to 200 post-dosing could be simulated from the predictive check (Figure 3). The predicted plasma concentration on days 60, 91, 120, and 202 are 1.48, 0.14, 0.043, and 0.006 µg/mL, respectively.

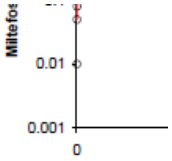


Figure 3. Semi-log plot of observed and population predicted miltefosine plasma concentrations with 95% CI (Visual predictive check was based on 2000 simulated datasets using the final model)

Estimates of C_{max}, AUC_{tau}, AUC_{24} for Day 27 (Table 17) were based upon the population PK analysis. A dataset containing 20 simulated miltefosine plasma concentrations for each subject during the last dosing interval of day 27 was prepared with equal time spacings of 0.015 hr. Each subject's simulated plasma concentration profile was based on their individual post hoc PK as obtained from NONMEM modeling with the final model. The simulations were also performed using the NONMEM program and the final model.

Table 17. PK parameter estimate of miltefosine on Day 27 following oral administration of 50 mg three times a day in patients with CL

	Cmax (µg/mL)	**AUCtau** (µg·day/mL)	**AUCtau** (µg·day/mL)	**AUC24** (µg·day/mL)	**AUC24** (µg·day/mL)
Mean	37.3	12.3	294.7	36.8	884.0
SD	8.2	2.7	64.3	8.0	193.0
%CV	21.9	21.8	21.8	21.8	21.8
Min	25.1	8.3	198.0	24.8	594.1
Med	34.4	11.3	272.1	34.0	816.2
Max	57.8	18.9	454.6	56.8	1363.7

In summary, miltefosine PK during multiple dosing was best described by a 2-compartment population model with first-order absorption in patients with CL. The $t_{1/2\alpha}$ was 6.75 days from bootstrapping. C_{max} and AUC_{tau} were 37 µg/mL and 295 µg·hr/mL, respectively, based on simulated plasma concentrations after the last dosing on day 27. The apparent terminal $t_{1/2}$ was approximately 30 days and explains the fact that steady-state plasma concentrations were not achieved by 28 days of dosing.

The different PK parameter values between patients with VL (Study 3109) *vs.* patients with CL (Dutch PK Study) (e.g., AUC_{tau} was 486 and 295 µg·hr/mL for Study 3109 and Dutch PK Study, respectively) may be, in part, due to different body weight in patients involved in two studies; mean body weight-normalized dose was 3.1 mg/kg/day and 1.8 mg/kg/day for Study 3109 and Dutch PK Study, respectively.

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

All PK information of miltefosine was obtained from patients. No clinical studies were conducted in healthy volunteers as miltefosine has been shown to cause hemolysis.

2.2.5.3. What are the characteristics of drug absorption?

Absolute bioavailability has not been determined because intravenous administration of miltefosine is not feasible. See **2.2.5.1** for other absorption characteristics of miltefosine.

2.2.5.4. What are the characteristics of drug distribution?

No clinical studies provided the characteristics of miltefosine distribution. In rats, radioactivity of [^{14}C]miltefosine and derived material is widely distributed after both single and repeated oral administration. Radioactivity decreased very slowly over the time with tissue $t_{1/2}$ in most tissues between 8 and 16 days following 21 repeat daily oral doses of [^{14}C]miltefosine.

Human plasma protein binding of miltefosine, evaluated by an ultracentrifugation method, was 98% over the drug concentration range from 0.1 to 10 µg/mL.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

No radiolabelled mass-balance studies were conducted to assess the metabolism of miltefosine in humans. In rats, only 16 and 5% of the total [^{14}C]miltefosine-related radioactivity was excreted in urine and feces, respectively, 264 h after oral dosing (15 and 5% after intravenous administration, respectively). The high levels of radioactivity in tissues (liver, kidney, stomach, large intestine, small intestine, testes, epididymes, and seminal vesicles) at late time points (up to 21 days) indicated that slow elimination of radioactivity from the tissues. This can easily be explained by references to choline as the primary metabolic product of miltefosine (see **2.2.5.6**). The radiolabeled metabolite choline is assumed to be incorporated into the endogenous choline pool and slowly eliminated from tissues.

2.2.5.6. What are the characteristics of drug metabolism?

Miltefosine is metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol which is oxidized to palmitic acid.

The biotransformation of miltefosine was studied in reconstituted enzyme systems (phospholipases A-D and CYP monooxygenases) and in cultures of human, rat and dog hepatocytes by radio-HPLC and HPLC-MS methods (Report 9321010056). Whereas phospholipases A-C showed no metabolic conversion of miltefosine, phospholipase D was highly active to produce choline as metabolite (Table 18).

Table 18. Metabolism of miltefosine following incubation with various phospholipase (radio-HPLC analysis)

Phospholipase	Miltefosine peak area (cpm)	% Recovery[a]
Control without phospholipase	2148	100
Phospholipase A	2011	94
Phospholipase B	1910	89
Phospholipase C	2365	110
Phospholipase D	371	17

[a]: control was set to 100%

No oxidative metabolism of miltefosine was observed with any of the reconstituted cytochrome P450 (CYP) monooxygenase systems, comprising the following CYP enzymes: 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, 4A1.

2.2.5.7. What are the characteristics of drug excretion?

Urinary excretion of miltefosine was evaluated in Study 3109. In total 42 urine samples were analyzed. Eight of the samples had measurable concentrations in the range of 5.53 to 115.34 ng/ml urine, which were much lower than the plasma concentrations, whereas 34 samples had results of BLD (LOD = 2 ng/ml) or BLQ (LOQ = 5 ng/ml). The urinary excretion of the unchanged drug on Day 23 after repeated oral administration of miltefosine was below 0.2% of the daily dose.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In Study 3109, the PK of miltefosine was evaluated following four dosing regimens. However, as discussed in 2.2.5.1, dose-proportionality could not be evaluated with the data because (a) plasma concentration did not reach a steady state, (b) the changes in dose were not consistent among group (i.e., dose was increased after the first week in Groups 2 and 4, but not in Groups 1 and 3), and (c) dosing intervals were not consistent (i.e., QD for Group 1, BID for Groups 2 and 3, and TID for Group 4). (see **2.2.5.1** for further details)

2.2.5.9. How do the PK parameters change with time following chronic dosing?

Due to a long half-life of miltefosine (> 6 days), plasma drug concentrations do not appear to reach a steady state at the end of treatment (Day 28). See **2.2.5.1** for further details.

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the final parameter estimates and associated standard errors for the population pharmacokinetic model, the magnitude of the interindividual variability was moderate for Cl/F (24% CV) and Vc/F (18% CV), but substantially high for Ka/F (87%). The high inter-subject variability of these parameters may result in the high inter-subject variability of plasma exposure to miltefosine. The reason for the high inter-subject variability is unknown.

The intra-subject variability of miltefosine PK was not assessed because the plasma concentrations did not reach a steady state.

2.3. Intrinsic Factors

The effects of intrinsic factors on miltefosine PK were not addressed in this NDA.

2.4. Extrinsic factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure or response?

The effects of extrinsic factors on the pharmacokinetics of miltefosine were not assessed in this NDA.

2.4.2. Drug-drug interactions

2.4.2.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

There is no *in vitro* basis to suspect *in vivo* drug-drug interactions

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No oxidative metabolism of miltefosine was observed with any of the reconstituted cytochrome P450 (CYP) monooxygenase systems, comprising the following CYP enzymes: 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, 4A1.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

There was little or no evidence of time- or metabolism-dependent inhibition of the CYP enzymes examined at up to 100 μM miltefosine, approximately the mean C_{max} observed across all clinical studies ((b) (4) report (b) (4) 125006). Significant levels of inhibition were observed at 300 and 1000 μM miltefosine, with a complete loss in marker substrate activity observed at all intervals at 1000 μM, including the zero-minute pre-incubation time suggesting the possibility of an in vitro artifact such as micelle formation. Treatment with 3 μM miltefosine had little or no effect on CYP3A4/5 activity following in vitro evaluation as an inducer of CYP450 expression in cultured human hepatocytes ((b) (4) report (b) (4) 123010). Treatment with 37, 250 or 1,000 μM miltefosine resulted in decreased or undetectable CYP3A4/5 activity that was attributed to the cytotoxicity observed in the culture.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The sponsor did not assess the potential of miltefosine to act as a substrate or inhibitor of P-glycoprotein

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

There are no other metabolic/transporter pathways that may be important.

2.4.2.6. Does label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

No co-administered drug is specified in the label.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

Anti-HIV drugs may be co-administered with miltefosine in patients with HIV co-infection. However, no drug-drug interaction is expected between miltefosine and anti-HIV drugs.

2.4.2.8. Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No drug-drug interaction studies were conducted in this NDA.

2.4.2.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions.

2.4.2.10. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved issues related to metabolism, active metabolites, or metabolic drug interactions, or protein binding.

2.4.3. What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no other unresolved dose issues.

2.5. General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

No claim is made regarding BCS classification. Miltefosine is freely soluble (b) (4) in water, 0.1N hydrochloric acid, 0.1N sodium hydroxide, methanol, ethanol and (b) (4) and insoluble (b) (4)

Twelve (12) capsule dissolution profiles for each of two drug product batches (1F2639 and 1C2130) at pH 1.2, 4.5 and 6.8 (using USP buffer systems) were generated using a commercial dissolution methodology. The dissolution data indicate that maximum dissolution is achieved at all pH values (b) (4)

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The proposed to-be-marketed formulation was used in the pivotal clinical trials. Thus, no relative BE studies were conducted.

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on the BA of miltefosine has not been evaluated. However, miltefosine was given with food in all clinical trials because administration with food ameliorates gastrointestinal adverse reactions. Thus, the sponsor proposed that miltefosine should be given with food and the proposal is acceptable from a Clinical Pharmacology perspective.

2.5.4. When would a fed BE study be appropriate, and was one conducted?

Not Applicable.

2.5.5. How do the dissolution conditions and specifications ensure *in vivo* performance and quality of the product?

Not applicable.

2.5.6. If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable.

2.5.7. If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PK-PD relationship?

Not applicable.

2.5.8. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?

Not applicable.

2.5.9. What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Miltefosine was the active moiety measured in human plasma in clinical studies.

2.6.2. Which metabolites have been selected for analysis and why?

Miltefosine is metabolized to choline in human (See section **2.2.5.6.**). No metabolites were analyzed.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

In vitro studies demonstrated that miltefosine is 97.5%, 97.4%, and 97.6% bound to human plasma proteins at 0.1, 1, and 10 μg/mL, respectively, indicating that miltefosine plasma

protein binding is not concentration-dependent. Thus, total drug concentration (free + unbound) for miltefosine was measured in human plasma.

2.6.4. What bioanalytical methods are used to assess concentrations?

The Miltefosine concentrations in the plasma and urine samples were analyzed by a validated HPLC-MS/MS method.

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Human and urine blank plasma was 'spiked' with Miltefosine resulting in the following concentrations: 5, 10, 20, 50, 100, 200, 400, 1000, and 2000 ng/ml plasma. The plasma concentration of the internal standard was 400 ng/ml. Acceptance criteria for the calibration curve according to an internal standard operating procedure. If more than 20% out of 9 calibration standards showed a deviation higher than 20% from the theoretical value the calibration curve was not accepted and the test samples of this batch had to be reanalyzed.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Quantification was performed with calibration lines from spiked blank human plasma or urine. The lower limit of quantification (LOQ) of the method was 5 ng/ml and the lower limit of detection (LOD) was 2 ng/ml.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

In order to ensure consistent accuracy and precision of the measured concentrations of Miltefosine in plasma throughout all analytical series, quality control (QC) samples were analyzed together with every analytical series (batch). QC samples at 3 concentrations (20, 200, and 1600 ng/ml) had been spiked and frozen by an independent analyst not involved in this study. These 3 QC samples were analyzed at least in duplicate together with the unknown study samples. If more than 2 of 6 QC samples differed more than ±20 % from the expected value within a batch the analytical series was not accepted and the unknown study samples had to be reanalyzed.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Stability of the analyte in human plasma after thawing/freezing cycles was shown in leteratures (Van der Viis, Verheij, 1996; Knebel et al., 1999). It was shown that human quality control plasma samples are stable for approximately 6 years.

3. Labeling Recommendation

(As of September 24, 2014)

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SEONG H JANG
09/24/2013

PHILIP M COLANGELO
09/24/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204684	**Reviewer:** Mark R. Seggel	
Submission Date:	Original: 27-SEP-2012 Resubmission: 19-APR-2013 Amendment: 07-JUN-2013		
Division:	DAIP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Paladin Therapeutics	**Supervisor:** Rik Lostritto, Ph.D.	
Trade Name:	Impavido Capsules	**Date Assigned:**	02-OCT-2012
Generic Name:	Miltefosine capsules	**Date of Review:**	30-JUL-2013
Indication:	Treatment of leishmaniasis	**Type of Submission:**	505(b)(1)
Formulation / strengths	Capsule, 50 mg	**GRMP Goal:**	10-OCT-2013
Route of Administration	Oral	**PDUFA Goal:**	19-DEC-2013

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission: Miltefosine is an alkylphosphocholine with activity against visceral, mucosal and cutaneous leishmaniasis. It was originally developed as a topical antineoplastic, but has found use as an oral antiprotozoal drug. AEterna Zentaris Inc. sold the commercial rights to miltefosine to Paladin Labs in 2008. Miltefosine is currently marketed in India, Colombia, Germany, and several other countries. Miltefosine is available as 10 mg and 50 mg miltefosine capsules; however under NDA 204684, Paladin is currently seeking USFDA approval of only the 50 mg strength. Impavido (miltefosine) capsules also contain colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The proposed treatment regimen is one capsule taken two or three times a day, for 28 days. Because of its emetogenic effect, the product is taken with food.

Review: This review focuses on the Biopharmaceutics evaluation and acceptability of the dissolution method and acceptance criterion.

Dissolution Method and Acceptance Criterion

Miltefosine is freely soluble (b) (4) in water, 0.1N hydrochloric acid, and in 0.1N sodium hydroxide. The drug is (b) (4) dissolved across the physiological pH range. As such, the Applicant proposed dissolution testing in USP Apparatus II (paddle), 50 rpm, and a medium consisting of 750 mL of 0.1 N HCl. An acceptance criterion of NLT (b) (4) (Q) dissolved in the (b) (4) was originally proposed. Supporting data include profiles (5, 10, 15, 20, 30, 45 and 60 minutes at pH 1.2, 4.5 and 6.9) of two drug product batches (one 'pre-change' batch and one 'post-change' batch, (b) (4) As the Applicant has noted, "the raw dissolution data indicate that maximum dissolution is achieved at all pH values [1.2, 4.5, and 6.8] (b) (4) Unfortunately, only data from the (b) (4) sampling time point were provided for all other batches, including the stability batches.

The Applicant was asked to provide dissolution profiles (including 15, 20, 30, and 45 minutes sampling time points, n=12) for the drug product at release and on stability. Based on the results, the Applicant was to propose a sampling time point at which a mean of Not Less Than (b) (4) (Q) is dissolved. The Applicant chose not to provide additional dissolution data, nor did they propose an alternate sampling time point.

The Applicant was subsequently advised to change the acceptance criterion from NLT [(b) (4)] to NLT [(b) (4)] (Q) at 15 minutes. The Applicant revised the acceptance criterion accordingly, and noted that, "the proposed dissolution spec of NLT [(b) (4)] (Q) dissolved in 15 minutes is based on the [(b) (4)] solubility of the drug substance and correspondingly [(b) (4)] dissolution across the physiological pH range and the release/stability data"

RECOMMENDATION:

From the Biopharmaceutics perspective, it is recommended that NDA 204684, (as amended) for Impavido (miltefosine) Capsules, 50 mg, is approved with the following regulatory dissolution method and acceptance criterion:

Apparatus	USP Type-II, Paddle
Medium	0.1 N HCl
Volume	750 mL
Paddle Rotation Speed	50 RPM
Temperature	37.0°C ± 0.5°C
Acceptance Criterion	NLT [(b) (4)] (Q) of Miltefosine is dissolved in 15 minutes

Signature
Mark R. Seggel
Reviewer
Office of New Drug Quality Assessment

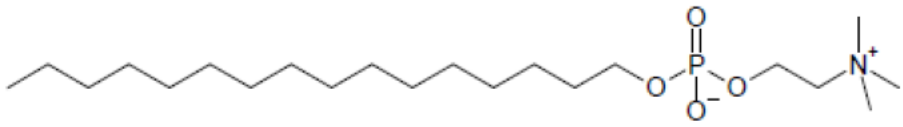
Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: D.Matecka, M.Zhou, A.Banerjee, R.Madurawe, G.DiBernardo, N.Bhandari, R.Lostritto

BIOPHARMACEUTICS ASSESSMENT - REVIEW NOTES

NDA 204684 was originally submitted on 27-SEP-2012. A Refuse to File letter was issued -26-NOV-2012 due to clinical and statistical issues; the application was fileable from the CMC and Biopharmaceutics perspectives. The NDA was resubmitted on 19-APR-2013.

DRUG SUBSTANCE:



• Systematic names:
Choline hydroxide, hexadecyl hydrogen phosphate, inner salt (USAN);
2-(Hexadecoxy-oxido-phosphoryl)oxyethyl-trimethyl-azanium (IUPAC);
2-[[(Hexadecyloxy)hydroxyphosphenyl]oxy]-N,N,N-trimethylammonium inner salt;
Hexadecylphosphocholine
• CAS No.: 58066-85-6
• Solution pH: The pH of a 1% aqueous solution is between 5.0-8.0.
• Solubility: By USP definition, miltefosine is freely soluble (b) (4) in water, 0.1N hydrochloric acid, 0.1N sodium hydroxide, methanol, ethanol (b) (4) and insoluble (b) (4) (b) (4)
• Dissociation constant: A pKa of 7.2 was determined by acid-base titration.

DRUG PRODUCT:

Background Information: Miltefosine is reported to have high bioavailability. However, because miltefosine has been shown to cause hemolysis in vitro, no clinical studies were conducted with intravenous administration that would allow assessment of absolute bioavailability. In animal models, after oral administration miltefosine is slowly absorbed with an absolute bioavailability of 82-94% and T_{max} between 4 and 48 hours (see Dorlo, et al, JAC, 67, 2012 and references therein).

The same basic capsule formulation of miltefosine has been used throughout clinical development. Accordingly, bioequivalence studies were not thought necessary to compare different formulations.

A potential effect of food on relative bioavailability of miltefosine was not investigated. Administration of the drug with food is necessitated to ameliorate the emetogenic effect of the drug.

Miltefosine is chemically and metabolically very stable. Therefore, prolonged residence of miltefosine in the gastrointestinal tract is not expected to cause increased degradation of the active substance if taken with food.

The clinical sections of this application are supported by data obtained from 7 pivotal clinical studies and 15 supporting clinical studies.

Drug Product Formulation:

Table 1. Composition of Miltefosine Capsules, 50 mg

Component	Composition		Function
	mg/capsule	wt %	
Miltefosine	50.0	(b) (4)	Active ingredient
Colloidal Silicon Dioxide NF	(b) (4		(b) (4)
Microcrystalline Cellulose NF (b) (4)			
Lactose Monohydrate NF			
Talc NF			
Magnesium Stearate NF			
Opaque red hard gelatin capsule size 2*			
(b) (4) white ink			
Total Capsule Content	190.0		

Proposed Dissolution Method and Acceptance Criterion:

Table 2. Proposed Dissolution Method

Apparatus	USP Type-II, Paddle
Medium	0.1 N HCl
Volume	750 mL
Paddle Rotation Speed	50 RPM
Temperature	37.0°C ± 0.5°C
Acceptance Criteria	NLT (b) (4) (Q) of Miltefosine is dissolved in (b) (4)
Assay	HPTLC
Calculations and Data Reporting	Calculate the miltefosine concentration in the Sample Preparation (corrected for any absorbance from the Blank Preparation) by fitting on the least squares linear regression from the 80, 100 and 120% Standard Preparations. Report the amount of miltefosine as % label claim to the nearest 0.1%.

According to the Applicant, "the proposed dissolution spec of NLT (b) (4) dissolved in (b) (4) is based on the (b) (4) solubility of the drug substance and correspondingly (b) (4) dissolution across the physiological pH range (Sections 3.2.S.1.3 and 3.2.P.2.2.3, respectively), the release/stability data (Sections 3.2.P.5.4 and 3.2.P.8.3, respectively), and the lower limit of (b) (4) avoids coinciding with the lower individual weight variation limit of (b) (4) (See Section 3.2.P.5.6, eCTD seq. 0000.)

It should be noted that the Applicant previously stated, "while we agree that a tighter specification [15 minutes] could be implemented, our concern is that the amount of tightening which would be needed to show any differences between batches, if this is even possible, would require very short sample withdrawal times, which would be random in nature and would not be

a diagnostic control to differentiate batches based on quality criteria," (see section 3.2.R.4, pre-NDA correspondence).

Dissolution Data:

The supporting data submitted in the NDA includes dissolution profiles of two batches at various pH, and single-point (b) (4) dissolution data from several batches at release and on stability.

The profile data were obtained on two batches of miltefosine capsules, representing product manufactured prior to (lot 1C2130) and after (lot 1F2639) a change in the product manufacturing process was implemented. The revised manufacturing process incorporate (b) (4)

Dissolution Profiles of Pre- and Post-change Batches at Various pHs (3.2.P.2.2):

The dissolution profile data are provided in Tables 3 to 8. The Applicant notes, "the raw dissolution data, provided in Table 3.2.P.2.2.3-1 to Table 3.2.P.2.2.3-6, indicate that maximum dissolution is achieved at all pH values (b) (4) (See page 3, section 3.2.P.2.2.3, eCTD seq. 0000.)

"To minimize dissolution differences due to normal variability in miltefosine content between batches," 'assay adjusted' dissolution profiles were also estimated by the Applicant by "normalizing the data to the average raw dissolution value at the 60 minute time point for each run." The results of this normalization for the pH 1.2 data are summarized in Tables 3 and 4, and plotted in Figure 1. Similar calculations were performed on the pH 4.5 and pH 6.8 data (see eCTD 3.2.P.2.2).

Table 3. Dissolution Profile of Batch 1F2639 in pH 1.2 Medium (Post-change batch)

Vessel No.	Amount Dissolved (%) at Stated Time						
	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	60 mins
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	90.8	102.2	92.4	101.7	95.7	105.9	104.5
Range	(b) (4)						
Std. Dev.							
*ADJUSTED^*							
Mean	*86.9*	*97.8*	*88.5*	*97.3*	*91.6*	*101.3*	***100.0***
Range	(b) (4)						
Std. Dev.							

*Passes Stage 2 testing at 15 minutes.
^Summary data from assay-adjusted results.

(b) (4)

Table 5. Dissolution Profile Summary Data for Batch 1F2639 in pH 4.5 Medium (Post-change batch)

Vessel No.	Amount Dissolved (%) at Stated Time						
	5 mins	10 mins	15 mins	20 mins	30 mins	45 mins	60 mins
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean (n=12)	85.1	101.9	102.4	99.2	101.0	99.5	99.7
Range	(b) (4)						
Std. Dev.							

(b) (4)

Table 7. Dissolution Profile Summary Data for Batch 1F2639 in pH 6.8 Medium (Post-change batch)							
Vessel No.	**Amount Dissolved (%) at Stated Time**						
	5 mins	**10 mins**	**15 mins**	**20 mins**	**30 mins**	**45 mins**	**60 mins**
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean	86.5	101.8	97.2	102.0	101.9	102.9	100.4
Range	(b) (4)						
Std. Dev.							

(b) (4)

Figure 1. Plot of pH 1.2 Assay-Adjusted Dissolution Profile Data for Drug Product Batches 1F2639 and 1C2130:

(b) (4)

<u>Comments</u>: The value of the intra-batch adjustment of dissolution data based on the average "assay" value (mean amount dissolved at the 60 minute time point) is unclear.

Table 9. Batch Analyses (3.2.P.5.4)

Batch No.	Batch Use	Date Manufactured	Dissolution (at (b) (4) Mean (Range)	Assay
7G5416	Stability	2007	(b) (4)	
8J7717	Stability	7/2008		
0G0288	Stability	2010		
0G0289	Stability	2010		
0G0290	Stability	2010		
1C2130	Dev	2/2011		
1F2639	PV/Stability	8/2011		
1M3150	PV/Stability	10/2011		
2C3816	PV/Stability	2/2012		

Table 10. Batch Analyses (3.2.P.2.2)

Batch No.	Batch Use	Date Manufactured	Dissolution (at (b) (4) Mean	Assay
9512-001/01	Clin	12/1995	(b) (4)	
9710-001/02	Clin	10/1997		
9803-001/03	Clinical	3/1998		
9809-001/04	Clin	9/1998		
ID0251	Dev	3/2001		
ID0252	Clin/dev	3/2001		
ID0253	Dev	3/2001		

Table 11. Stability Data (3.2.P.8.3) (as updated 07-JUN-2013 (0007)

Batch	Stability Condition	Time Point	Dissolution at (b) (4) Mean (Range)	Assay
7G5416	25°C/60% RH	0	(b) (4)	
		3		
		6		
		9		
		12		
		18		
		24		
		36		
		48		
7G5416	40°C/75% RH	0		
		3		
		6		
8J7717	30°C/65% RH	12		
		24		
		36		
0G0288	25°C/60% RH	0		
		3		
		6		
		9		
		12		
		15		
		18		
0G0288	30°C/75% RH	0		
		3		
		6		
		9		
		12		
		15		
		18		
0G0288	40°C/75% RH	0		
		3		
		6		
0G0289	25°C/60% RH	0		
		3		
		6		
		9		
		12		
		15		
		18		
0G0289	30°C/75% RH	0		
		3		
		6		
		9		
		12		
		15		
		18		
0G0289	40°C/75% RH	0		
		3		
		6		
0G0290	25°C/60% RH	0		
		3		

			(b) (4)
		6	
		9	
		12	
		15	
		18	
0G0290	30°C/75% RH	0	
		3	
		6	
		9	
		12	
		15	
		18	
0G0290	40°C/75% RH	0	
		3	
		6	
1F2639	25°C/60% RH	0	
		3	
		6	
		9	
		12	
		18	
1F2639	30°C/65% RH	0	
		3	
		6	
1F2639	30°C/75% RH	0	
		3	
		6	
		12	
		18	
1F2639	40°C/75% RH	0	
		1	
		2	
		3	
		6	
1M3150	25°C/60% RH	0	
		3	
		6	
		9	
		12	
1M3150	30°C/75% RH	0	
		3	
		6	
		9	
		12	
1M3150	40°C/75% RH	0	
		1	
		2	
		3	
		6	
2C3816*	25°C/60% RH	0	
		3	
		6	
		9	
2C3816*	40°C/75% RH	0	

		1	(b) (4)
		2	
		3	
		6	

* Packaged in (b) (4) blisters with (b) (4) (carton); all others in (b) (4) blisters without (b) (4)

^ A single dissolution OOS result was observed for batch 0G0290 at the 40°C/75% RH 3 month time point, but the result at the 6 month time point was well within [the proposed]specifications. [*It is not clear if Stage 2 testing was conducted.*]

Based on these data, the Applicant has proposed an expiration dating period of (b) (4) months for the commercial drug product when stored at 15-30°C.

Comments: The dissolution profile results, as well as the batch release and stability data, clearly indicate that the (b) (4) sampling time point is not ideal for detecting any batch to batch variations since the observed mean values range from ca. (b) (4) On the other hand, given the overall (b) (4) dissolution of the product and the (b) (4) solubility of miltefosine, it appears unlikely that any clinically relevant differences would be seen among capsules meeting the proposed acceptance criterion. Alternatives to the proposed acceptance criterion include NLT (b) (4) (Q) dissolved at (b) (4), NLT (b) (4) (Q) dissolved at (b) (4), and NLT (b) (4) (Q) dissolved at 15 minutes. The challenge with the latter two approaches is that dissolution profiles of stability samples were not obtained. The Applicant was therefore asked to provide additional data and propose a suitable acceptance criterion.

Comment to Applicant: (24-JAN-2013)

The proposed regulatory dissolution test for miltefosine capsules, 50 mg, is conducted with USP Apparatus Type II (paddle) at 50 rpm in a medium consisting of 750 mL of 0.1 N HCl at 37°C. An acceptance criterion of Not Less Than (b) (4) dissolved in (b) (4) is proposed. However, the observed mean amount dissolved at (b) (4) is typically at least (b) (4)

For immediate release product the selection of the test sampling time point should be where Q= (b) (4) dissolution occurs. Therefore, please provide dissolution profiles (including 15, 20, 30, and 45 minutes sampling time points, n=12) for your drug product at release and on stability. Based on the results, propose a sampling time point at which a mean of Not Less Than (b) (4) (Q) is dissolved (see USP <711> Acceptance Table 1).

Comments: This particular issue does not appear to be discussed in the 19-APR-2013 NDA resubmission. Now new dissolution data were provided. Further justification for the proposed acceptance criterion cannot be located in the resubmission. A second information request was sent to the Applicant.

Information Request: (31-MAY-2013)

Based on the available dissolution data, a mean of (b) (4) miltefosine dissolved occurs at (b) (4) 15 minutes. The proposed acceptance criterion of NLT (b) (4) at (b) (4) is not justified. Accordingly, revise the acceptance criterion for miltefosine capsules to NLT (b) (4) (Q) at 15 minutes (see USP <711> Dissolution, Acceptance Table 1).

Applicant Response: (07-JUN-2013, 0007)

"The acceptance criterion for drug product dissolution has been changed to NLT (b) (4) (Q) at 15 minutes. The updated drug product specifications are provided in Section 3.2.P.5.1; the updated dissolution method is provided in Section 3.2.P.5.2.4; the updated justification for specifications is provided in Section 3.2.P.5.6; and the updated marketed stability protocol is provided in Section 3.2.P.8.2."

In Section 3.2.P.5.6, the Applicant notes that, "the proposed dissolution spec of NLT (b) (4) (Q) dissolved in 15 minutes is based on the (b) (4) solubility of the drug substance and correspondingly (b) (4) dissolution across the physiological pH range…and the release/stability data…"

Comments: The Applicant has chosen not to provide dissolution profiles of stability samples, but has nevertheless agreed to the 15-minute sampling time point. Given the (b) (4) dissolution (b) (4) of miltefosine, it does not appear that an acceptance criterion of NLT (b) (4) (Q) at 15 minutes will result in unwarranted or excessive batch failure. It should be noted that occasional Stage 2 or Stage 3 dissolution testing is acceptable.

The HPTLC assay used to determine the amount of miltefosine dissolved is comparable to the method used for the capsule assay and determination of impurities in the capsule. It was developed since miltefosine does not have a strong chromophore (necessary for HPLC with UV detection) and because of reported interference by excipients when HPLC is used. The Applicant has been advised that they should develop and validate a more robust analytical procedure for drug product assay, impurities and dissolution (see the CMC reviews associated with this NDA).

While the Applicant has requested a (b) (4)-month shelf life, from the CMC perspective, only a 24-month expiration dating period can be granted at this time. This is appropriate from the Biopharmaceutics perspective as well, especially given the lack of dissolution profile data on stability batches.

###

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

/s/

MARK R SEGGEL
08/12/2013

ANGELICA DORANTES
08/12/2013

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA/BLA Number	**204684**	**Brand Name**	**Impavido®**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**Miltefosine**
Medical Division	**DAIP**	**Drug Class**	**Antineoplastic/Antileishimanial**
OCP Reviewer	**Seong Jang, PhD**	**Indication(s)**	**Treatment of visceral, cutaneous, and mucosal leishmaniasis**
OCP Team Leader	**Phil Colangelo, PhD**	**Dosage Form**	**Oral Capsules**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**For 28 days, 30-44 kg: one 50 mg capsule twice daily with food ≥45kg: one 50 mg capsule three times daily with food**
Date of Submission	**April 19, 2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**October 1, 2013**	**Sponsor**	**Paladin Therapeutics, Inc**
Medical Division Due Date	**October 7, 2013**	**Priority Classification**	**Priority**
PDUFA Due Date	**December 19, 2013**	**AC Meeting (if applicable)**	**October 18, 2013**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS -				Because of the cytostatic/cytotoxic potential of the drug substance, PK studies in healthy subjects were not feasible.
single dose:				
multiple dose:				
PATIENTS -				
single dose:				
multiple dose:	**X**	**2**		**Visceral Leishmaniasis**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**6**		**Dose Ranging Studies**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**1**		**Pop PK study (Cutaneous Leishmaniasis)**
Data rich:				
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability				**No IV formulation is available**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				**The same formulation as been used from clinical development**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
TOTAL NUMBER OF STUDIES		***9***		

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The same basic capsule formulation has been used throughout clinical development
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			No protein binding information was provided.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Weight-based dosing is proposed.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		Several dose-finding studies were conducted.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed			X	

	effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the resubmission is fileable from a clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

We will request the sponsor provide information about the in vitro protein binding of miltefosine, which may come from the literature, if available.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

SEONG H JANG
05/20/2013

PHILIP M COLANGELO
05/21/2013

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA/BLA Number	**204684**	**Brand Name**	**Impavido®**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**Miltefosine**
Medical Division	**DAIP**	**Drug Class**	**Antineoplastic/Antileishimanial**
OCP Reviewer	**Seong Jang, PhD**	**Indication(s)**	**Treatment of visceral, cutaneous, and mucosal leishmaniasis**
OCP Team Leader	**Kimberly Bergman, PharmD**	**Dosage Form**	**Oral Caupsues**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**For 28 days, 30-44 kg: one 50 mg capsule twice daily with food ≥45kg: one 50 mg capsule three times daily with food**
Date of Submission	**September 27, 2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**January 27, 2013**	**Sponsor**	**Paladin Therapeutics, Inc**
Medical Division Due Date	**February 27, 2013**	**Priority Classification**	**Priority**
PDUFA Due Date	**March 27, 2013**	**AC Meeting (if applicable)**	**February 26, 2013**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS -				Because of the cytostatic/cytotoxic potential of the drug substance, PK studies in healthy subjects were not feasible.
single dose:				
multiple dose:				
PATIENTS -				
single dose:				
multiple dose:	**X**			**Visceral Leishmaniasis**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**6**		**Dose Ranging Studies**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**			**Pop PK study (Cutaneous Leishmaniasis)**
Data rich:				
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability				**No IV formulation is available**
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				**The same formulation as been used from clinical development**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
TOTAL NUMBER OF STUDIES				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The same basic capsule formulation has been used throughout clinical development
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			No protein binding information was provided.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Weight-based dosing is proposed.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		Several dose-finding studies were conducted.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed			X	

	effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the resubmission is fileable from a clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

SEONG H JANG
11/26/2012

KIMBERLY L BERGMAN
11/26/2012