MILTEFOSINE

Generic	Brand	HICL	GCN	Exception/Other
MILTEFOSINE	IMPAVIDO	16200		

GUIDELINES FOR USE

1. Does the patient have a diagnosis of Leishmaniasis and meets **ALL** of the following criteria?
   - Patient is 12 years of age or older
   - Infection type is **ONE** of the following:
     - Visceral leishmaniasis caused by *Leishmania donovani*
     - Cutaneous leishmaniasis caused by **ALL** of the following: *Leishmania braziliensis, Leishmania guyanensis*, and *Leishmania panamensis*
     - Mucosal leishmaniasis caused by *Leishmania braziliensis*
   - Leishmaniasis species is identified via **ONE** of the following CDC recommended tests:
     - Stained slides (using tissue from biopsy specimens, impression smears or dermal scrapings
     - Culture medium
     - Polymerase chain reaction (PCR)
     - Serologic testing (e.g. rK39 Rapid Test)

     If yes, **approve for 12 months by HICL with a quantity limit of #84 capsules per 28 days.**
     If no, do not approve
     DENIAL TEXT: The guideline for **MILTEFOSINE (Impavido)** requires that the patient is 12 years of age or older and has a diagnosis of Leishmaniasis with one of the following types of infection:
     - Visceral leishmaniasis due to *Leishmania donovani*
     - Cutaneous leishmaniasis due to **ALL** of the following: *Leishmania braziliensis, Leishmania guyanensis*, and *Leishmania panamensis*
     - Mucosal leishmaniasis due to *Leishmania braziliensis*

     In addition, species identification must be confirmed via one of the following CDC recommended tests:
     - Stained slides (using tissue from biopsy specimens, impression smears or dermal scrapings
     - Culture medium
     - Polymerase chain reaction (PCR)
     - Serologic testing (e.g. rK39 Rapid Test)

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RATIONALE

Promote appropriate utilization of **MILTEFOSINE** based on FDA approved indication

Impavido (miltefosine) is the first FDA-approved drug to treat cutaneous and mucosal leishmaniasis, and the first oral treatment approved for visceral leishmaniasis. Pentostam (sodium stibogluconate) has been the standard of care for treating leishmaniasis since the 1940s; however, it is not commercially available in the US, but in some cases, may be obtained via an investigational new drug (IND) protocol through the CDC and FDA. Amphotericin B (liposome and conventional) is the only FDA-approved treatment for visceral leishmaniasis and has been used off label as rescue therapy for cutaneous and mucosal leishmaniasis. Ambisome (amphotericin B liposomal) is preferred due to a better safety profile and shorter treatment duration. Topical paromomycin, is not available commercially in the US, but may be obtained via an IND protocol. Prior to Impavido's approval, off label use of oral azoles have been used in specific circumstances, although efficacy is limited and treatment failure is common.

Leishmaniasis is a disease caused by *Leishmania,* a parasite which is transmitted to humans through sand fly bites and occurs primarily in the topic, subtropics and southern Europe. Overall, infection in humans is caused by more than 20 species of *Leishmania* parasites, which are spread by about 30 species of sand fly vectors. New cases diagnosed in the US are most often as a result of acquired disease during overseas travel. According to the Centers for Disease Control (CDC), the estimated number of new cases of cutaneous leishmaniasis ranges approximately from 700,000 to 1.2 million and for visceral leishmaniasis, estimates range from approximately 200,000 to 400,000.

Leishmaniasis encompasses multiple clinical syndromes including cutaneous, mucosal, and visceral forms, which result from infection of macrophages in the dermis, in the naso-oropharyngeal mucosa, and throughout multiple organ systems, respectively. For all three forms, the infection can range from asymptomatic to severe. Cutaneous and mucosal leishmaniasis can cause lesions associated with substantial morbidity, whereas visceral leishmaniasis can be life threatening. Clinical manifestation of disease after initial exposure is typically delayed in all forms of leishmaniasis. In general, skin lesions caused from cutaneous leishmaniasis develop within several weeks or months after exposure and can persists for months or years. Mucosal leishmaniasis develops as a result of untreated or suboptimal treatment of cutaneous leishmaniasis. Thus, mucosal lesions may not appear for several years after the original cutaneous lesions. If left untreated, cutaneous leishmaniasis and mucosal leishmaniasis can progress to ulcerative destruction, disfigurement, and/or secondary bacterial infections. Visceral leishmaniasis is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anemia. The onset of visceral leishmaniasis can present as chronic, subacute or acute and may not be clinically evident for years to decades after exposure. In the absence of treatment, the case fatality rate of visceral leishmaniasis is more than 90 percent.

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RATIONALE (CONTINUED)

Diagnosis of leishmaniasis is made by combining clinical signs with parasitological or serological tests. Detection of parasites can be made from tissue specimens, such as from skin lesions for cutaneous and mucosal leishmaniasis, or from bone marrow, for visceral leishmaniasis. Blood tests that detect antibodies to the parasite may assist diagnosis of visceral leishmaniasis. Due to limited availability of laboratory methods used for diagnosis, the CDC can assist with testing. The CDC provides the following diagnostic services as gratis: examination of slides (e.g., of biopsy specimens, impression smears, and dermal scrapings), provision of leishmanial culture medium, *In vitro* culture and PCR for diagnosis of leishmaniasis and species identification, serologic testing using the rK39 Rapid Test, for detection of antibodies against organisms in the *Leishmania donovani* species complex (useful primarily for visceral leishmaniasis).

Treatment decisions should be individualized, taking into account the form of leishmaniasis, species, geographic region of acquired infection, and the patient's underlying health. Expert consultation is highly recommended, preferably with guidance from the CDC staff to determine the appropriate course. In general, all clinically manifest cases of visceral leishmaniasis and mucosal leishmaniasis should be treated, whereas not all cases of cutaneous leishmaniasis require treatment.

DOSAGE

The treatment duration is 28 consecutive days. Administration with food is recommended to ameliorate gastrointestinal adverse reactions. Dosage is based on weight:

- 30kg to 40kg – administer one 50mg capsule twice daily with food (breakfast and dinner)
- ≥45kg – administer one 50mg capsule three times daily with food (breakfast, lunch, and dinner)

FDA APPROVED INDICATION

Impavido (miltefosine) is an antileishmanial drug indicated in adults and adolescents ≥12 years of age weight ≥30kg (66lbs) for the 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.

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REFERENCES

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- FDA Press Release [Online Press Release]. FDA approves Impavido to treat tropical disease leishmaniasis. March 19,2014. Accessed April 19, 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm389671.htm
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- UpToDate, Inc [database online]. Treatment of visceral leishmaniasis. Last updated March 2016. Accessed on April 19, 2016. Available at: http://www.uptodate.com/contents/treatment-of-visceral-leishmaniasis?source=machineLearning&search=impavido&selectedTitle=4%7E7&sectionRank=1&anchor=H17#H17
- UpToDate, Inc [database online]. Treatment of cutaneous leishmaniasis. Last updated Feb 3 2016. Accessed on April 19, 2016. Available at : http://www.uptodate.com/contents/treatment-of-cutaneous-leishmaniasis?source=search_result&search=impavido&selectedTitle=5%7E7

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 07/01/16

Created: 04/16
Client Approval: 06/16

P&T Approval: 05/16