Antiparasitic **December 2016**
Miltefosine (Impavido, Paladin Therapeutics) **Non-formulary**

Criteria for Formulary Consideration of miltefosine

Efficacy
Miltefosine is FDA approved for the visceral leishmaniasis *(Leishmania donovani), c*utaneous leishmaniasis *(Leishmania braziliensis, guyanensis, panamensis),* and mucosal leishmaniasis *(Leishmania braziliensis)* in adult patients (≥12 years) weighing ≥30kg. FDA approval for use of miltefosine in visceral leishmaniasis (VL) is based on a randomized, open-label non-inferiority trial versus amphotericin B deoxycholate which found the final cure rate to be 94.3% (miltefosine) vs 97% (amphotericin). FDA approval for use of miltefosine in cutaneous leishmaniasis (CL) is based on a randomized, placebo-controlled trial conducted in Colombia and Guatemala which found a higher definite cure rate (66%) than placebo (30%) in the ITT population. FDA approval for use of miltefosine in mucocutaneous leishmaniasis (ML) was based on a single-arm study conducted in Bolivia which showed a complete healing rate of 62% of ITT subjects. This was numerically higher and lower than historical results using various therapies in different countries (37%, 52%, 82%, 91%).[6,7]

Miltefosine has also been used on a case-by-case basis for treatment of free-living amoebas (FLA).[12,16,17,19] Literature on the efficacy of miltefosine for use in FLA infections is scarce. Regardless of this scarcity, the CDC notes that miltefosine could be used for the treatment of *Acanthamoeba, Balamuthis mandrillaris*, and *Naegleria fowleri* infections.[9-11] Infections caused by *Naegleria fowleri* are often treated with multiple medications, at different times from onset of symptoms, and with variations in the supportive care therapy administered which makes it difficult to quantify the contribution of miltefosine in the small number of patients who have received this therapy.[15-17]

Safety
Miltefosine has several contraindications for use; these include pregnancy, Sjogren-Larsson-Syndrome, and hypersensitivity to it or its components. Miltefosine has a black box warning for embryo-fetal toxicity. Gastrointestinal associated side effects are the most common (i.e., nausea, vomiting, diarrhea). These GI side effects can lead to volume depletion and decreased absorption of oral contraceptive agents.[5,6]

It is possible that miltefosine could be confused with other medications with similar looking names (i.e., mifepristone).

Uniqueness
The uniqueness of miltefosine is its route of administration (oral) compared to other agents typically used for ML, VL, and CL.[5]

Cost [20]
50mg (28 capsules) = $19,200 [AWP]
50mg capsule = ~$685

Cost per day:
- 50mg PO BID: ~$1,400
- 50mg PO TID: ~$ 2,000

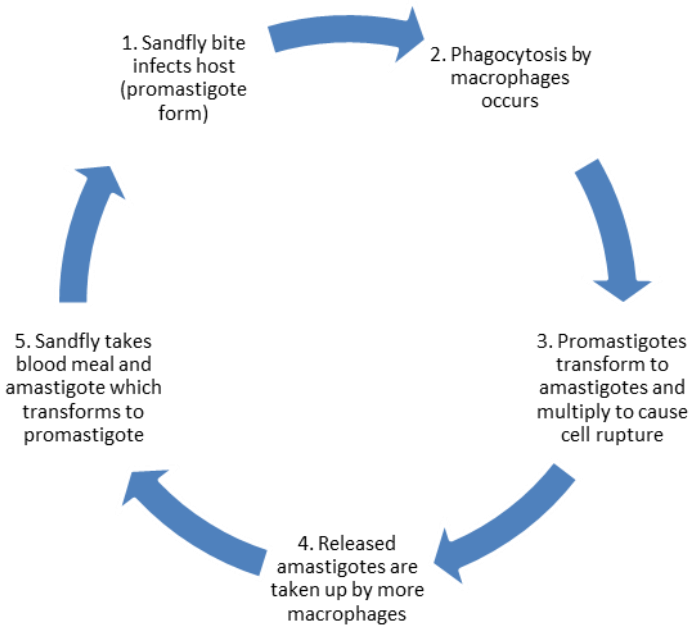
Recommendations

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

Introduction

Leishmaniasis, a neglected tropical disease, is caused by the protozoa of the genus *Leishmania*. Mammals are infected by about 30 different species of which ~20 infect humans. The sand fly is often the vector which transmits the protozoa to humans (see simplified cycle below). Several variables, such as species of the parasite, location of bite, distribution of infected macrophages, and the human's immune response, determine the type of syndrome that is displayed. These infections can be classified into three main types: cutaneous (CL), mucocutaneous (ML), and visceral (VL).[1-3]

Type	Description
Cutaneous	Cutaneous forms tend to be self-limiting and leave scars. It is the most common form. Generally caused by: *Leishmania tropica*, *L. major*, *L. aethiopica*, *L. infantum, L. donovani*. *L. mexicana*, *L. amazonensis*, *L. venezuelensis, L. [V.] braziliensis*, *L. [V.] guyanensis*, *L. [V.] panamensis, L. [V.] peruviana*
Mucocutaneous	This develops as sequela from a cutaneous infection. It affects the naso-oropharyngeal mucosa. *L. [V.] braziliensis*, *L. [V.] panamensis*, *L. [V.] guyanensis, L. (Leishmania) amazonensis*
Visceral	This form affects the internal organs such as the spleen, liver, and bone marrow. It can manifest years later in patients whose immune system becomes compromised (ex: HIV/AIDS). *Caused by: L. donovani*, *L. infantum*



Leishmania species are found in over 80 countries; leishmaniasis occurs often in Asia, the Middle East, Africa, southern Europe, Mexico, Central & South America, and sometimes in parts of Texas and Oaklahoma.[2, 3] Treatment options vary by country due to drug availability and *Leishmania* species susceptibility. Pentavalent antimony (i.e., meglumine antimoniate, sodium stibogluconate) is often used first line for treatment of leishmaniasis, however, resistance has limited its use in certain parts of the world. Liposomal amphotericin B, miltefosine, paromomycin, 'azoles', and pentamidine have also been used for treatment of leishmaniasis.[1, 2] Several other agents and combination therapy have also been studied.[3]

Miltefosine is one of the five antileishmaniasis medicines included in the World Health Organization's list of essential medicines.[4] Miltefosine is approved in various areas for different forms: Nepal (VL), Argentina, Bangladesh, Bolivia, Colombia, Ecuador, Germany, Guatemala, Honduras, India, Mexico, Pakistan, Paraguay and Peru (VL, CL). [5] It was most recently approved in the United States (VL, CL, ML).[6]

Pharmacokinetics [7]

The pharmacokinetic properties of miltefosine are obtained from adult patients who received treatment for VL or CL.

Parameter	Outcome
Absorption	Absolute bioavailability not known
Distribution	All characteristics not known. Protein binding 98% (conc: 0.1-10 micrograms/mL.)
Metabolism	Metabolized by phospholipid D to choline (incorporated into tissues) and hexadecanol (oxidized to palmitic acid).
Elimination	Urinary excretion of unchanged drug is low (<0.2% of daily dose) in adult patients after repeated oral administration. The half-life of the medication is >6 days (dosing range 50mg/day to 50mg TID) and steady state plasma concentrations are anticipated to occur at day 30.

Pharmacology[6, 8]
The mechanism of action for miltefosine for the treatment of *Leishmania* species is not well described. Miltefosine is an alkyllysophospholipid analog active against *Leishmania* species in the amastigote and promastigote stages. For entry into the cell, a protein complex on the plasma membrane is required. It antiprotozoal activity is thought to be due to its interaction with membrane lipids, inhibition of cytochrome c oxidase, and contributing to apoptosis-like cell death. Drug resistance is possible based on in vitro studies and some strains of *L. braziliensis* have intrinsic resistance. Resistance to miltefosine may develop if the translocation proteins concentrations are reduced or if efflux pumps are employed.

FDA Approved Indications [6]
Miltefosine is FDA approved for the following indications:
1.Visceral leishmaniasis *(Leishmania donovani)*
2.Cutaneous leishmaniasis *(Leishmania braziliensis, guyanensis, panamensis)*
3. Mucosal leishmaniasis *(Leishmania braziliensis)*
These indications apply to adults 12 years of age and older and weighing 30 or more kilograms.

Guidelines
The Infectious Disease Society of America's Guidelines on Leishmania do not list a preferred first line medication or 'treatment of choice' for CL or ML. Amphotericin B liposomal is the preferred treatment for VL.[21]

Trials
Although clinical trials on the use of miltefosine for the treatment of VL, CL and ML are not rare, they are highly variable. Additionally, because of the variability in response to miltefosine based on the species and geographical location, extrapolation of the clinical trial data to other populations and species is problematic. Dorlo et al summarizes 25 trials, ranging from phase I – IV, on the use of oral miltefosine for VL, CL and ML in a variety of countries in children and adults (HIV+/-). In patients with VL, cure rates range from 72-97% in noted phase III & IV trials. In patients with CL or ML, the cure rates range from 53-72% in noted phase III trials.[5]

In an updated systematic review, miltefosine was not found to have a difference in complete cure rate at 6 months when compared to meglumine antimoniate, however 3 of trials favored miltefosine in the 4 trial meta-analysis.[18]

The following table highlights the trials submitted to the FDA for review.

Trials Submitted to FDA [7]

Trial	Type	Species	Study design/information	Results
3154	VL	*L. donovani* (epi)	Bihar, India: 1999-2000. Open-label, non-inferiority trial of MLT 2.5mg/kg/day x 28 days (50mg Qday <25kg, 100mg Qday ≥25kg) vs AMB EOD x 15. PE: final cure (initial cure + no s/s at 6m)	MLT ITT n=299, PP n= 287 AMB ITT n=99, PP n=94 Final cure: MLT 94.3% (ITT), 97.2% (PP) AMB 97% (ITT), 100% (PP) Note: median weight was 40kg (highest 67kg) – diff than expected US size
Z025	VL	*L. donovani* (epi)	Ethiopia: 2003-2005. Randomized, open-label comparator study in males: MLT 100mg daily x 28 vs IM SSG 20mg/kg daily x 30. PE: final cure (initial cure + no s/s at 6m)	MLT n=290, SSG n=290 Final cure: MLT 60% (ITT), 79.5% (PP) SSG 65.2% (ITT), 82.2% (PP) *Only considered supportive for FDA review.*
Z013	VL	Not noted	India (post-marketing), 2.5mg/kg/day for children, 50mg or 100mg/day x28 for adults (<25kg, ≥25kg)	n=1132 Final cure: 81.9% (ITT) Final cure evaluable: 95.5%
Z013b	VL	Not noted	Nepal (post-marketing) 2.5mg/kg/day for children, 50mg or 100mg/day x28 for adults (<25kg, ≥25kg)	n=125 Final cure: 94% (ITT) Final cure evaluable: 89.7%
3168	CL	*L. braziliensis* (epi – Colombia)	Colombia & Guatemala: 2000-2002. Randomized, placebo-controlled. MLT 50mg BID or 50mg TID (<45kg, ≥45kg). PE: Apparent or partial cure at 2 weeks + definite cure at 6m.	Placebo n=44, MLT n=89 Definite cure: Placebo 29.6% (ITT), 31% (PP) MLT 66.3% (ITT), 69.4% (PP) Note: pivotal trial, MLT superior to placebo

Z2020	CL	*L.guyanensis* (epi), *L. braziliensis* (epi)	Brazil: 2007-2009. Randomized, open-label, comparative trial. MLT 2.5mg/kg/day x 28 vs Meglumine IM 20mg/kg/day x 21. PE: definite cure (complete re-epithelialization of ulcers at 2 & 6m, no new/residual lesions)	Trial divided in two: a, b Z020a Definite cure: 67.5% MLT vs 60% Meglumine Z020b Definite cure: 85% MLT vs 45% Meglumine Note: supportive
Soto	CL	*L. braziliensis* (epi)	Brazil: 2005-2007. Open-label comparative study. MLT 2.5mg/kg/day x 28 or Meglumine IM 20mg/kg/day x 20. PE: definite cure (compete re-epithelialization at 6m)	MLT n=40, Meglumine n=15 Definite cure: 80% MLT vs 86.7% Meglumine Note: supportive
Z2022	ML	*L. braziliensis* (epi)	Bolivia: 2004-2006. Single-arm, MLT 2.5mg/kg/day x 28 days. PE: cure at 12m (≥90% ↑mucosal severity score)	ITT n= 79, PP n= 76 Cured: 62% (ITT), 64.5% (PP)

MLT: miltefosine, AMB: amphotericin B deoxycholate, ITT: intention to treat, PP: per protocol, EOD: every other day, PE: primary endpoint, epi: epidemiologically known/predominant infecting species, SSG: sodium stibogluconate

Warnings, Precautions, and Adverse Effects[6]

The following contraindications exist for miltefosine: pregnancy, Sjogren-Larsson-Syndrome, and hypersensitivity to it or its components. Miltefosine has a black box warning for embryo-fetal toxicity.

Warning	Description
Embryo-Fetal Toxicity	Embryo-fetal toxicity was reported in animals receiving miltefosine through different phases of the reproductive cycle. Death and teratogenicity occurred. Females should have a pregnancy test prior to starting therapy and use contraception during and after therapy (5m) with miltefosine.
Reproductive effects	There is a potential for both males and females to have impaired fertility based on animal models.
Renal effects	Elevations in serum creatinine can occur. Renal function should be monitored during and after therapy (4w) with miltefosine.
Hepatic effects	Elevations in liver transaminases and bilirubin can occur. Monitor liver function during therapy.
Gastrointestinal effects	Diarrhea and vomiting can occur during therapy. These adverse effects can lead to volume depletion.
Thrombocytopenia	Thrombocytopenia can occur (ex: VL). Monitor platelets during therapy.
Absorption of oral contraceptives	The absorption of oral contraceptives may be affected during therapy with miltefosine due adverse effects of vomiting and diarrhea. This decreased absorption may affect the effectiveness of the oral contraceptive. Alternative/additional forms of contraception should be used during therapy if these adverse effects occur.
Stevens-Johnson Syndrome	This syndrome has been reported during therapy with miltefosine. Therapy should be discontinued if exfoliative or bullous rash occurs.

Common adverse effects (>10%)

- Headache, dizziness, nausea, vomiting, motion sickness, decreased appetite, diarrhea, abdominal pain, decreased platelet count, increased serum transaminases, increased serum creatinine.

Pregnancy and breastfeeding

- Pregnancy category D
- Breastfeeding: It is unknown if miltefosine enters breastmilk. Since there is a potential for serious adverse effects in infants, either the drug or nursing should be discontinued. Breastfeeding should be avoided for 5 months after cessation of miltefosine therapy.

Pediatric patients
- Miltefosine is not labeled for use in those less than 12 years of age. When testing miltefosine in rat models, juvenile rats were more sensitive to the adverse effects when compared to the adult rats.

Renal and Hepatic Impairment
- The pharmacokinetics of miltefosine have not been adequately studied in patients with renal and hepatic impairment.

Toxicology (animal)
- Retinal degeneration
- Proximal tubule epithelium damage (reversible)

Interactions [6]
Miltefosine does not induce or inhibit the major CYP P450 enzymes. There are currently no known/reported drug interactions. Interactions with drug transporters have not been tested.

Dosage and Administration [6]
For VL, CL, and ML, miltefosine 50mg is administered twice daily with food (30-44kg) or 50mg thrice daily with food (45 kg or more). Miltefosine should be taken with food/meal to decrease gastrointestinal adverse reactions.

Monitoring Parameters[8]
Pregnancy testing should be completed prior to therapy initiation in females of child-bearing age. CBC, serum creatinine and bilirubin as well as LFTs should be monitored. Although monitoring is recommended, no specific dose alterations are recommended for renal or hepatic impairment.

How Supplied/Cost
Miltefosine is available as an oral 50mg capsule.[6]
50mg (28 capsules) = $19,200 [AWP] [20]

Prepared by: Emily Kreikemeier, MPH, Pharm.D., BCPS
Reviewed by: Scott Bergman, Pharm.D., BCPS (AQ ID)

Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Miltefosine (Impavido)
Drug manufacturer	Paladin Therapeutics Inc
Schedule of medication	n/a
Anticipated use per month, anticipated patient population	unknown
Route of administration	oral
Preparation	50 mg capsule
Stability	n/a
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Store at 20-25 °C (68-77 °F)
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No specific criteria
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☐ Yes ☐ N/A ☒
Can medication doses be sent to patient care units via pneumatic tube system? See IC24.	No ☒ Yes ☐ N/A ☐ *It should not be tubed due to the cost of the medication.*
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☐ Yes ☒ *It is not a restricted distribution program, but it is available on consignment.*
Safety/Policy Information	

Will this impact a dynamic alternative alert?	No ☐ Yes ☐ *Potentially yes as there are other antiparasitic medications on and off formulary.*
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐ *It is not on the ISMP list but miltefosine could be confused with other medications which also are not used often such as mifepristone.*
Does the product package insert currently have any black box warning? For what?	No ☐ Yes ☒ Embryo-fetal toxicity
Is this medication a hazardous agent?	No ☒ Yes ☐ It is not listed as such in Lexicomp. However, it does have embryo-fetal toxicity and effects on reproduction.
Is the medication a vesicant or irritant?	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02.	No ☒ Yes ☐
Are there contraindications or significant warnings against medication use?	No ☐ Yes ☒ The following contraindications exist for miltefosine: pregnancy, Sjogren-Larsson-Syndrome, and hypersensitivity to it or its components
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry, BP, etc)?	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Will the medication be restricted: MS68 Levels of Care • To a specific level of care (LOC)? • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☐ Yes ☒ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ *If added to formulary, the medication should be restricted to use by the infectious disease services.*

Appendix A

Miltefosine for use against free living amoebas

Miltefosine is used off-label for treatment of free living amoebas. The Centers for Disease Control and prevention (CDC) note that miltefosine is available for treatment of the following free living amoebas. [9-11]

Centers for Disease Control and Prevention (CDC)	Year Updated	Published case reports of MLT use
Acanthamoeba-Granulomatous Amebic Encephalitis (GAE); Keratitis	August 2012	Yes[12]
Balamuthia mandrillaris-Granulomatous Amebic Encephalitis (GAE)	February 2016	Yes[19]
Naegleria fowleri-Primary Amebic Meningoencephalitis (PAM)	April 2016	Yes[16,17]

Miltefosine for treatment of *Naegleria fowleri*-Primary Amebic Meningoencephalitis (PAM)

Primary amoebic meningoencephalitis (PAM) is caused by the free-living thermophilic ameba *Naegleria fowleri.* Infections occur when *Naegleria fowleri* enters the brain by way of contaminated water exposure up the nose. Initial symptoms tend to occur 5 days after the infection and are similar to those seen with bacterial meningitis. Death, from brain tissue destruction and swelling, usually occurs within 5 days from symptom onset. Survival from PAM is considered rare (<3%).[13]

In the United States, between 1962-2015, a total of 138 cases of primary amebic meningoencephalitis have been reported (range 0-8 cases/year). Males comprise 77% of the cases with over half of the male cases occurring between the ages 5-14 years. The majority of cases occurred during July, August and September likely from exposure to lakes, ponds, and reservoir water. Although these cases have been reported in several states, nearly half of the cases have occurred in Texas and Florida (n=68). [14]

Survivors of PAM in the United States have received different treatments although several medication therapies were common amongst them. Those medications include: conventional amphotericin B, rifampin, an azole (miconazole/fluconazole), azithromycin, and dexamethasone. The most recent two cases also received miltefosine. Supportive therapy, such as that for control of intracranial pressure, varied (none, mannitol, hypertonic saline, induced hypothermia). Although three patients have been noted to survive, only 2 made a complete recovery. Not all cases that have received MLT have survived.[15, 16]

Recent reported cases of MLT use for PAM[16, 17]

Author	Case	Treatment	Outcome
Cope JR, et al. 2016	12 y/o M	Acyclovir, L-AMB, FLU, RIF, Vancomycin, Ceftriaxone. Changed to cAMB, FLU, Azithromycin, RIF, **MLT**, IT amphotericin B. Hypertonic saline, mannitol, surgical decompression, therapeutic hypothermia.	Death on day 16
Cope JR, et al. 2016	8 y/o M	cAMB, RIF, FLU, Azithromycin, **MLT** 150mg/day divided TID, DEX, CSF drainage, mannitol	Discharged alive. Patient has mental disability & seizure disorder. Patient is nonverbal & cannot complete self-cares.
Linam WM, et al. 2015	12 y/o F	cAMB 1.5mg/kg/day. FLU, RIF, & Azithromycin 10mg/kg/day. DEX. **MLT** 50mg Q8h. Ventricular drain, IT amphotericin B, mannitol, 3% Saline, hyperventilation, induced hypothermia	Discharged alive. Normal functioning and no residual effects at 6 months.
Not published[¥]	16 y/o M	Treatment details unknown except that **MLT** was provided to this patient at Florida Hospital for Children.	Unknown

cAMB: conventional amphotericin B, L-AMB: liposomal amphotericin B, FLU: fluconazole, DEX: dexamethasone, CSF: cerebrospinal fluid,
[¥]Information derived from Kyle Cares webpage (http://www.kylelewisamoebaawareness.org/) and Yahoo [Aug 24, 2016] (http://finance.yahoo.com/news/orlando-patient-survives-primary-amebic-100000975.html) This case would make for a total of 4 US survivors. The first documented US survivor did not receive MLT.

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