**IMPAVIDO® (miltefosine)**

**Capsules for Oral use**

**In the management of**

**Cutaneous, Mucocutaneous and Visceral Leishmaniasis**

**and**

**Free-Living Amebic Infections**

**(Primary Amebic Meningoencephalitis (PAM), Acanthamoeba Keratitis, Balamuthia mandrillaris)**

****

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# Executive Summary

IMPAVIDO is a single oral agent for treatment of visceral, cutaneous, and mucosal leishmaniasis. It is the only agent currently approved for all three indications by the US Food and Drug Administration. Administered for a single, 28 day, course of therapy, IMPAVIDO does not require any adjunct therapy.

IV liposomal amphotericin B (AmBisome®) was FDA approved in 1997, but only for the treatment of visceral leishmaniasis. In addition to its limited approval, AmBisome has several disadvantages when compared to IMPAVIDO: mode of administration (IV vs oral) and the associated risks of administration; drug toxicity; and the significant infrastructure required to support treatment.

Miltefosine has also received orphan drug designation approval from the FDA for (A) Treatment of granulomatous amebic encephalitis (GAE); (B) Treatment of schistosomiasis; (C) Treatment of Acanthamoeba keratitis; (D) Treatment of primary amebic encephalitis (PAM); (D) Topical treatment of cutaneous lymphoma encompassing cutaneous manifestations of T-cell lymphoma and B-cell lymphoma and (E) Treatment of disseminated amebiasis.

Because of the rarity of diagnosed leishmaniasis and other conditions in the United States, this document is intended to provide background information on the clinical picture of these diseases; the role of IMPAVIDO in their management; and the efficacy and safety of IMPAVIDO.

# Leishmaniasis

Leishmaniasis is caused by infection with Leishmania parasites, which are spread by the bite of phlebotomine sand flies. Infection of the macrophages of the skin, mucosal membranes, and visceral reticuloendothelial system with *Leishmania* leads to three different forms of the infection.

* **cutaneous leishmaniasis (CL)**, which causes skin sores,
* mucosal leishmaniasis (ML), in which the *Leishmania* parasite infests the mucosal lining causing its progressive destruction and destruction of cartilage and bones of nose and pharynx, leading to a severe facial disfiguration, and
* **visceral leishmaniasis (VL)**, which affects several internal organs (usually spleen, liver, and bone marrow).

In cutaneous and mucocutaneous leishmaniasis, clinical manifestation with parasitological tests confirm the diagnosis but serological tests have limited value.

According to the World Health Organization (WHO), *Leishmania* infection is found in 98 countries or territories with a yearly reported incidence of 300,000 cases of visceral leishmaniasis (VL) and l.0 million cases of cutaneous leishmaniasis (CL).[[1]](#endnote-1) It is relatively unknown in the United States because few cases originate here. Its epidemiology in the US typically reflects travel and immigration patterns. For example, many of the cases of **cutaneous leishmaniasis** in U.S. civilian travelers have been acquired in tourist destinations, such as Brazil, Costa Rica, and the Middle East. U.S. military personnel have become infected in Iraq and Afghanistan. A few cases of **cutaneous leishmaniasis** have originated in Texas and Oklahoma. No cases of visceral leishmaniasis are known to have originated in the United States.

## 2.1. Cutaneous Leishmaniasis (CL)

Cutaneous leishmaniasis (CL) generally presents as a papule that enlarges to a nodule and, if it ulcerates, does so over a period of 1 to 3 months. CL lesions are often found at exposed areas of the skin (face, arms, legs), as either single or multiple lesions. Lesions can develop in any person living or traveling in an endemic region and who is bitten by an infected sand fly. Insect repellant is highly recommended in areas known to harbor leishmaniasis parasites. Although CL lesions can heal on their own, the parasite remains and may re-emerge years later as potentially disfiguring and fatal mucosal leishmaniasis.

Decisions about whether and how to treat should be individualized. The treatment approach depends in part on the Leishmania species/strain and the geographic area in which infection was acquired; the natural history of infection, the risk for mucosal dissemination/disease, and the drug susceptibilities in the pertinent setting; and the number, size, location, evolution, and other clinical characteristics of the patient's skin lesions.

* About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia
* Over two thirds of new CL cases occur in 6 countries: Afghanistan, Algeria, Brazil, Colombia, Iran and Syria. An estimated 0.7 million to 1.3 million new cases occur worldwide annually.[[2]](#endnote-2)
* Leishmaniasis infection has surged in some areas of the world where it was relatively uncommon, such as Israel.[[3]](#endnote-3)
* The primary species causing CL are diverse: *L. mexicana, L. amazonensis*, *L. viannia (v) panamensis*, *L. (v) braziliensis*, *L. (v****)*** *peruviana*, and *L. (v) guyanensis* in the New World and *L. major*, *L.* *tropica*, *L. aethiopica,* and *L. infantum* in the Old World.

## 2.2 Mucosal Leishmaniasis (ML)

Mucosal leishmaniasis (ML) may result from dissemination of cutaneous organisms (particularly *Leishmania* species of the subgenus *Vianna*: *L. (v).braziliensis*, *L.(v). guyanensis* and *L.(v) panamensis*) to the nares, nasal septum, palate, pharynx, and larynx. Almost 90% of mucocutaneous leishmaniasis cases occurs in Bolivia, Brazil and Peru.[[4]](#endnote-4)

The skin sores of cutaneous leishmaniasis (CL) usually heal on their own, even without treatment. But this can take months or even years, and the sores can leave ugly scars. In up to 10% of patients with New World CL, Leishmania disseminates from the skin to the nasooropharyngeal mucosa, resulting in mucosal leishmaniasis (ML) and causes progressive destruction of the mucosa, the cartilage and bones of nose and pharynx, leading to a severe facial disfiguration. It can be lethal by aspiration pneumonia or other complications.

Prompt treatment of cutaneous leishmaniasis with IMPAVIDO is an essential element of patient care because classic mucosal leishmaniasis typically occur months to years after healing of untreated CL lesions. ML may also occur virtually simultaneously with CL

It has been shown that *asymptomatic infection of the mucosal membranes* is common for CL patients infected with members of the *L. viannia* subgenus. Two patients with ML and 26 patients with CL due to *L. v. panamensis, L. v. guyanensis,* and *L. v.* *braziliensis* had *Leishmania* kinetoplast minicircle deoxyribonucleic acid (kDNA) examined in mucosal tissues. kDNA was amplified from swab samples of nasal mucosa from 14 (58%) of 24 patients, tonsils from 13 (46%) of 28 patients, and conjunctiva from 6 (25%) of 24 patients. Cutaneous infection with any of these 3 species has to be regarded as leading to mucosal infection and potentially to mucosal disease with its possibly fatal outcome.[[5]](#endnote-5)

## 2.3 Visceral Leishmaniasis (VL)

Visceral leishmaniasis (VL) also known as Kala-azar, is an infection of the liver, spleen, and bone marrow. It presents with fever, hepatosplenomegaly, and pancytopenia. It is the second largest parasitic killer in the world, after malaria.[[6]](#endnote-6) The majority of VL occurs in the Indian subcontinent. Approximately 30% of the world’s cases occur in Africa especially Sudan, Ethiopia, and Kenya; there is also a focus of disease in Brazil. The main species causing VL are *Leishmania ( L). donovani* in India and Africa, *L. infantum* in Europe and the Mediterranean, and *L. infantum chagasi* in the New World.

A recent study[[7]](#endnote-7) examining the potential for vertical transmission of the visceral leishmaniasis from dogs to humans, known as ZVL or Zoonotic visceral leishmaniasis, found evidence that vertical transmission of ZVL may be a driving force for ongoing disease in an otherwise non-endemic region. This has significant implications for current control strategies for ZVL as, at present, parasite elimination efforts in endemic areas are largely focused on vector-borne transmission between canines and people. Determining frequency of vertical transmission and incorporating canine sterilization with vector control may have a more significant impact on ZVL transmission to people in endemic areas than current control efforts.

Diagnosis of visceral leishmaniasis is made by combining clinical signs with parasitological or serological tests (mainly rapid diagnostic tests).

* A sudden onset of fever with rigor and chills herald the onset of VL, which may subside only to recur again.
* Splenomegaly soon follows and may become remarkable.
* Hepatomegaly and lymphadenopathy (rare) are other clinical features.
* Anemia is universal and may be quite severe leading to weakness, fatigue and heart failure.
* Thrombocytopenia and subsequent bleeding episodes such as epistaxis, intestinal bleeding, and retinal hemorrhages are not uncommon.
* Concurrent illnesses including pneumonia, herpes zoster, tuberculosis, amebic or bacillary dysentery, boils, and scabies are common.
* VL and coinfection with HIV or other immunocompromising diseases is an increasingly serious health threat.

According to the World Health Organization, an estimated 200,000-400,000 cases of visceral leishmaniasis and over 20,000 deaths occur annually.[[8]](#endnote-8) Over 90% of new cases occur in 6 countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan.[[9]](#endnote-9)

## 2.4 Free Living Amoeba Infections (PAM, Acanthamoeba (ie Acanthamoeba Keratitis), Balamuthia Mandillaris)

* + 1. [Primary Amebic Meningoencephalitis (PAM)](http://www.lcra.org/water/recreation-and-safety/safe-swimming/pages/recreational-water-illnesses.aspx)

Miltefosine is a drug used to treat leishmaniasis, a rare tropical parasitic disease. It’s also shown promise in treating free-living ameba (FLA)–a single-cell living organism commonly found in warm freshwater or soil. FLA infections are considered to be “low incidence but high impact”—meaning, they are rare, but deadly. Because of this, miltefosine has its own pager number that physicians can access 24/7.

According to the CDC, through the years 1962 – 2015, there have been 138 cases of (PAM) in the United States. In these case reports, exposure primarily occurred in untreated, warm, freshwater lakes or rivers during the months of July – September. The fatality rate is over 97%. Only 3 people out of 138 known infected individuals in the United States from 1962 to 2015 have survived. One that did survive was treated with miltefosine.[37]

Since 2009, CDC has helped treating physicians obtain miltefosine from FDA on a patient-by-patient basis. Until recently, the only source of miltefosine was from Germany. The drug often took over a week to get to a hospital, frequently being held up in customs despite having proper approvals and paperwork.

In late 2011, difficulties in obtaining miltefosine in a timely manner prompted CDC to find ways to keep a supply of the drug at the agency for FLA infections. A CDC scientist drafted the required FDA-documentation that allows the use of investigational drugs for patients with serious or immediately life-threatening diseases who lack other treatment options.

Over the next two years, **CDC gathered evidence to justify treatment of FLA infections with miltefosine.**  On May 24, 2013, CDC received the “safe to proceed letter” from FDA. After an urgent plea to rush the order to be available for “ameba season” (mid-to-late summer when amoebas living in warm, stagnant water grow rapidly), miltefosine arrived at the agency.

The drug arrived just in time. Less than a week later, an Arkansas physician contacted CDC about a young patient named Kali that urgently needed miltefosine. Despite multiple hurdles, Kali received miltefosine approximately 36 hours after CDC was notified. After swimming in a local waterpark, 12-year old Kali Hardig developed a high fever, headache, and nausea. When she worsened, her parents rushed Kali to Arkansas Children’s Hospital. Within 30 hours of becoming ill, doctors had diagnosed Kali with primary amoebic meningoencephalitis (PAM) caused by the free-living ameba Naegleria fowleri. Because it destroys brain cells, Naegleria fowleri has also been called a brain-eating ameba. Infections are nearly always fatal.

Doctors treated Kali with antibiotics and antifungals and aggressively managed her brain’s swelling–including cooling her body below normal body temperature. They consulted with CDC about the investigational drug miltefosine, found to help kill brain-eating amoebas in the laboratory. CDC was able to rapidly supply miltefosine because of an agreement with FDA to keep the drug on site at CDC and ship by physician request.

After 22 days in intensive care that included a drug-induced coma, lowered body temperature, and multiple drugs–including miltefosine–Kali left the hospital. She’s since made a full recovery and returned to school. Kali is one of three Naegleria fowleri survivors in the U.S. in the past 35 years and the first since 1978. Today, Kali has fully recovered and is back at school.[2]

On August 23, 2013, **CDC announced an agreement with FDA to make miltefosine available directly from CDC to doctors treating FLA infections in the United States.** **It is available for treatment of free-living ameba (FLA) infections caused by Naegleria fowleri, Balamuthia mandrillaris, and Acanthamoeba species.** Clinicians can contact the CDC Emergency Operations Center at 770-488-7100 to consult with a CDC expert about obtaining this drug.[1]

Other so-called free-living amoeba infections include granulomatous amebic encephalitis, a serious infection of the brain and spinal cord that often strikes people with weakened immune systems, and is caused by Balamuthia mandrillaris and Acanthamoeba species. Miltefosine has shown ameba-killing activity against free-living amebae, including Naegleria fowleri, in the laboratory.[3,4] Miltefosine has also been used to successfully treat patients infected with Balamuthia[5] and disseminated Acanthamoeba infection.[6]

Impavido was launched in the United States for Leishmaniasis by Profounda on March 22, 2016.

Small free-living amoebas belonging to the genera Acanthamoeba and Naegleria occur world-wide. They have been isolated from a variety of habitats including fresh water, thermal discharges of power plants, soil, sewage and also from the nose and throats of patients with respiratory illness as well as healthy persons. Although the true incidence of human infections with these amoebas is not known, it is believed that as many as 200 cases of central nervous system infections due to these amoebas have occurred world-wide. A majority (144) of these cases have been due to Naegleria fowleri which causes an acute, fulminating disease, primary amebic meningoencephalitis (PAM). The remaining 56 cases have been reported as due either to Acanthamoeba or some other free-living ameba which causes a subacute and/or chronic infection called granulomatous amebic encephalitis (GAE). Acanthamoeba, in addition to causing GAE, also causes nonfatal, but nevertheless painful, vision-threatening infections of the human cornea, Acanthamoeba keratitis. Infections due to Acanthamoeba have also been reported in a variety of animals. These observations, together with the fact that Acanthamoeba spp., Naegleria fowleri, and Hartmannella sp. can harbor pathogenic microorganisms such as Legionella and/or Mycobacteria indicate the public health importance of these amoebas.[8]

Although most cases of primary amebic meningoencephalitis (PAM) caused by Naegleria fowleri infection in the United States have been fatal (122/123 in the U.S.,[14]), there have been two well-documented survivors in North America: one in California[15, 16] and one in Mexico.[18] It has been suggested that the survivor’s strain of Naegleria fowleri was less virulent, which contributed to the patient’s recovery. In laboratory experiments, the California survivor’s strain did not cause damage to cells as rapidly as other strains, suggesting that it is less virulent than strains recovered from other fatal infections.[9, 18]

Multiple patients have received treatment similar to the California survivor, including amphotericin B, miconazole/fluconazole/ketoconazole, and/or rifampin but only the patient in Mexico has survived making it difficult to determine the efficacy of the treatment regimen.[9]

The survivors received the following medications:[9]

Survivor Medications

U.S. California Survivor [16, 17] (1978) Mexico Survivor [15] (2003)

Amphotericin B Amphotericin B

Rifampicin Rifampicin

Miconazole – no longer available in US Fluconazole

Dexamethasone Dexamethasone

Sulfisoxazole (IV) – discontinued after Naegleria diagnosed Ceftriaxone

Phenytoin

Recently an investigational breast cancer and anti-leishmania drug, miltefosine,[19] has shown some promise in combination with some of these other drugs. Miltefosine has shown ameba-killing activity against free-living amebae, including Naegleria fowleri, in the laboratory.[3, 4] Miltefosine has also been used to successfully treat patients infected with Balamuthia[5] and disseminated Acanthamoeba infection.[6] CDC now has a supply of miltefosine for treatment of Naegleria fowleri infection.[9, 20]

This therapy is needed for the treatment of PAM because according to the CDC, through the years 1962 – 2015, there have been 138 cases of (PAM) in the United States and only 3 of the known infected individuals have survived.[21] One that did survive was treated with miltefosine.[1]

Only 3 people out of 138 known FLA infected individuals in the United States from 1962 to 2015 have survived.[21] One that did survive was treated with miltefosine.[1] Miltefosine was tested in vitro against Balamuthia mandrillaris, Acanthamoeba spp., and Naegleria fowleri and demonstrated its potential use for treatment of free-living amebic infections.[3] Miltefosine has also been tested in vitro and in vivo by Kim et al. Miltefosine effectively inhibited growth in vitro. In vivo, the inoculated mice had a survival rate of 55%.[4]

 Miltefosine possesses activity against various other protozoan parasites as well. Although less potent than against leishmania, activity was demonstrated against Entamoeba histolytica, a protozoan parasite causing amoebic dysentery and liver abscesses. For example, the median EC50 after 48 h was 53 µM (range 28 – 99 µM) [corresponding to 22 µg/mL (11-40 µg/mL)] for the most susceptible Entamoeba strain, which was comparable to that of metronidazole.[22] Comparable amoebastatic activity was shown against free-living amoebae of the Acanthamoeba genus, causative species for both keratitis and granulomatous amoebic encephalitis, with complete cell death at 40 µM (16 µg/mL).[23] The amoeba species displayed miltefosine-induced alterations of the membrane architecture.[22, 23] The anti-Acanthamoebic activity of miltefosine was confirmed in an Acanthamoeba keratitis hamster model in which topically applied miltefosine [160 µM (65 µg/mL), 28 days] resulted in complete cure of the infection in 85% of the hamsters.[24] Also, against Trichomonas vaginalis, the causative agent of trichomoniasis, miltefosine showed modest activities, most notably also against metronidazole-resistant strains, with EC50 values between 8 and 40 µM (3.3 and 16.3 µg/mL).[25] Miltefosine is therefore also a potential new treatment for this commonly sexually transmitted disease. The activity of miltefosine against Cryptosporidium parvum was demonstrated in vitro,[26] but its clinical application seems to be limited in HIV-infected immunocompromised hosts.[27, 28] Miltefosine has been approved for the oral and topical treatment of leishmaniasis, and has already been successfully used to treat Acanthamoeba skin lesions in a case of disseminated Acanthamoeba infection.[6] It may thus be a promising candidate for the topical treatment of Acanthamoeba infections.[29]

Miltefosine was first approved in India in 2002 for visceral leishmaniasis and has received marketing authorization for leishmaniasis in 13 other countries including: Argentina, Bangladesh, Bolivia, Colombia, Ecuador, Germany, Guatemala, Honduras, India, Mexico, Pakistan, Paraguay and Peru.[28]

Miltefosine has also been added to the WHO Model List of Essential Medicines.[31]

### Acanthamoeba Keratitis

Early diagnosis is essential for effective treatment of Acanthamoeba keratitis. Several prescription eye medications are available for treatment. However, the infection can be difficult to treat.[9]

Skin infections that are caused by Acanthamoeba but have not spread to the central nervous system can be successfully treated. Because this is a serious infection and the people affected typically have weakened immune systems, early diagnosis offers the best chance at cure.[9]

However, most cases of brain and spinal cord infection with Acanthamoeba (Granulomatous Amebic Encephalitis) are fatal.[9]

In an in vivo study, a series of compounds – miltefosine, polyhexamethylene biguanide, chlorhexidine, and propamide isethionate – and combinations of the latter three agents with miltefosine were prepared and used in a rat model for the topical treatment of AK. The best treatment results were obtained from the polyhexamethylene biguanide plus miltefosine group. Approximately 86% of the eyes were cleared from amoebae.[30]

In a case study by the CDC, patients with non-keratitis Acanthamoeba infections showed a significantly improved survival rate when treated with miltefosine. In the miltefosine treated group, 5/7 patients survived. The group not treated with miltefosine only had 9 survivors of the 56 total patients.[10]

In Syria, the anti-Acanthamoebic activity of miltefosine was confirmed in an Acanthamoeba keratitis hamster model in which topically applied miltefosine [160 µM (65 µg/mL), 28 days] resulted in complete cure of the infection in 85% of the hamsters.[24]

Keratitis cases substantially increased in the 1980s with the introduction of disposable soft contact lenses.[38] Some evidence shows that the rate has subsequently declined, especially with the introduction of multipurpose cleaning solutions. The estimated rate of Acanthamoeba keratitis is 1 per 250,000 people in the United States, although rates vary among studies: from 1.65-2.01 per million population up to 1 per 10,000 people who wear contact lenses.[39]

### Balamuthia mandrillaris

Although there have been more than 200 cases of Balamuthia infection worldwide, few patients are known to have survived as a result of successful drug treatment.[5, 11] Early diagnosis and treatment might increase the chances for survival.[9, 12]

Drugs used in treating Granulomatous Amebic Encephalitis (GAE) caused by Balamuthia have included a combination of flucytosine, pentamidine, fluconazole, sulfadiazine and either azithromycin or clarithromycin.[5,11,13] Recently, miltefosine in combination with some of these other drugs has shown some promise.[5] Much more information is needed in treating patients with GAE due to Balamuthia.[9]

In a case study by the CDC, patients with Balamuthia infections showed a significantly improved survival rate when treated with miltefosine. In the miltefosine treated group, 6/14 patients survived. In the group not treated with miltefosine, only 4/46 survived.[10]

Although there have been more than 200 cases of Balamuthia infection worldwide, few patients are known to have survived as a result of successful drug treatment.[5, 11] Early diagnosis and treatment might increase the chances for survival.[9, 12]

GAE and disseminated Acanthamoeba disease are very rare, but rates may be increasing given the rising number of persons living with immunocompromising conditions. More than 100 cases of GAE have been described to date.

### Naegleria fowleri

Miltefosine was granted marketing authorization by the Federal Health Office in Germany as an anti-cancer drug known as Miltex on December, 14th 1992.[35]

In the Republic of Korea, miltefosine has also been tested in vitro and in vivo by Kim et al. Miltefosine effectively inhibited growth in vitro. In vivo, the inoculated mice had a survival rate of 55%.[4]

A study in Lima, Peru demonstrated miltefosine’s ability to pass through the blood brain barrier and stimulate T-cells to activate cytokines that induce cell death indicating its potential as a clinical cure.[5]

A patient with an Acanthamoeba infection in Austria responded favorably to treatment with miltefosine with no signs of infection 2 years after treatment cessation.[6]

In Vienna, miltefosine’s activity was demonstrated against Entamoeba histolytica, a protozoan parasite causing amoebic dysentery and liver abscesses. For example, the median EC50 after 48 h was 53 µM (range 28 – 99 µM) [corresponding to 22 µg/mL (11-40 µg/mL)] for the most susceptible Entamoeba strain, which was comparable to that of metronidazole.[22] Comparable amoebastatic activity was shown in the same lab against free-living amoebae of the Acanthamoeba genus, causative species for both keratitis and granulomatous amoebic encephalitis, with complete cell death at 40 µM (16 µg/mL).[23]

In Vienna, against Trichomonas vaginalis, the causative agent of trichomoniasis, miltefosine showed modest activities, most notably also against metronidazole-resistant strains, with EC50 values between 8 and 40 µM (3.3 and 16.3 µg/mL).[25]

A phase-1 – phase 2-study of miltefosine (given at 2.5 mg/kg for 14 days, with the dose capped at 100 mg/day) was initiated among Zambian adults with HIV-related cryptosporidiosis. Seven patients were recruited before the trial was terminated prematurely because of lack of efficacy and the development of severe adverse events. The latter may have been entirely drug-related or the result of extreme metabolic abnormalities already present in the patients enrolled in the trial.[27]

Acanthamoeba can cause keratitis, GAE, and disseminated disease worldwide. Data on the incidence rates of these infections internationally are not available since it is not a reportable disease.

Given the low incidence and highly fatal nature of the conditions, there are few patients with FLA infections in the USA.

# IMPAVIDO

**Generic Name: Miltefosine Capsules**

**Brand Name: Impavido®** (NDC 69051-300-01)

**Manufacturer: Profounda Inc.**

## 3.1 Indication

IMPAVIDO is an anti-leishmanial drug indicated in adults and adolescents ≥12 years of age and weighing ≥30 kg (66 lbs) for treatment of:

* Visceral leishmaniasis due to *Leishmania donovani*.
* Cutaneous leishmaniasis due to *Leishmania braziliensis, Leishmania guyanensis,* and *Leishmania panamensis*.
* Mucosal leishmaniasis due to *Leishmania braziliensis*.

**Limitations of use**: *Leishmania* species evaluated in clinical trials were based on epidemiologic data. There may be geographic variation in the response of the same *Leishmania* species to IMPAVIDO. The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

### Orphan Drug Designation

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Orphan Designation** | **Designation Date** | **Designation Status** |
| 1 | Treatment of granulomatous amebic encephalitis (GAE) | 06/19/2017 | Designated |
| 2 | Treatment of schistosomiasis | 08/02/2017 | Designated |
| 3 | Treatment of Acanthamoeba keratitis | 12/06/2016 | Designated |
| 4 | Treatment of primary amebic encephalitis (PAM) | 12/06/2016 | Designated |
| 5 | Topical treatment of cutaneous lymphoma encompassing cutaneous manifestations of T-cell lymphoma and B-cell lymphoma | 03/18/2009 | Designated |
| 6 | Treatment of disseminated amebiasis | 06/19/2017 | Designated |
| 7 | Treatment of leishmaniasis. | 10/10/2006 | Designated/Approved |

##  3.2 Mechanism of Action

The specific mode of action of IMPAVIDO against *Leishmania* species is unknown but is likely to involve IMe interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death.

##  3.3 Dosage and Administration

|  |  |
| --- | --- |
| Weight | Dosage and Administration |
| 30 kg to 44 kg | One 50 mg capsule twice daily with food (breakfast and dinner)  |
| 45 kg or greater  | One 50 mg capsule three times daily with food (breakfast, lunch, and dinner) |

# 4. Efficacy and Safety

Nine Industry-sponsored clinical trials have been performed in both VL and CL. Seven of these, conducted in adults and children age 12 and older, are shown in Table 1. The remainder were conducted in children age 11 and younger. All studies were conducted according to Good Clinical Practice (GCP) principles; the Industry sponsor’s study ID number is indicated. VL studies (except 033 and 3089) were conducted in collaboration with WHO/TDR.

All studies used appropriate criteria for evaluating the safety and efficacy of the product, *e.g*. recording of adverse events and repeated evaluations of laboratory and 6 month post treatment follow-up to verify definitive cure, respectively. While dose-finding studies had sequential or parallel dose groups without use of an active comparator drug, the Phase III trial in adult VL patients was active controlled (intravenous amphotericin B), while the confirmatory study in CL patients was placebo controlled.

|  |
| --- |
| **Table 1: Summary of****Industry Sponsored IMPAVIDO Clinical Trials (adults and children age 12+)** |
| **Study**  | **Principal Investigators** | **Group: Dosages / ranges tested No. of patients** | **No. of patients** |
| 0033 (1)[VL] | S. Sundar | 50 mg q2d x 14 days up to250 mg/day x 28 days | 30 |
| 3089 (2)[VL] | S. Sundar | 100 mg/day x 28 days up to200 mg/day x 28 days | 46 |
| 3109 (3)[VL] | TK Jha, S. Sundar CP Thakur | 50 mg/day x 42 days up to 100 mg/day x 7 days + 150 mg/day x21 days | 120 |
| 3127 (4)[VL] | S. Sundar | 100 mg/day x 14 days up to100 mg/day x 28 days | 54 |
| 3154 (5)[VL] | TK Jha, S. Sundar, CP Thakur | Miltefosine: 100 mg/day x 28 days(below 25 kg: 50 mg/day x 28 days)Amphotericin B: 1 mg/kg/day x 30 days 400 (300 +100) | 300 100400 total |
| 3092 (6)[CL] | J Soto, Bolivia | 50 mg/day x 20 days up to 150 mg/ day x 28 days | 64 |
| 3168 (7)[CL] | J Soto, BoliviaB Arana / M Gilardi, Guatemala | 150 mg/day x 28 days vs.Placebo | 133 (89 + 44) |
| (1) Sundar S. 1998; (2) Sundar S. 1999; (3) Jha TK. 1999 ; (4) Sundar S. 2000; (5) Sundar S. 2002; (6) Soto J. 2001; (7) Soto J. 2004 |

In addition to the above Industry-sponsored data from clinical trials in VL and CL patients, data on HIV co-infected patients are available from an MSF study in Ethiopia[[10]](#endnote-10), and data on mucosal leishmaniasis is available from an investigator-initiated study in Bolivia[[11]](#endnote-11)

## 4.1 IMPAVIDO global cure rates, by study

Table 2 (below)shows the final cure rates irrespective of dosage used for the intent-to-treat (ITT) populations of all studies. Except for the dose-finding pilot study (0033), all subsequent studies resulted in high global rates of final cure rates, underlining the therapeutic potential of miltefosine in this indication.

|  |
| --- |
| **Table 2****IMPAVIDO Global Cure Rates (by study)** |
| **Study** | **Final parasitological cure, ITT population** |  |
| **Missing/ not****assessable** | **No** | **Yes** | **All** |
| n | % | n | % | n | % | n |
| 0033 (VL) | All patients treatedwith miltefosine,irrespective of daily dose,age, and treatment duration | 0 | 0 | 8 | 26.7 | 22 | 73.3 | 30 |
| 3127 (VL) | 1 | 2.2 | 0 | 0 | 44 | 97.8 | 45 |
| 3109 (VL) | 0 | 0 | 6 | 5.0 | 114 | 95 | 120 |
| 3127 (VL) | 0 | 0 | 2 | 3.7 | 52 | 96.3 | 54 |
| 3154 (VL) | 8 | 3.0 | 9 | 3.0 | 282 | 96.6 | 299 |
| 3092 (CL) | 1 | 2.6 | 4 | 10.3 | 34 | 87.2 | 39 |
| 3068 (CL) | 2 | 2.5 | 3 | 10.7 | 75 | 93.4 | 80 |
| All patients treated withmiltefosine aged > 12 years | 9 | 1.6 | 25 | 4.6 | 514 | 93.8 | 667 |

All dose groups with a daily dosage of 100 mg and higher showed final cure rates around 95%, which is not significantly different from the active control, Amphotericin B, a drug that is administered by IV infusion.

## 4.2 IMPAVIDO Efficacy by Infection Type

## 4.2.1 Efficacy in Cutaneous Leishmaniasis

IMPAVIDO has demonstrated statistical superiority (Table 3) over placebo for disease from 2 locales: *L. panamensis* areas in Colombia and *L. braziliensis*/*L. Mexicana* in Guatemala.

Table 3: Efficacy of IMPAVIDO vs. Placebo in the Treatment of Cutaneous Leishmaniasis in Colombia and Guatemala

|  |  |  |
| --- | --- | --- |
|  | IMPAVIDO | Placebo |
| Definite Cure\* | 59/89 (66%) | 13/44 (30%) |
|  Colombia | 40/49 (82%) | 9/24 (38%) |
|  Guatemala | 19/40 (48%) | 4/20 (20%) |

\* The difference (95% CI) between groups is 36.8% (20.1%, 53.4%) with P-value<0.0001.

An additional study of IMPAVIDO was conducted in Bahia and Manaus, two regions in Brazil where *L. braziliensis* and *L. guyanensis* are the prevalent infecting pathogens. Patients, aged 12-65 years, received IMPAVIDO orally for 28 days. The target dose was 2.5 mg/kg/day: patients weighing 15-29 kg received 50 mg once daily, patients weighing 30-45 kg received 50 twice mg daily and patients weighing > 46 kg received 50 mg three times daily. The efficacy criteria were initial cure (complete re-epithelialization of the ulcer at 2 months after the end of therapy) followed by definite cure (complete re-epithelialization at 6 months after the end of therapy). Definitive cure rate in patients aged ≥12 years was 27/40 (67.5%) for Manaus, Brazil and 34/40 (85%) for Bahia, Brazil.

## 4.2.2 Efficacy in Mucosal Leishmaniasis

No comparative trials of IMPAVIDO *vs* amphotericin B, liposomal amphotericin B, or topical paromomycin have been performed in ML. However, the IMPAVIDO data from Bolivia (described below) suggests it is as least as effective as historic values for antimony, amphotericin B, and liposomal amphotericin B without the complications of IV administration.

A single arm study was conducted to evaluate the efficacy of IMPAVIDO capsules for the treatment of mucosal leishmaniasis. The study was conducted in Bolivia where *L. braziliensis* is epidemiologically the prevalent species.

Seventy nine (79) patients ≥18 years of age with a cutaneous leishmaniasis scar plus parasites observed or cultured from lesion material or a positive skin test, and no clinically significant concomitant disease received miltefosine at a target dose of 2.5 mg/kg/day for 28 days.

By 12 months after the end of therapy, 49 of the patients (62%) had complete resolution of edema, erythema, infiltration and erosion from the involved mucosal sites.

## 4.2.3 Efficacy in Visceral Leishmaniasis

One Phase 3 trial comparing IMPAVIDO vs. amphotericin B was conducted in patients ≥ 12 years of age in Bihar, India, an area where *L. donovani* is known epidemiologically to be the prevalent infecting species. Cure was achieved in 98% of patients in each arm. Both agents are approved for this indication in the U.S., although IMPAVIDO is oral and amphotericin B is for IV administration.

|  |
| --- |
| Table 4: Efficacy of IMPAVIDO in Visceral Leishmaniasisin Patients ≥12 years of Age in India |
|  | IMPAVIDO PON = 299 | Amphotericin B Deoxycholate IVN = 99 |
| End of therapy |
| Initial Cure | 293 (98%) | 97 (98%) |
| 6 months after therapy |
| Final Cure\*  | 282 (94%) | 96 (97%) |
| Treatment Failure  | 9 (3%) | 0 (0) |
| Not Assessable  | 8 (3%) | 3 (3%) |
| \* The 95% exact confidence interval for the difference (IV Amphotericin B – IMPAVIDO) in final cure is (-3.0%, 6.8%). |

# 5. IMPAVIDO Adverse Effects

* The most commonly reported adverse drug reactions are transient gastrointestinal discomfort, vomiting, diarrhea, elevation of liver enzymes and serum creatinine. These effects are usually mild to moderate and transient or reversible at the end of treatment and therefore do not require discontinuation of treatment or dosage reduction.
* Embryo-fetal Toxicity: Women who are or might become pregnant must not use IMPAVIDO because it can cause fetal harm. Obtain a urine or serum pregnancy test prior to prescribing IMPAVIDO to females of reproductive potential. Women who can become pregnant during treatment and need IMPAVIDO must use effective contraception during IMPAVIDO therapy and for 5 months after completion of therapy.
* Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect the absorption of oral contraceptives, possibly compromising their efficacy. If vomiting and/or diarrhea occur during IMPAVIDO therapy, women should use additional non-hormonal or alternative method(s) of effective contraception.
* IMPAVIDO may affect human fertility (male and female), but human studies of this have not been done. IMPAVIDO caused testicular atrophy and impaired fertility in male rats and impaired fertility in female rats. Advise patients of reproductive toxicities in animal studies and that the potential effects on human fertility have not been adequately evaluated.
* IMPAVIDO is contraindicated in patients who have Sjögren-Larsson-Syndrome, a rare autosomal, recessive, neurocutaneous disease.
* Stevens-Johnson syndrome, a rare, serious disorder of skin and mucous membranes, may rarely occur in patients taking IMPAVIDO. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then the top layer of the affected skin dies and sheds. It is a medical emergency that requires hospitalization.
* Monitoring
* Renal function should be monitored during therapy and for 4 weeks after therapy is complete.
* Liver transaminase and bilirubin should be monitored during therapy.
* Thrombocytopenia may occur during treatment for visceral leishmaniasis. Platelet count should be monitored during treatment

## 5.1 Adverse Effects Reported During Clinical Trials

### 5.1.1 Cutaneous Leishmaniasis Trials

The efficacy of IMPAVIDO in the treatment of cutaneous leishmaniasis was evaluated in one placebo-controlled trial conducted in Colombia and Guatemala and in two comparative trials conducted in Bolivia and Brazil respectively. In the placebo-controlled trial, eighty-nine (89) patients ≥12 years of age received a target IMPAVIDO dose of 2.5 mg/kg/day for 28 days and forty-four (44) received placebo.

Table 5: Adverse Reactions Occurring in ≥2% of IMPAVIDO-Treated Patients ≥12 Years of Age with Cutaneous Leishmaniasis in the Placebo-Controlled Trial

|  |  |  |
| --- | --- | --- |
| System Organ Class**Preferred Term** | IMPAVIDO**N = 89** | Placebo**N = 44** |
| Ear and Labyrinth Disorders |
|  Motion Sickness | 26 (29.2%) | 10 (22.7%) |
| Gastrointestinal Disorders |
|  Abdominal Pain | 10 (11.2%) | 3 (6.8%) |
|  Diarrhea | 7 (7.9%) | 2 (4.5%) |
|  Nausea | 32 (35.9%) | 5 (11.1%) |
|  Vomiting | 4 (4.5%) | 0 |
| General and Administration Site Disorders |
|  Malaise | 3 (3.4%) | 1 (2.3%) |
|  Pyrexia | 5 (5.6%) | 2 (4.5%) |
| Nervous System Disorders |
|  Dizziness | 4 (4.5%) | 0 |
|  Headache | 25 (28.1%) | 10 (22.7%) |
|  Somnolence | 3 (3.4%) | 0 |
| Skin and Subcutaneous Tissue Disorders |
|  Pruritus | 4 (4.5%) | 0 |

In comparative trials vs. antimony (Table 6), one hundred and twenty (120) patients ≥12 years of age received a target IMPAVIDO dose of 2.5 mg/kg/day for 28 days and fifty eight (58) patients received 20 mg/kg/day pentavalent antimony (meglumine) parenterally for 20 days.

Table 6: Adverse Reactions Occurring in ≥2% of IMPAVIDO-Treated Patients ≥ 12 Years of Age with Cutaneous Leishmaniasis in Two Comparative Trials

|  |  |  |
| --- | --- | --- |
| System Organ Class**Preferred Term** | IMPAVIDO**N = 120** | Meglumine**N = 58** |
| Gastrointestinal Disorders |
|  Abdominal Pain | 9 (7.5%) | 3 (5.2%) |
|  Diarrhea | 18 (15.0%) | 3 (5.2%) |
|  Nausea | 50 (41.7%) | 3 (5.2%) |
|  Vomiting | 33 (27.5%) | 0 |
| Infections and Infestations |
|  Lymphangitis | 7 (5.8%) | 0 |
| Metabolism and Nutrition Disorders |
|  Decreased Appetite | 13 (10.8%) | 4 (5.8%) |
| Nervous System Disorders |
|  Dizziness | 15 (12.5%) | 4 (6.9%) |
| Skin and Subcutaneous Tissue Disorders |
|  Pruritus | 7 (5.8%) | 0 |

### 5.1.1.1 Renal and hepatic function in cutaneous leishmaniasis trials

In the placebo controlled trial (Table 5), 12/89 (13.4%) IMPAVIDO subjects had serum creatinine increases of 1.5-3 times above baseline, compared to 2/44 (4.5%) placebo subjects at end of therapy. The frequency of AST and ALT increase above upper limit of normal at end of therapy was similar in IMPAVIDO and placebo recipients (approximately 5%).

In the comparative trial vs. antimony (Table 6), a similar percentage of subjects who received IMPAVIDO or pentavalent antimony had Cr elevations above baseline at 3 and 6 months after therapy (approximately 5%). Approximately 25% of IMPAVIDO subjects and 11% of pentavalent antimony subjects had Cr elevations 1.5-3 times above baseline at the end of therapy in the two active controlled trials.

Other adverse events seen at less than 2% incidence in the IMPAVIDO group included anemia, lymphadenopathy, abdominal distension, constipation, dysphagia, flatulence, fatigue, malaise, abscess, cellulitis, ecthyma, paresthesia, testicular pain, testicular swelling, Stevens-Johnson syndrome, urticaria, rash, pyoderma.

### 5.1.2 Adverse Effects in Visceral Leishmaniasis

A single Phase 3 trial was conducted in patients ≥ 12 years of age in India. Two-hundred and ninety-nine (299) patients (211 men and 88 women) received oral IMPAVIDO at a target dose of 2.5 mg/kg/day for 28 days (50 mg capsule once daily if weight was less than 25 kg and 50 mg capsule twice daily if weight was 25 kg or greater). Patients ranged between 12 and 64 years of age. Weight ranged between 15 and 67 kg (mean weight 38.6 kg) and BMI ranged between 8.2 and 24 (mean 16.1). Ninety-nine (99) patients received 1 mg/kg/day amphotericin B deoxycholate intravenously every other day for 15 doses. A significantly higher percentage of men received IMPAVIDO compared to amphotericin B. Adverse reactions reported during this study are summarized in Table 7, below.

Less than 1% of patients who received IMPAVIDO died (2/299) and no patient who received amphotericin B died. Serious adverse reactions were reported in 2% of IMPAVIDO recipients (6/299) and 1% of amphotericin B recipients (1/99). Approximately 3% of patients discontinued treatment in each treatment arm due to an adverse reaction. Serious adverse reactions and adverse reactions leading to drug discontinuation that were thought to be related or possibly related to IMPAVIDO included Stevens-Johnson syndrome, melena and thrombocytopenia, arthritis and skin rash, CTCAEF Stevens[[12]](#footnote-1) Grade 4 diarrhea (≥10 stools per day) and CTCAE Grade 4 hyperbilirubinemia (≥10x upper limit of normal ULN).

Table 7: Treatment Emergent Adverse Reactions Occurring in ≥2% of Visceral Leishmaniasis Patients Receiving IMPAVIDO

|  |  |  |
| --- | --- | --- |
| **System Organ Class****Preferred Term** | **IMPAVIDO****N = 299** | **Amphotericin B Deoxycholate****N = 99** |
| Gastrointestinal Disorders |
|  Diarrhea | 61 (20.4%) | 6 (6.1%) |
|  Vomiting | 113 (37.8%) | 20 (20.0%) |
| General Disorders  |
|  Asthenia | 19 (6.3%) | 4 (4.0%) |
| Metabolism and Nutrition Disorders |
|  Decreased Appetite | 69 (23.1%) | 22 (22.2%) |

In this study, creatinine (Cr) elevations ≥ 1.5 times above baseline occurred in approximately 10% of IMPAVIDO recipients and in 40% of amphotericin B recipients at the end of therapy. Ten percent of subjects in each arm had Cr elevations ≥1.5 times above baseline at 6 months follow up. No IMPAVIDO recipient discontinued therapy due to Cr elevation.

Elevations of transaminases during therapy occurred in up to half of IMPAVIDO recipients and up to a third of amphotericin B recipients. The elevations were mild (< 3x ULN) or moderate (3-5x ULN) in 94% and 6% respectively of IMPAVIDO-treated patients who experienced an elevation. No patient discontinued therapy due to elevations in transaminases.

At the end of therapy, 62% and 2.4% of IMPAVIDO recipients and 54% and 2% of amphotericin B recipients had a platelet count < 150,000 and < 50,000 respectively

# 6. Conclusion

IMPAVIDO is a safe and effective oral medicine for the treatment of cutaneous, mucosal and visceral leishmaniasis infection. It is the only medication approved for these indications by the US Food and Drug Administration. Special consideration must be given to women who are or might become pregnant due to its toxic effects on the developing fetus.

IMPAVIDO has also shown to be useful in rare conditions that have a high impact on survival and quality of life.

Administered for a single, 28-day, course of therapy, IMPAVIDO does not require any adjunct therapy. Amphotericin B is an effective agent for the treatment of visceral leishmaniases. Its disadvantages when compared to IMPAVIDO are modes of administration (IV vs. PO), and toxicity (for amphotericin B deoxycholate).

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