

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMPAVIDO safely and effectively. See full prescribing information for IMPAVIDO.

IMPAVIDO (miltefosine) capsules, for oral use
Initial U.S. Approval: 2014

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Pregnancy:** IMPAVIDO is contraindicated in pregnancy. Based on animal data, miltefosine may cause fetal harm (4.1, 5.1, 8.1).
- **Females of Reproductive Potential:** Verify pregnancy status prior to initiating IMPAVIDO treatment in females of reproductive potential. To prevent pregnancy, females of reproductive potential should use effective contraception during IMPAVIDO treatment and for 5 months after the last dose (2, 5.1, 8.3, 13.1).

RECENT MAJOR CHANGES

Warnings and Precautions, Impaired Semen Quality and Impaired Spermogenesis (5.2) 5/2021
Warnings and Precautions, Absorption of Oral Contraceptives (5.4) 5/2021

INDICATIONS AND USAGE

IMPAVIDO is an antileishmanial drug indicated in adults and pediatric patients 12 years of age and older weighing greater than or equal to 30 kg (66 lbs) for the treatment of:

- Visceral leishmaniasis due to *Leishmania donovani* (1).
- Cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis* (1).
- Mucosal leishmaniasis due to *Leishmania braziliensis* (1).

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 (1, 14). The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

DOSAGE AND ADMINISTRATION

Administer with food to ameliorate gastrointestinal adverse reactions.

- 30 to 44 kg: one 50 mg capsule twice daily for 28 consecutive days (2).
- 45 kg or greater: one 50 mg capsule three times daily for 28 consecutive days (2).

DOSAGE FORMS AND STRENGTHS

Each IMPAVIDO capsule for oral use contains 50 mg miltefosine (3).

CONTRAINDICATIONS

- Pregnancy (4.1, 5.1, 8.1).

FULL PRESCRIBING INFORMATION: CONTENTS*

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- Sjögren-Larsson-Syndrome (4.2, 12.3).
- Hypersensitivity to miltefosine or any of its excipients (4.3).

WARNINGS AND PRECAUTIONS

- **Impaired Semen Quality and Spermogenesis:** Advise male patients that semen quality may be adversely affected after treatment with IMPAVIDO and that effects on spermogenesis may persist for an unknown duration of time. IMPAVIDO may impair male fertility (5.2, 6.1, 8.3).
- **Female Reproductive Effects:** IMPAVIDO caused impaired fertility in female rats. Advise females of reproductive potential of the reproductive toxicities found in animal studies. The potential effects of IMPAVIDO on female fertility have not been adequately evaluated (5.3, 13.1).
- **Absorption of Oral Contraceptives:** Advise females to use an additional non-oral method of effective contraception if vomiting and/or diarrhea occur (5.4).
- **Renal Effects:** Monitor serum creatinine during therapy and for 4 weeks after end of therapy (5.5, 6.1).
- **Hepatic Effects:** Monitor transaminases and bilirubin during therapy (5.6, 6.1).
- **Gastrointestinal Effects:** Encourage fluid intake (5.7).
- **Thrombocytopenia:** Monitor platelet count during therapy for visceral leishmaniasis (5.8, 6.1).
- **Stevens-Johnson Syndrome:** Discontinue IMPAVIDO (5.9).

ADVERSE REACTIONS

- Adverse reactions occurring in $\geq 2\%$ of patients include nausea, vomiting, diarrhea, headache, decreased appetite, dizziness, abdominal pain, pruritus, somnolence, elevated transaminases, and elevated creatinine (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact **Profunda, Inc. at 1-866-588-5405 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

DRUG INTERACTIONS

- IMPAVIDO did not inhibit human cytochrome P450 enzymes in vitro.
- IMPAVIDO did not induce cytochrome 3A activity in rats (7, 12.3).

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise patients not to breastfeed during IMPAVIDO treatment and for 5 months after the last dose (8.2).
- **Females and Males of Reproductive Potential:** Advise females and males of reproductive potential that IMPAVIDO may impair fertility (2, 5.1, 5.2, 5.3, 5.4, 8.3).

See **17** for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Revised: 5/2021

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Pregnancy:** IMPAVIDO is contraindicated in pregnancy. Based on animal data, miltefosine may cause fetal harm [see *Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)*].
- **Females of Reproductive Potential:** Verify pregnancy status prior to initiating IMPAVIDO. To prevent pregnancy, females of reproductive potential should use effective contraception during treatment and for 5 months after the last dose [see *Dosage and Administration (2), Warnings and Precautions (5.1), Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)*].

1 INDICATIONS AND USAGE

IMPAVIDO (miltefosine) capsules are indicated in adults and pediatric patients 12 years of age and older weighing greater than or equal to 30 kg (66 lbs) for the treatment of:

- Visceral leishmaniasis caused by *Leishmania donovani* [see *Clinical Trials (14.1)*].
- Cutaneous leishmaniasis caused by *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis* [see *Clinical Trials (14.2)*].
- Mucosal leishmaniasis caused by *Leishmania braziliensis* [see *Clinical Trials (14.3)*].

Limitations of Use:

- *Leishmania* species studied in clinical trials evaluating IMPAVIDO were based on epidemiologic data [see *Clinical Trials (14.1, 14.2)*].
- There may be geographic variation in clinical response of the same *Leishmania* species to IMPAVIDO [see *Clinical Trials (14.1, 14.2)*].
- The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

2 DOSAGE AND ADMINISTRATION

Verify pregnancy status prior to initiating IMPAVIDO in females of reproductive potential [see *Use in Specific Populations, (8.3)*].

The treatment duration is 28 consecutive days. Administer with food to ameliorate gastrointestinal adverse reactions.

Table 1: IMPAVIDO Dosage

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)

3 DOSAGE FORMS AND STRENGTHS

IMPAVIDO® (miltefosine) oral capsules are opaque, red, hard gelatin capsules with “PLB” imprinted on the capsule body and “MILT 50” imprinted on the cap using a white ink. Each capsule contains 50 mg miltefosine [see *Description (11), How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

4.1 Pregnancy

IMPAVIDO is contraindicated in patients who are pregnant. Based on animal data, miltefosine may cause fetal harm. [see *Boxed Warning, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

4.2 Sjögren-Larsson-Syndrome

IMPAVIDO is contraindicated in patients who have Sjögren-Larsson-Syndrome [see *Clinical Pharmacology (12.3)*].

4.3 Hypersensitivity

IMPAVIDO is contraindicated in patients who are hypersensitive to miltefosine or any IMPAVIDO excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

IMPAVIDO is contraindicated in patients who are pregnant. Based on animal data, miltefosine may cause fetal harm. Embryo-fetal toxicity, including death and fetal malformations, was observed in animals administered miltefosine prior to mating, during early pregnancy, and during organogenesis at doses lower than the maximum recommended human dose (MRHD). Advise females of reproductive potential of the potential risk to a fetus. Verify pregnancy status prior to initiating IMPAVIDO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with IMPAVIDO and for 5 months after the last dose [see *Boxed Warning, Contraindications (4.1) and Use in Specific Populations (8.1, 8.3)*].

5.2 Impaired Semen Quality and Impaired Spermatogenesis

IMPAVIDO may impair male fertility. Reductions in semen parameters (ejaculate volume, total sperm count, sperm concentration, sperm morphology, sperm motility) were observed in a clinical study evaluating the effects of IMPAVIDO on spermatogenesis. For all parameters, except sperm concentration, the observed reductions were reversible in most affected patients and improved within 3 to 6 months. Reductions in sperm concentration of > 50% persisted in up to 26% of patients. Reductions up to the lower limit of normal in sperm concentration (< 20

million/ mL) persisted in up to 8% of patients. Per protocol, semen parameters were not assessed beyond 6 months in any patient. The effect of IMPAVIDO on spermatogenesis may persist for an unknown duration. [see *Adverse Reactions (6.1)* and *Use in Specific Populations (8.3)*].

Reductions in ejaculate volume, temporary absence of ejaculate, and scrotal tenderness were reported in an observational study of male patients who received IMPAVIDO. These adverse reactions resolved in all patients upon completion of IMPAVIDO therapy [see *Adverse Reactions (6.2)*].

5.3 Female Reproductive Effects

IMPAVIDO caused impaired fertility in female rats and follicular atresia and reversible anestrus/diestrus in dogs at doses approximately 1.0 and 0.2 times the MRHD based on body surface area comparisons, respectively [see *Nonclinical Toxicology (13.1)*]. The effects of IMPAVIDO on human female fertility have not been formally studied [see *Use in Specific Population (8.3)*].

5.4 Absorption of Oral Contraceptives

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect the absorption of oral contraceptives, and therefore compromise their efficacy. If vomiting and/or diarrhea occur during IMPAVIDO therapy, advise females to use an additional non-oral method of effective contraception [see *Boxed Warning, Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].

5.5 Renal Effects

Elevations of serum creatinine (Cr) were noted in clinical trials evaluating IMPAVIDO in the treatment of cutaneous, mucosal and visceral leishmaniasis. Monitor renal function weekly in patients receiving IMPAVIDO during therapy and for 4 weeks after end of therapy [see *Adverse Reactions (6.1)*].

5.6 Hepatic Effects

Elevations in liver transaminases (ALT, AST) and bilirubin were noted in clinical trials evaluating IMPAVIDO in the treatment of visceral leishmaniasis. Monitor liver transaminases (ALT, AST) and bilirubin during therapy in patients receiving IMPAVIDO [see *Adverse Reactions (6.1)*].

5.7 Gastrointestinal Effects

Vomiting and/or diarrhea commonly occur during IMPAVIDO administration and may result in volume depletion. Encourage fluid intake to avoid volume depletion [see *Adverse Reactions (6.1)*].

5.8 Thrombocytopenia

Thrombocytopenia during therapy has been reported in patients treated for visceral leishmaniasis. Monitor platelet count during therapy for visceral leishmaniasis [*see Adverse Reactions (6.1, 6.2)*].

5.9 Stevens-Johnson Syndrome

Stevens-Johnson syndrome has been reported during IMPAVIDO therapy. Discontinue IMPAVIDO if an exfoliative or bullous rash is noted during therapy [*see Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Visceral Leishmaniasis

One 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 statistically significant higher percentage of men received IMPAVIDO compared to amphotericin B.

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, Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 diarrhea (≥ 10 stools per day) and CTCAE Grade 4 hyperbilirubinemia (≥ 10 x upper limit of normal ULN).

Table 2: Treatment Emergent Adverse Reactions Occurring in $\geq 2\%$ 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 platelet count $< 150,000$ and $< 50,000$ respectively.

Cutaneous Leishmaniasis

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 and older received a target IMPAVIDO dose of 2.5 mg/kg/day for 28 days and forty-four (44) received placebo. In the comparative trials, one hundred and twenty (120) patients 12 years of age and older 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 3: Adverse Reactions Occurring in $\geq 2\%$ of IMPAVIDO-Treated Patients ≥ 12 Years of Age with Cutaneous Leishmaniasis in the Placebo-Controlled Trial

System Organ Class Adverse Reaction	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

Table 4: Adverse Reactions Occurring in $\geq 2\%$ of IMPAVIDO-Treated Patients ≥ 12 Years of Age with Cutaneous Leishmaniasis in Two Comparative Trials

System Organ Class Adverse Reaction	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

In the placebo controlled trial, 12/89 (13.4%) IMPAVIDO subjects had Cr increases of 1.5-3 times above baseline, compared to 2/44 (4.5%) placebo subjects at end of therapy. In the comparative trial, 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. 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%).

Other adverse events seen at <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.

Adverse Effects on Semen Quality and Spermatogenesis

In an open-label, uncontrolled, single-center study that assessed the effects of IMPAVIDO on sperm parameters, a total of 58 Bolivian adult males with cutaneous or mucosal leishmaniasis were administered IMPAVIDO for 28 days at a target dose of 2.5 mg/kg/day. Patients underwent repeat semen analysis testing at baseline (prior to treatment), at the end of treatment (Day 25 to 28 of treatment), and at 3 months after completing treatment. If sperm concentrations were markedly reduced at 3 months, per protocol, one additional semen sample was collected at 6 months after completing treatment.

The primary safety endpoint was determined at the end of treatment and included the number and percentage of patients with abnormal sperm parameters and clinically relevant changes from baseline in semen volume, total sperm count, sperm concentration, sperm motility and sperm morphology as shown in Table 5. The secondary safety endpoints included: mean changes from baseline in semen volume, sperm concentration, total sperm count, sperm motility and sperm morphology. Mean changes from baseline in serum testosterone and FSH concentrations were also evaluated.

A total of 53 patients completed the study. The median patient age was 34 years (range 18 to 51 years). The majority of patients (70.7%) had cutaneous leishmaniasis, while 24.1% had mucosal leishmaniasis, and 5.2% had both forms.

Treatment with IMPAVIDO was associated with reductions in all sperm parameters at the end of treatment (see Table 5). All sperm parameter reductions, except for sperm concentration, recovered on follow-up assessments at 3 and 6 months after treatment completion. For sperm concentration, small mean decreases persisted on follow-up assessments at 3 and 6 months after treatment completion, with approximately 26% of subjects showing post-treatment sperm concentrations reductions of $\geq 50\%$, and 8% showing reductions to the lower limit of normal (< 20 million/ mL), on their last observed assessment.

Table 5 shows the results for the primary safety endpoint, the number and percentage of patients with abnormal sperm parameters at the end of treatment and in the post-treatment follow-up period, including assessments at 3 months or 6 months after treatment completion.

Table 5: Number (%) of Subjects with Abnormal Sperm Parameters, Based on Last Observation, n=55

Sperm Parameter	End of Treatment	Follow-up Period (Last observation*)
Semen volume		
< 1.5 mL	41/55 (75%)	8/53 (15%)
Total sperm count		
≥ 50% reduction from baseline	28/52 (54%)	10/53 (19%)
< 39 million	17/52 (33%)	3/53 (6%)
Sperm concentration		
≥ 50% reduction from baseline	11/52 (21%)	14/53 (26%)
< 20 million sperm/mL	6/52 (12%)	4/53 (8%)
Sperm motility		
≥ 25% reduction from baseline	28/55 (51%)	5/53 (9%)
< 40% with total motility	18/55 (33%)	3/53 (6%)
Sperm morphology		
≥ 25% reduction from baseline	17/55 (31%)	8/53 (15%)
< 4% normal forms	0/55 (0%)	0/53 (0%)

**Last observation=Patient's final semen analysis at either 3 months or 6 months after treatment completion*

Semen analyses were not conducted beyond 6 months in any patient; therefore, the duration of effect of IMPAVIDO on sperm concentration after treatment is unknown.

Table 6 shows the results for the secondary safety endpoints, mean sperm parameters at baseline, end of treatment, and 3 and 6 months after treatment completion.

Table 6: Mean Sperm Parameters Over Time

		n	Geometric Mean (SD)**
Semen Volume (mL)	Baseline	55	2.3 (0.4)
	End of Treatment	55	1.0 (0.4)
	3 Months	49	2.1 (0.3)
	6* Months	18	2.3 (0.4)
Total Sperm Count (millions)	Baseline	55	169 (1.0)
	End of Treatment	52	74 (3.8)
	3 Months	49	128 (1.3)
	6* Months	18	129 (1.9)
Sperm Concentration (million/mL)	Baseline	55	79 (1.2)
	End of Treatment	52	74 (2.8)
	3 Months	49	65 (1.3)
	6* Months	18	59 (1.5)
		n	Mean (SD)
Sperm Motility (%)	Baseline	55	59 (8.8)
	End of Treatment	55	39 (15.2)
	3 Months	49	57 (10.4)
	6* Months	18	54 (10.6)
Sperm Morphology (%)	Baseline	55	7 (4.2)
	End of Treatment	52	15 (5.1)
	3 Months	49	18 (5.7)
	6* Months	18	16 (5.5)

* If sperm concentrations were markedly reduced at 3 months, per protocol, one additional semen sample was collected at 6 months after completing treatment.

** Mean and SD of log(X+1) transformed data are calculated and transformed back to original unit using exp(X)-1 to derive Geometric Mean and Geometric SD in this table.

No clinically meaningful changes were observed in serum testosterone or FSH concentrations at the end of treatment or 3 months after treatment.

6.2 Postmarketing Experience

The following adverse reactions have been identified during use of IMPAVIDO or miltefosine worldwide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse Reactions from Postmarketing Spontaneous Reports

Blood and Lymphatics Disorders: thrombocytopenia, agranulocytosis

Gastrointestinal Disorders: melena

General Disorders: generalized edema, peripheral edema

Hepatobiliary Disorders: jaundice

Nervous System Disorders: seizure

Vascular Disorders: epistaxis

Adverse Reactions from Observational Studies

Reproductive System and Breast Disorders: scrotal pain, decreased ejaculate volume, absent ejaculation.

Reduced Ejaculate Volume and Scrotal Tenderness

Among 33 young male patients treated with miltefosine at a single Dutch center, 21 (64%) reported diminution of ejaculate volume and 2 (6%) reported temporary absence of ejaculate. In addition, 4 patients (12%) reported scrotal tenderness and 1 (3%) was diagnosed with epididymitis. These adverse reactions resolved in all patients upon completion of their miltefosine therapy.

7 DRUG INTERACTIONS

In vitro and animal metabolism studies showed that miltefosine did not markedly induce or inhibit the activity of the major human cytochrome P450 enzymes [see *Clinical Pharmacology (12.3)*]. The potential of miltefosine to interact with drug transporters has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to IMPAVIDO during pregnancy. Healthcare providers are encouraged to register patients by calling 1-866-588-5405 or visiting online at <http://www.impavido.com/mother-registry>.

Risk Summary

IMPAVIDO is contraindicated during pregnancy. Based on data from animal reproduction studies, IMPAVIDO may cause embryo-fetal toxicity when administered to pregnant women. There are no available data on IMPAVIDO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal and/or fetal outcomes. If a woman becomes pregnant while being treated with IMPAVIDO, treatment should be discontinued and the patient should be counseled about the potential risk to the fetus.

Embryo-fetal toxicity, including death and fetal malformations, was observed in embryo-fetal studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the maximum recommended human dose (MRHD) of 3.33 mg/kg/day. Numerous visceral and skeletal fetal malformations were observed in a fertility study in female rats administered miltefosine prior to mating through day 7 of pregnancy at doses 0.3 times the MRHD.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, miltefosine was administered in oral doses of 0.6, 1.2, 2.4, 6, 12, and 24 mg/kg/day during the period of organogenesis (Day 6 to Day 15 of gestation). Miltefosine dosages ≥ 1.2 mg/kg/day [0.06 times the MRHD based on body surface area (BSA) comparison] caused embryo-fetal toxicity including death and fetal malformations. Malformations included undeveloped cerebrum, hemorrhagic fluid filling the lumina of the skull, cleft palate and generalized edema. In an embryo-fetal development study in pregnant rabbits, miltefosine was administered in oral doses of 0.6, 1.2, 2.4, 6, 12, and 24 mg/kg/day during the period of organogenesis (Day 6 to Day 18 of gestation). Abortion and fetal resorption occurred with one dam receiving 2.4 mg/kg/day miltefosine (0.2 times the MRHD based on BSA comparison) and fetal resorptions occurred with all dams receiving ≥ 6.0 mg/kg/day miltefosine. In both rats and rabbits, there were no viable litters at miltefosine doses ≥ 6.0 mg/kg/day (0.3 or 0.6 times the MRHD based on BSA comparisons for rats and rabbits respectively).

In a separate fertility study in female rats, miltefosine was administered in oral doses of 2.15, 6.81, and 21.5 mg/kg for four weeks before mating and up to Day 7 of pregnancy. Miltefosine doses ≥ 6.81 mg/kg/day (0.3 times the MRHD based on BSA comparison) produced numerous visceral (misshapen cerebral structures, dilated ventricles filled with brown masses, misshapen spinal cord, misshapen and malpositioned eyes, hypophysis, and absent inner ear) and skeletal (cleft palate, dumbbell-shaped ossification of thoracic vertebral centers, markedly enlarged skull bones, and markedly dilated suturae) fetal malformations. [*see Contraindications (4.1), Nonclinical Toxicology (13.1)*].

8.2 Lactation

Risk Summary

There are no data on the presence of miltefosine in human or animal milk, the effects on the breastfed infants, or the effects on milk production. Because of the potential for serious adverse

reactions, breastfeeding is not recommended during treatment with IMPAVIDO and for 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status prior to initiating IMPAVIDO in females of reproductive potential [*see Boxed Warning and Use in Specific Populations (8.1)*].

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with IMPAVIDO and for 5 months after the last dose [*see Boxed Warning, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect absorption of oral contraceptives and therefore compromise their efficacy. If vomiting and/or diarrhea occur during IMPAVIDO therapy, advise females to use an additional non-oral method of effective contraception [*see Boxed Warning, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Infertility

Females

Based on animal fertility studies, IMPAVIDO may impair fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1)*]. The effects of IMPAVIDO on human female fertility have not been formally studied [*see Warnings and Precautions (5.3)*].

Males

Based on animal fertility and postmarketing studies, IMPAVIDO may impair fertility in males of reproductive potential [*see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)*].

In an open-label, uncontrolled, single-center study that assessed the effects of miltefosine on sperm parameters, a total of 58 adult males with cutaneous or mucosal leishmaniasis were administered miltefosine for 28 days at a target dose of 2.5 mg/kg/day and underwent semen analysis testing prior to treatment, at the end of treatment, at 3 months after completing treatment, and if needed, at 6 months after completing treatment. The primary safety endpoint was determined at the end of treatment and included the number and percentage of patients with abnormal sperm parameters and clinically relevant changes from baseline in sperm parameters. The secondary safety endpoints included mean sperm parameters at baseline, end of treatment, and 3 and 6 months after treatment completion. Mean serum testosterone and FSH

concentrations were also evaluated [see *Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].

Treatment with IMPAVIDO was associated with reductions in all sperm parameters at the end of treatment. All sperm parameters, except for sperm concentration, recovered on follow-up assessments at 3 and 6 months after treatment completion [see *Adverse Reactions (6.1)*].

For sperm concentration, small mean decreases persisted on follow-up assessments at 3 and 6 months after treatment completion, with approximately 26% of subjects showing post-treatment sperm concentrations reductions of $\geq 50\%$ and reductions to the lower limit of normal (< 20 million/mL) persisting in up to 8% of patients on their last observed assessment. Semen analyses were not conducted beyond 6 months in any patient, therefore, the duration of effect of IMPAVIDO on sperm concentration after treatment is unknown [see *Adverse Reactions (6.1)*].

No clinically meaningful changes were observed in serum testosterone or FSH concentrations.

Reductions in ejaculate volume and temporary absence of ejaculate were reported in an observational study of male patients who received IMPAVIDO. These adverse reactions resolved in all patients in this study upon completion of IMPAVIDO therapy [see *Warnings and Precautions (5.2) and Adverse Reactions (6.2)*].

The effect of IMPAVIDO on spermatogenesis may persist for an unknown duration.

Whether IMPAVIDO affects male fertility is unknown [see *Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients less than 12 years old have not been established. Juvenile rats were more sensitive to the miltefosine-induced effects, especially retinal and kidney effects, than adult rats [see *Indications and Usage (1)*].

8.5 Geriatric Use

Clinical studies of IMPAVIDO did not include sufficient numbers of subjects 65 years of age and over to determine if they respond differently than younger subjects.

8.6 Renal Impairment

Patients with serum creatinine or BUN levels ≥ 1.5 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with renal impairment.

8.7 Hepatic Impairment

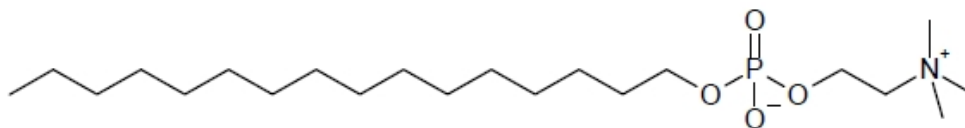
Patients with serum levels of ALT or AST ≥ 3 times the upper limit of normal and bilirubin levels ≥ 2 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with hepatic impairment.

10 OVERDOSAGE

The common adverse effects of vomiting, diarrhea, and abdominal pain are likely in case of overdose. Institute adequate hydration to prevent the risk of impaired renal function, and replace electrolytes as necessary. Because miltefosine is only slightly excreted in the urine, forced diuresis will not increase miltefosine excretion. Gastrointestinal lavage is of unknown value. A specific antidote to treat miltefosine overdose is not known.

11 DESCRIPTION

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



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Miltefosine is an anti-leishmanial agent [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

Cardiac Electrophysiology:

The effect of IMPAVIDO on the QTc interval was evaluated in 42 adult patients administered the recommended dosage regimen of IMPAVIDO capsules, 50 mg three times daily for 28 days.

No large increases (i.e., 20 msec) or any other evidence of prolongation of the corrected QTc interval (QTcF) from baseline were observed.

12.3 Pharmacokinetics

The pharmacokinetic parameters of miltefosine in patients with visceral and cutaneous leishmaniasis treated for 28 days with IMPAVIDO are listed in Table 7. Due to the long half-life of miltefosine (> 6 days), trough plasma concentrations did not appear to reach a steady state at the end of treatment (i.e., Day 28).

Table 7: Mean (%CV) Pharmacokinetic Parameters for Miltefosine Following Oral Capsule Administration to Adult Patients with Visceral and Cutaneous Leishmaniasis

	Dose	C _{max} (µg/mL)	T _{max} ^d (hr)	AUC _{tau} ^e (µg·hr/mL)	t _{1/2,α} ^f (day)	t _{1/2,β} ^g (day)
Visceral Leishmaniasis (on Day 23)	50 mg BID (4 wks) ^a	66.2 (28.5)	7(2-12)	636 (26.7)	6.4 (31.1)	
	50 mg BID (1 wk)/ 50 mg TID (3 wks) ^b	75.9 (17.6)	4 (2-8)	486 (18.1)	8.5 (28.9)	
Cutaneous Leishmaniasis ^c (on Day 27)	50 mg TID (4 wks)	37.3 (22) ^f		295 (22) ^f	6.8 (5.8) ^{g,h}	30.7 (18.3) ^{g,h}

a: Adolescent (≥12 years)/Adults, mean dose per kg was 3.1 mg/kg/day

b: Adolescent (≥12 years)/Adults, mean dose per kg was 3.6 mg/kg/day

c: Adults, mean dose per kg was 1.8 mg/kg/day

d: median (range)

e: AUC_{0-12h} for BID, AUC_{0-8h} for TID

f: t_{1/2,α} = distribution phase half-life; t_{1/2,β} = terminal elimination phase half-life

g: Estimates based on a population PK model

h: mean (% standard error)

Absorption

Absolute bioavailability of miltefosine has not been determined. In patients with visceral leishmaniasis, maximum miltefosine concentrations following oral administration of IMPAVIDO capsules were reached right before the next dose in many patients, indicating that the absorption of miltefosine may proceed throughout the dosing interval.

Distribution

The distribution of miltefosine has not been studied in humans. Human plasma protein binding of miltefosine, evaluated by an ultracentrifugation method, was 98% over the drug concentration range from 0.1 to 10 µg/mL. In rats, radioactivity of [¹⁴C] miltefosine is widely distributed after both single and repeated oral administration with highest uptake of radioactivity in kidney, liver, and spleen. Placental transfer and excretion into milk have not been investigated.

Metabolism and Excretion

No *in vitro* oxidative metabolism by 15 different human cytochrome P450 enzymes (1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, and 4A1) was observed.

A slow metabolic breakdown could be shown in human hepatocytes, resulting in the release of choline by phospholipase D-like cleavage of the miltefosine molecule. The fatty alcohol-containing fragment of miltefosine can enter the metabolism of fatty acids after being oxidized to palmitic acid. This oxidation is blocked in patients with Sjögren-Larsson syndrome, which is caused by a genetic defect in fatty aldehyde dehydrogenase activity. IMPAVIDO is contraindicated in patients who have Sjögren-Larsson-Syndrome [see *Contraindications* (4.2)].

There was little or no evidence of time or metabolism dependent inhibition of the cytochrome P450 enzymes examined at up to approximately 40 µg/mL miltefosine.

Oral administration of miltefosine did not markedly induce the content of hepatic CYP3A assayed by demethylation activity of erythromycin in rats.

In visceral leishmaniasis patients, <0.2% of the administered dose was excreted into the urine.

12.4 Microbiology

Mechanism of Action

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

Activity In Vitro and In Vivo

Miltefosine has anti-leishmanial activity *in vitro* and in clinical infections [see *Clinical Studies (14)*]. Sensitivity of different *Leishmania* species as well as different strains of a *Leishmania* species to miltefosine may vary in different geographic regions.

Drug Resistance

In vitro studies show a potential for development of resistance to miltefosine. Some strains of *L. braziliensis* with intrinsic resistance to miltefosine have been identified. However, the clinical relevance of these observations is not known.

Drug resistance could be due to a decrease in miltefosine accumulation within *Leishmania* parasite which is thought to be due to either an increase in drug efflux, mediated by the overexpression of the ABC transporter P-glycoprotein and/or a decrease in drug uptake by the inactivation of the miltefosine transport machinery that consists of the miltefosine transporter and its beta subunit. Mutation in the transporter gene was reported in the isolates from a relapsed patient in one study. However, the clinical relevance of these findings is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity/Carcinogenicity: Miltefosine tested negative in the AMES-Salmonella test, DNA-amplification test, chromosomal aberration test *in vitro*, UDS-test *in vivo/in vitro*, and oral mouse micronucleus test *in vivo*. The V 79 mammalian cell HPRT gene mutation test showed an increase in mutant frequency without dose dependency. In view of all mutagenicity test results, the single positive finding in the V 79 HPRT test is considered to be not of toxicological relevance with respect to a mutagenic risk to humans.

Carcinogenicity studies were not performed. In a 52-week oral rat toxicity study, benign and malignant neoplasms that occurred in high-dose animals administered 21.5 mg/kg/day miltefosine (1.0 times the MRHD based on BSA comparison) included testicular Leydig cell adenoma in 3 of 30 male rats, and histiocytic sarcoma with widespread multi-organ metastasis, squamous cell carcinoma in the uterus, and a malignant adenoacanthoma in the uterus with widespread metastasis in 3 individual female rats. The carcinogenic potential of miltefosine in humans is unknown.

In a fertility study in male rats, miltefosine was administered in oral doses of 3.16, 8.25 and 21.5 mg/kg/day from 4 weeks prior to mating until 7 days during mating. Testicular atrophy, reduced numbers of viable sperm, and impaired fertility were observed in rats following daily oral doses of ≥ 8.25 mg/kg (0.4 times the MRHD based on BSA comparison). These findings were reversible within a recovery period of 10 weeks except at the highest dose tested, 21.5 mg/kg/day (1.0 times the MRHD based on BSA comparison), where effects were not fully reversible.

In a fertility study in female rats, miltefosine was administered in oral doses of 2.15, 6.81, and 21.5 mg/kg/day for 4 weeks prior to mating, during mating, and until Day 7 of pregnancy. Estrus cycle arrest in the metestrus or diestrus phases occurred with the high-dose of 21.5 mg/kg (1.0 times the MRHD based on BSA comparison). At doses of 6.81 and 21.5 mg/kg (0.3 and 1.0 times the MRHD, respectively, based on BSA comparison) increased numbers of embryonic and fetal resorptions and dead fetuses were observed.

In a 52-week toxicology study in dogs, increased numbers of atretic follicles in the ovaries, and cycle arrest in the uterus, vagina, and mammary gland with morphology consistent with anestrus or diestrus were observed at doses ≥ 1 mg/kg/day (0.2 times the MRHD based on BSA comparison). The effects in dogs were fully reversible after a recovery period of 6 weeks.

13.2 Animal Toxicology and/or Pharmacology

Toxicological studies with miltefosine have been performed in mice, rats, dogs, and rabbits. Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Acute and chronic toxicity: The oral administration of miltefosine in rats was associated with lesions affecting the eyes (retinal degeneration). Retinal degeneration was observed after 8-weeks treatment at doses of 10 mg/kg/day (0.5 times the MRHD based on BSA comparison). Juvenile rats were more sensitive to the miltefosine-induced effects, especially on eyes and kidneys, than adult rats with retinal degeneration occurring at doses ≥ 2.15 mg/kg/day (0.1 times the MRHD based on BSA comparison), and reversible damage to proximal tubule epithelium occurring at doses ≥ 4.64 mg/kg/day (0.2 times the MRHD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Treatment of Visceral Leishmaniasis

One randomized, open-label, active-controlled study was conducted to evaluate the efficacy of IMPAVIDO in the treatment of visceral leishmaniasis in Bihar, India, an area where *L. donovani* is known epidemiologically to be the prevalent infecting species. Patients 12 years of age and

older with clinical signs and symptoms compatible with visceral leishmaniasis (fever, splenomegaly, and cytopenia) confirmed by the presence of *Leishmania* amastigotes in aspirates of spleen or bone marrow were randomized to receive oral IMPAVIDO or intravenous amphotericin B deoxycholate in a 3:1 ratio. Patients weighing greater than or equal to 25 kg received an IMPAVIDO 50 mg capsule with meals twice a day. Patients weighing less than 25 kg received an IMPAVIDO 50 mg capsule with meals once a day in the morning. Weight ranged between 15 and 67 kg (mean weight 38.6 kg) and BMI ranged between 8.2 and 24 (mean 16.1). No patient weighed more than 70kg. Amphotericin B was administered intravenously over 6 continuous hours at 1 mg/kg every other day for 15 doses. Patients were hospitalized for the duration of therapy.

Exclusion criteria included platelet count $<50 \times 10^9/L$, white cell count $<1 \times 10^9/L$, hemoglobin <6 g/100 mL, AST or ALT ≥ 3 times upper limit of the normal range, bilirubin ≥ 2 times upper limit of the normal range, serum creatinine or BUN >1.5 times upper limit of the normal range, prothrombin time >5 seconds above control, and any non-compensated or uncontrolled condition including human immunodeficiency virus (HIV) infection. Women of reproductive potential were required to use effective contraception for the duration of therapy and for 2 months post therapy.

Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at 6 months follow up. Initial cure at the end of therapy was evaluated by repeat spleen or bone marrow aspiration. Patients with initial parasitologic cure were followed for 6 months; patients without absence of clinical signs and symptoms of visceral leishmaniasis were to be evaluated with repeat spleen or bone marrow aspiration to determine final cure.

Two hundred and ninety nine (299) patients received IMPAVIDO and 99 patients received amphotericin B. Approximately, 70% of patients in each arm had previously failed treatment with pentavalent antimony. Initial cure was achieved in 98% of patients in each treatment arm. At 6 months after therapy, 88 (29.5%) IMPAVIDO recipients and 12 (12.1%) amphotericin B recipients continued to have signs and symptoms suggestive of visceral leishmaniasis. These signs or symptoms were attributed to alternative diagnosis in 73 patients. The remaining 27 patients, all in the IMPAVIDO arm, underwent evaluation with splenic or bone marrow aspiration, and 9 (3.0%) were positive for *Leishmania* amastigotes, indicating relapse. The final cure rates for IMPAVIDO and amphotericin B were 94% and 97%, respectively.

Table 8: Efficacy of IMPAVIDO in Visceral Leishmaniasis in Patients ≥ 12 years of Age in India

	IMPAVIDO N = 299	Amphotericin B Deoxycholate N = 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%).

14.2 Treatment of Cutaneous Leishmaniasis

A placebo controlled study was performed in Colombia where *L. panamensis* and *L. braziliensis* are epidemiologically known to be the prevalent infecting *Leishmania* species, and in Guatemala where *L. braziliensis* is epidemiologically known to be the prevalent infecting species. The study included male and female patients older than 12 years of age who had newly diagnosed or relapsing cutaneous leishmaniasis without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer with minimum area of 50 mm². Exclusion criteria were AST or ALT ≥ 2 times upper limit of normal range, bilirubin ≥ 1.5 times upper limit of normal range, and serum creatinine or BUN > 1.5 times upper limit of normal range. Women of reproductive potential were required to use effective contraception for the duration of therapy and for 2 months post therapy.

Patients were randomized to receive IMPAVIDO or placebo in a 2:1 allocation. Patients who weighed less 45 kg received IMPAVIDO 50 mg capsule twice a day, and patients who weighed greater or equal to 45 kg received IMPAVIDO 50 mg capsule three times a day. No patient weighed more than 84 kg. Definite cure was defined as apparent (complete epithelialization of all lesions) or partial cure (incomplete epithelialization, no enlargement by $> 50\%$ in lesions, no appearance of new lesions, and negative parasitology if done) at 2 weeks after end of therapy and complete epithelialization of all ulcers at 6 months after end of therapy. The definite cure rate for IMPAVIDO was statistically significantly higher than the cure rate for placebo.

Table 9: Efficacy of IMPAVIDO Compared to 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 respectively *L. braziliensis* and *L. guyanensis* are epidemiologically the prevalent infecting pathogens. Adolescent/adult patients aged 12-65 years received IMPAVIDO orally for 28 days. IMPAVIDO 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 greater than 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). Definite cure rate in patients aged 12 years and older was 27/40 (67.5%) for Manaus, Brazil and 34/40 (85%) for Bahia, Brazil.

14.3 Treatment of Mucosal Leishmaniasis

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 greater than or equal to 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each IMPAVIDO capsule contains 50 mg miltefosine in an opaque, red, hard gelatin capsule. IMPAVIDO capsules are supplied in a folded peel/push-through child-resistant blister card. Each blister card contains 14 capsules. Each carton contains two blister cards (NDC 69051-300-01).

Store at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. Protect from moisture.

Dispense only in the original carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Dosing Instructions

- IMPAVIDO is administered with food to ameliorate gastrointestinal side effects.
- Instruct the patient to swallow the capsule whole and not to chew it or break it apart. Instruct the patient to complete the full course of therapy.
- Inform the patient that abdominal pain, nausea, vomiting, and diarrhea are common side effects of therapy with IMPAVIDO and instruct the patient to inform their healthcare provider if these gastrointestinal side effects are severe or persistent. Instruct the patient to consume sufficient fluids to avoid dehydration and, consequently, the risk of kidney injury.

Embryo-fetal Toxicity

- Advise pregnant women and females of reproductive potential that IMPAVIDO may cause fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Boxed Warning, Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

- There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to IMPAVIDO during pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

- Advise women not to breastfeed during treatment with IMPAVIDO and for 5 months after the last dose [*see Use in Specific Populations (8.2)*].

Females and Males of Reproductive Potential

- Advise women of reproductive potential to use effective contraception during treatment with IMPAVIDO and for 5 months after the last dose [*see Boxed Warning, and Use in Specific Populations (8.1, 8.3)*].
- Advise women who use oral contraceptives to use an additional non-oral method of effective contraception during IMPAVIDO therapy, if vomiting and/or diarrhea occurs [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.3)*].
- Advise women who become pregnant while being treated with IMPAVIDO, to discontinue treatment with IMPAVIDO and seek counseling from their healthcare provider about the potential risk to the fetus [*see Boxed Warning and Use in Specific Populations (8.1)*].
- Advise male patients that semen quality and sperm parameters may be adversely affected by treatment with IMPAVIDO. Advise male patients that the effects of IMPAVIDO on spermatogenesis may persist for an unknown duration of time [*see Warnings and Precautions (5.2) and Use in Specific Populations (8.3)*].
- Advise females and males of reproductive potential that IMPAVIDO may impair fertility. [*see Warnings and Precautions (5.2, 5.3), Use in Specific Populations (8.3), and Nonclinical Toxicology (13.1)*].
- Advise male patients that diminution in ejaculate volume, including temporary absence of ejaculate, and scrotal tenderness may occur during treatment with IMPAVIDO. Male patients should report any concerning genitourinary symptoms to their healthcare provider [*see Warnings and Precautions (5.2), Adverse Reactions (6.2), and Use in Specific Populations (8.3)*].



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MEDICATION GUIDE
IMPAVIDO® (Im-PA-vee-do)
(miltefosine)
capsules, for oral use

Read this Medication Guide before you start taking IMPAVIDO and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about IMPAVIDO?

IMPAVIDO may cause serious risks to pregnancy:

- **Do not** take IMPAVIDO if you are pregnant. If you take IMPAVIDO during pregnancy, your baby is at risk for death or serious birth defects. If you become pregnant while taking IMPAVIDO, stop taking IMPAVIDO and talk to your healthcare provider right away if you become pregnant during treatment with IMPAVIDO.
- You should have a pregnancy test before you start taking IMPAVIDO.
- Women who can become pregnant should use effective birth control (contraception) during IMPAVIDO treatment and for 5 months after their last dose of IMPAVIDO. Talk to your healthcare provider about which birth control method is right for you.
- **Pregnancy Registry:** There is a registry for women who become pregnant during treatment with IMPAVIDO. If you become pregnant or think you may be pregnant while taking IMPAVIDO, tell your healthcare provider right away. Talk to your healthcare provider about registering with the IMPAVIDO Pregnancy Registry. The purpose of this registry is to collect information about your health and your baby's health. Your healthcare provider can enroll you in this registry by calling 1-866-588-5405 or by going to <http://www.impavido.com/motherregistry>.

What is IMPAVIDO?

IMPAVIDO is prescription medicine used to treat certain types of leishmaniasis in adults and children 12 years of age and older weighing 66 pounds or more with:

- visceral leishmaniasis (affecting your internal organs) caused by *Leishmania donovani*
- cutaneous leishmaniasis (affecting the skin) caused by *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*
- mucosal leishmaniasis (affecting the nose, mouth and throat) caused by *Leishmania braziliensis*

It is not known if IMPAVIDO is safe and effective in other types of leishmaniasis.

It is not known if IMPAVIDO is safe and effective in children under 12 years of age.

Do not take IMPAVIDO if you:

- **are pregnant, plan to become pregnant, or become pregnant during treatment with IMPAVIDO. See “What is the most important information I should know about IMPAVIDO?”**
- have Sjögren-Larsson syndrome
- are allergic to miltefosine or any of the ingredients in IMPAVIDO. See the end of this Medication Guide for a complete list of the ingredients in IMPAVIDO.

Before taking IMPAVIDO, tell your healthcare provider about all your medical conditions, including if you:

- have kidney or liver problems. Your healthcare provider should do blood tests to check your kidneys and liver before you start, during and after your treatment with IMPAVIDO.
- are breastfeeding or plan to breastfeed. It is not known if IMPAVIDO passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take IMPAVIDO. You should not breastfeed while you take IMPAVIDO and for 5 months after your last dose of IMPAVIDO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take IMPAVIDO?

- Take IMPAVIDO exactly as your healthcare provider tells you to.
- Complete your full 28-day IMPAVIDO treatment.
- Take IMPAVIDO capsules whole. Do not break, crush, dissolve, or chew IMPAVIDO before swallowing.
- Take IMPAVIDO with food to help reduce stomach problems.

What are the possible side effects of IMPAVIDO?

IMPAVIDO may cause serious side effects, including:

See “What is the most important information I should know about IMPAVIDO?”

- **possible fertility problems.** When used in both male humans and animals, IMPAVIDO decreased semen quality, sperm count and semen volume (the amount of fluid released upon ejaculation). IMPAVIDO may cause fertility problems in males. It is not known how long these problems may last.

When used in female animals, IMPAVIDO caused abnormal changes to their menstrual cycles. IMPAVIDO may cause fertility problems in females.

Talk to your healthcare provider if fertility problems are a concern for you.

- **decreased effectiveness of oral contraceptive pills.** If you take birth control pills, vomiting, diarrhea or both may cause your birth control pills to be less effective at preventing pregnancy. If you have vomiting, diarrhea, or both together while taking IMPAVIDO, use an additional non-oral method of birth control, such as male condoms with spermicide, until you are no longer having vomiting or diarrhea, but do not stop taking IMPAVIDO. Talk with your healthcare provider if you have questions about birth control methods that may be right for you during this time.
- **testicular pain and absent or decreased ejaculation.**
- **kidney problems.** Your healthcare provider will do tests every week and for 4 weeks after your treatment with IMPAVIDO has ended to check your kidneys.
- **liver problems.** Your healthcare provider will do tests to check your liver while you are taking IMPAVIDO.
- **stomach problems.** IMPAVIDO can cause vomiting, diarrhea, and dehydration. Call your healthcare provider right away if you have severe vomiting and diarrhea that does not go away. Drink a lot of fluids to help prevent dehydration or kidney problems if you are having vomiting and diarrhea.
- **decreased platelet count (thrombocytopenia).** Some people who were treated for visceral leishmaniasis had decreased platelets. If you have visceral leishmaniasis, your healthcare provider will check your platelet count while you are taking IMPAVIDO. Tell your healthcare provider if you have unusual bleeding or bruising during treatment with IMPAVIDO. This could be a sign of decreased platelet counts, which may reduce the ability of your blood to clot.
- **severe skin reactions.** IMPAVIDO can cause a rare but serious skin reaction called Stevens-Johnson Syndrome. This may need to be treated in a hospital and may be life-threatening. If you develop a skin rash with blisters, peeling rash, sores in the mouth, hives or any other allergic reactions while taking IMPAVIDO, stop taking IMPAVIDO. Call your healthcare provider right away or get emergency help.

The most common side effects of IMPAVIDO include:

- | | | | |
|----------------------|------------------------|-------------------------|------------------------|
| • nausea | • vomiting | • diarrhea | • stomach pain |
| • decreased appetite | • dizziness | • headache | • sleepiness |
| • skin itching | • abnormal liver tests | • abnormal kidney tests | • motion sickness |
| • fever | • tiredness | • weakness | • enlarged lymph nodes |

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of IMPAVIDO. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store IMPAVIDO?

- Store IMPAVIDO at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect IMPAVIDO from moisture.

Keep IMPAVIDO and all medicines out of the reach of children.

General information about the safe and effective use of IMPAVIDO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use IMPAVIDO for a condition for which it was not prescribed. Do not give IMPAVIDO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMPAVIDO that is written for health professionals.

What are the ingredients in IMPAVIDO?**Active ingredient:** miltefosine**Inactive ingredients:** colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water.**Distributed by:** Profounda, Inc.**PR034-01**

For more information, go to www.IMPAVIDO.com or www.dailymed.nlm.nih.gov, or call 1-866-588-5405.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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