

miltefosine (Impavido[®])

Policy # 00547

Original Effective Date: 02/15/2017

Current Effective Date: 03/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider miltefosine (Impavido[®])[†] for the treatment of leishmaniasis and free-living amoeba infections to be **eligible for coverage**.^{**}

Patient Selection Criteria

Coverage eligibility for miltefosine (Impavido) will be considered when the following criteria are met:

- Patient has a diagnosis of visceral, cutaneous, or mucosal leishmaniasis; AND
- Patient is at least 12 years of age; AND
- Patient weighs at least 30 kilograms; AND
- There is clinical evidence or patient history that suggests the use of liposomal amphotericin B will be ineffective or cause an adverse reaction to the patient; **OR**
*Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient is being treated for a free-living amoeba infection including but not limited to primary amebic meningoencephalitis (PAM) caused by *Naegleria fowleri* and granulomatous amebic encephalitis (GAE) or other infections caused by *Balamuthia mandrillaris* or *Acanthamoeba*.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of miltefosine (Impavido) for the treatment of visceral, cutaneous, or mucosal leishmaniasis without clinical evidence or patient history that suggests the use of liposomal amphotericin B will be ineffective or cause an adverse reaction to the patient to be **not medically necessary**.^{**}

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of miltefosine (Impavido) when patient selection criteria are not met to be **investigational*** (with the exception of the criterion denoted above as **not medically necessary****).

Background/Overview

Impavido is an anti-leishmanial drug indicated in adults and adolescents at least 12 years of age or older who weigh at least 30 kg for the treatment of visceral, cutaneous, or mucosal leishmaniasis. For patients that weigh 30 to 44 kg, the recommended dose for the treatment of leishmaniasis is one 50 mg capsule twice daily for 28 days. For those weighing 45 kg or greater, the dose is one 50 mg capsule three times daily for 28 days for the treatment of leishmaniasis. Impavido has a black box warning for embryo-fetal toxicity and should not be administered to pregnant women. A serum or urine pregnancy test should be performed in females of reproductive potential prior to prescribing Impavido. Females of reproductive age should be advised to use effective contraception during and for 5 months following therapy with Impavido.

Leishmaniasis

Leishmaniasis is a vector-borne disease that is transmitted by sandflies. There are over 20 species of *Leishmania* parasites that are spread by about 30 species of sand flies that can affect mammals. It can be found in people in focal areas of more than 90 countries in the tropics, subtropics, and southern Europe. There are three primary forms of leishmaniasis: cutaneous, mucosal, and visceral. Cutaneous leishmaniasis is the most common form. The main manifestation is skin sores, which may start out as papules or nodules and progress to ulcers. The sore may take weeks or months to appear after the bite from the sand fly. The mucosal form of leishmaniasis is the least common form. It can usually be a sequela of cutaneous leishmaniasis. The first manifestations typically include unusual nasal or oral or pharyngeal symptoms. If left untreated, mucosal leishmaniasis can progress to ulcerative destruction of the naso-pharyngeal mucosa. Visceral leishmaniasis can affect several internal organs and can be life-threatening. If left untreated, visceral leishmaniasis can be fatal.

Before the approval of Impavido, liposomal amphotericin (Ambisome®) was the only U.S. Food and Drug Administration (FDA) approved product for the treatment of visceral leishmaniasis. There were no FDA approved therapies for the treatment of cutaneous or mucosal leishmaniasis prior to the approval of Impavido. Even though there were no approved therapies prior to this product for cutaneous and mucosal forms of leishmaniasis, amphotericin has been utilized in these conditions.

Free-Living Amoeba Infections

Free-living amoebas are protozoan parasites found globally in soil and water. Four genera of amoebas cause disease in humans: *Acanthamoeba*, *Balamuthia*, *Naegleria*, and *Sappinia* (only *S. pedata*). Two distinctive clinical syndromes associated with free-living amoebas are well recognized: primary amebic meningoencephalitis (PAM) and granulomatous amebic encephalitis

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(GAE). PAM is an acute, and usually lethal, hemorrhagic meningoencephalitis caused by *N. fowleri*. Clinical and laboratory features of PAM typically resemble acute bacterial meningitis. GAE is a rare subacute-chronic infection of the CNS caused by *Acanthamoeba* species, *B. mandrillaris*, and *S. pedate*. Signs and symptoms of GAE are typical of meningoencephalitis and encephalitis, and involve varying degrees of neurological impairment. There are very few known survivors of GAE. *Acanthamoeba* can also cause infection outside of the central nervous system (CNS); these include localized infections involving the skin, the nasopharyngeal area, and keratitis but disseminated infections have also been reported.

The Centers for Disease Control and Prevention and the American Hospital Formulary Service have published recommendations for use of Impavido for the treatment of amoeba-related infections caused by *Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthamoeba* species. Impavido is recommended as part of a multi-drug regimen for these infections. The CDC offers detailed dosing recommendations and access to its Emergency Operations Center, which supports clinicians with diagnostic assistance, specimen collection and shipping guidance, and treatment recommendations. Medical compendia have not recommended Impavido for the treatment of infections caused by *S. pedata*.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Impavido was approved by the FDA in March of 2014 for the treatment of visceral, cutaneous, or mucosal leishmaniasis. Despite its approval, the drug wasn't available in the United States until late 2016.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The approval of Impavido was based on three pivotal studies in which the drug was given for 28 days. In the first study, Impavido was shown to be non-inferior to intravenous amphotericin B in patients with visceral leishmaniasis. The cure rates at 6 months after the end of therapy were 94% in the Impavido group compared to 97% in the amphotericin group. In the second study, Impavido was shown to be significantly more efficacious than placebo in patients with cutaneous leishmaniasis. The cure rates at 6 months after the end of therapy were 66.3% for Impavido and 29.6% for placebo. In the third study, 71% of patients with mucosal leishmaniasis were cured with Impavido 12 months after the end of therapy.

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References

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3. Clinical Care of *Naegleria fowleri* Infection. Available at: <https://www.cdc.gov/naegleria/hcp/clinical-care/index.html>. Accessed on January 15, 2026.
4. Clinical Treatment of Non-keratitis *Acanthamoeba* Infections. Available at: <https://www.cdc.gov/acanthamoeba/hcp/clinical-care/index.html>. Accessed on January 15, 2026.
5. Clinical Care of *Balamuthia* Infection. Available at: <https://www.cdc.gov/balamuthia/hcp/clinical-care/index.html>. Accessed on January 15, 2026.
6. Seas, C. & Bravo F. (2026). Free-living amebas and *Prototheca*. Bogorodskaya, M (Ed.), *UpToDate*. Retrieved January 20, 2026 from <https://sso.uptodate.com/contents/free-living-amebas-and-prototheca>.
7. UpToDate® Lexi-Drug™. 2026. Drug monograph: miltefosine. Wolters Kluwer. Accessed January 15, 2026. <https://www.uptodate.com/contents/miltefosine-drug-information>.

Policy History

Original Effective Date: 02/15/2017

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02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. New policy.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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02/06/2025 Medical Policy Committee review

02/12/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/05/2026 Medical Policy Committee review

02/11/2026 Medical Policy Implementation Committee approval. Added coverage criteria for free-living amoeba related infections, and updated background section.

Next Scheduled Review Date: 02/2027

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.