

Summary of Product Characteristics

Boxed Warning: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

IMPAVIDO may cause fetal harm. Fetal death and teratogenicity, occurred in animals administered miltefosine at doses lower than the recommended human dose. Do not administer IMPAVIDO to pregnant women. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing IMPAVIDO.

Advise females of reproductive potential to use effective contraception during therapy and for 5 months after therapy

1. NAME OF THE MEDICINAL PRODUCT

Impavido 10 mg hard capsules Impavido 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 hard capsule contains:

Impavido 10 mg: 10 mg Miltefosine.

Impavido 50 mg: 50 mg Miltefosine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Impavido 10 mg hard capsules

White powder in a red, opaque hard capsule of size 3 with a white imprint „PLB“ on the body and „MILT 10“ on the cap.

Impavido 50 mg hard capsules

White powder in a red, opaque hard capsule of size 2 with a white imprint „PLB“ on the body and „MILT 50“ on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of visceral Leishmaniasis caused by *Leishmania donovani*, indicated in adults and adolescents ≥ 12 years of age weighing ≥ 30 kg (66 lbs).

Treatment of cutaneous Leishmaniasis caused by *Leishmania brasiliensis* complex or *Leishmania mexicana* complex, indicated in adults and adolescents ≥ 12 years of age weighing ≥ 30 kg (66 lbs).

4.2 Posology and method of administration

Impavido hard capsules are for oral use.

The dosage of Impavido hard capsules depends on body weight.

Visceral leishmaniasis

Bodyweight	Daily Dosage	Number of Hard capsules
30 – 31 kg	60 mg	6 hard capsules Impavido 10 mg
32 – 39 kg	80 mg	8 hard capsules Impavido 10 mg
40 kg and above	100 mg	2 hard capsules Impavido 50 mg

No data from clinical studies are available for patients with a bodyweight higher than 67 kg. An increase of the daily dosage to 150 mg (3 hard capsules Impavido 50 mg) could be considered in patients with a bodyweight above 67 kg under monitoring of the tolerability.

Cutaneous leishmaniasis

The daily dosage for children aged 12 years and older with a body weight of at least 30 kg, adolescents and adults with a body weight of lower than 45 kg is 100 mg miltefosine (2 hard capsules Impavido 50 mg).

Patients with a bodyweight higher than 45 kg receive 150 mg miltefosine daily (3 hard capsules Impavido 50 mg).

No data from clinical studies are available for patients with a bodyweight lower than 30 kg.

The hard capsules should be taken with meals. Dosages of 2 - 8 hard capsules per day should be divided into 2 - 3 individual doses to be taken either in the morning and in the evening or in the morning, at noon and in the evening.

The duration of treatment is 28 days. Immunocompromised patients may require prolonged treatment (see section 4.4.)

4.3 Contra-indications

- Hypersensitivity to the active substance or any of the excipients.
- Pre-existing severe damage of liver or kidney function (see section 4.4).
- Sjögren - Larsson Syndrome.
- Pregnancy and women of childbearing potential who do not use a reliable contraception during and up to 5 months after treatment.
- Women who can become pregnant and have not had a pregnancy test. Women who can get pregnant must have a urine or blood pregnancy test before taking Impavido.

4.4 Special warnings and special precautions for use

In immunocompromised patients Impavido may only be used after failure of standard therapy as only limited experience is available on therapeutic use of Impavido in such patients.

In 39 HIV co-infected patients with a mean body weight of 59 kg (range 43 – 99 kg) Impavido was used at a dosage of 100 mg per day for treatment of visceral Leishmaniasis that was recurrent after or refractory to drug therapy. After a mean treatment duration of 55 days (median: 30 days, range 4 – 732 days) 25 patients (65 %) responded to therapy; of these, 16 patients (43 %) showed negative parasitology. 22 patients received at least one further treatment course with similar response rate and tolerability.

The results of a clinical study in cutaneous Leishmaniasis caused by *Leishmania brasiliensis* indicate, that the efficacy of Impavido against this pathogen may be somewhat lower than against other Leishmaniaspecies.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Embryo-Fetal Toxicity

Miltefosine may cause fetal harm. Embryo-fetal toxicity, including death and teratogenicity, 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). Do not use Impavido in pregnant women. Obtain a urine or serum pregnancy test prior to prescribing Impavido to females of reproductive potential. Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after completion of therapy

Data should be collected regarding pregnancy outcomes for 10 years after approval of Impavido (Miltefosine) in women who become pregnant while taking Impavido (Miltefosine) or during 5 months after end of Impavido (Miltefosine) therapy.

Reproductive Effects

Females

Miltefosine caused impaired fertility in rats and reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD based on body surface area comparisons Impavido. The efficacy of Impavido in the treatment of other *Leishmania* species has not been evaluated. Effects on human female fertility have not been formally studied.

Males

Miltefosine caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the MRHD. A higher dose in rats, approximately 1.0 times the MRHD, caused testicular atrophy and impaired fertility that did not fully reverse 10 weeks after drug administration ended.

Scrotal pain and decreased or absent ejaculation during therapy have been reported during Impavido therapy. The effects of Impavido on human male fertility have not been adequately studied.

Data should be collected regarding the effects of Impavido (Miltefosine) on spermatogenesis and male hormones in patients with leishmaniasis receiving Impavido (Miltefosine) treatment. Evaluations will include semen volume, sperm count, sperm concentration and motility as well as evaluation of total testosterone and FSH.

Advise women and men of the animal fertility findings, and that the potential for impaired fertility with Impavido therapy in humans has not been adequately evaluated.

Renal and Hepatic 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.

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.

In patients with clinically significant abnormality in kidney function monitoring should be continued until normalization

Patients with severe damage of liver and kidney functions were not investigated

Sufficient data of patients with mild and moderate impairment of liver and kidney function are not available. Patients with liver values (GOT, GPT, alkaline phosphatase) 3 times and kidney values (serum creatinine, BUN) 1.5 times above the normal range, were excluded from the clinical study.

Gastrointestinal Effects

Vomiting and diarrhea are possible side effects of a therapy with Impavido (see section 4.8). The patients must be instructed that in case of prolonged persistence of these symptoms a sufficient fluid intake must be ensured, to avoid dehydration and consequently the risk of an impaired renal function.

Thrombocytopenia

Thrombocytopenia during therapy has been reported in patients treated for visceral leishmaniasis.

Monitor platelet count during therapy for visceral leishmaniasis

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 additional non-hormonal or alternative method(s) of effective contraception

Stevens - Johns on Syndrome

Stevens-Johnson syndrome has been reported during Impavido therapy. Discontinue Impavido if an exfoliative or bullous rash is noted during therapy.

QT interval

Data should be collected regarding QT interval in leishmaniasis patients receiving Impavido (Miltefosine) treatment to evaluate the effects of Impavido (Miltefosine) on the QT interval. ECGs and PK samples will be obtained to identify potential effects of Impavido (Miltefosine) on the QT interval or other ECG parameters.

Patients weigh more than 75 KG

Data should be collected regarding efficacy outcome and adverse reactions in patients with leishmaniasis who weigh more than 75kg.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated otherwise. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of miltefosine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Impavido is contraindicated in pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during and up to 5 months after treatment. Vomiting and diarrhea are very common side effects of therapy with Impavido and can compromise the efficacy of oral contraception. The patient must be informed by her physician, accordingly. If necessary, suitable alternative methods of contraception must be used.

During pregnancy, visceral leishmaniasis may be life-threatening for the mother and may result in adverse fetal outcomes, including spontaneous abortion, congenital disease due to vertical transmission, small for gestational age newborn, and severe anemia. During pregnancy, cutaneous leishmaniasis may manifest with larger and atypical appearing lesions and may be associated with increased risk for adverse fetal outcomes, including preterm births and stillbirths.

The patient has to be advised to immediately contact her physician for pregnancy testing as soon as there is any suspicion of pregnancy. If the test is positive, the physician and patient must discuss the risks associated with this pregnancy.

Lactation

It is not known whether miltefosine is excreted in the milk. Impavido must not be used during lactation; Breastfeeding should be avoided for 5 months after Impavido therapy.

Fertility

Studies in rats revealed testicular atrophies and an impairment of fertility after the treatment with miltefosine. These results were reversible after a recovery period of 10 weeks. Data with regard to the impact of miltefosine to the fertility in men are not available.

Advise women and men of the animal fertility findings, and that the potential for impaired fertility with Impavido therapy has not been adequately evaluated.

4.7 Effects on ability to drive and use machines

Impavido may cause undesirable effects such as nausea which may impair the patient's ability to concentrate and react properly. In such cases patients should refrain from driving cars and using machines.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are transient gastrointestinal discomfort, vomiting, diarrhea, and 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.

In clinical trials and during therapeutic use at the recommended dosages the following undesirable effects were observed:

Organ systems	Very common (≥1/10)	Common (≥1/100 to <1/10)	Unommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)
Immune system disorders					Stevens Johnson Syndrome
Blood and lymphatic system disorders					Thrombocytopenia
Gastrointestinal disorders	Vomiting, diarrhea, nausea	Anorexia	Abdominal pain		
Hepatobiliary disorders	Increase in liver enzymes (SGOT, SGPT, AP)				
Renal and urinary disorders		Increase of BUN and creatinine			

Reporting of suspected adverse reactions

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

A specific antidote against miltefosine is not known.

Gastrointestinal symptoms (nausea, vomiting, loss of appetite) are to be expected in case of acute overdose. Adverse effects on liver, kidney, and retinal function cannot be excluded in case of substantial 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoal, ATC code: P01CX

Miltefosine has a marked direct antileishmanial activity *in vitro* and in animal models. *Leishmania donovani* was the most sensitive species in promastigote and amastigote test systems, with the ED₅₀ concentrations around 1 µmol/l. For promastigotes the sensitivity decreased in the following order: *Leishmania donovani* > *Leishmania aethiopica* > *Leishmania tropica* > *Leishmania panamensis* > *Leishmania mexicana* > *Leishmania major*. For amastigotes the ranking was: *Leishmania donovani* > *Leishmania aethiopica* > *Leishmania tropica* > *Leishmania mexicana* > *Leishmania panamensis* > *Leishmania major*.

The specific mode of action of miltefosine in leishmaniasis is unknown. Among others, miltefosine can inhibit the metabolism of phospholipids in cell membranes of parasites.

5.2 Pharmacokinetic properties

Due to the hemolytic nature of miltefosine, no study in humans with intravenous administration can be performed to assess the bioavailability after oral use. In rats and dogs, however, an absolute bioavailability of 82% and 94%, respectively, has been shown with t_{max} values ranging from 4 to 48 h.

Miltefosine is widely distributed in the body, however, without evidence of melanin binding in pigment containing tissues. Placental transfer and excretion in milk have not been investigated but can be assumed.

No data are available from pharmacokinetic studies in healthy subjects. The following table summarizes the results of studies in patients with visceral leishmaniasis. Because of the severity of the disease only limited blood sampling was feasible, particularly in children. Therefore, only a subset of the typical pharmacokinetic parameters could be determined.

Parameter	Adults	Children(above 12 years old)
t_{max}	8 -24 hours	(not determined)
Plasma concentration after repeated dosing	$C_{max,day 23} = 70 \mu\text{g/ml}$ (Dosage: 100 mg/day)	$C_{min,day26-28} = 24 \mu\text{g/ml}^*$ (Dosage: 2.5 mg/kg/day)
$t_{1/2}$	150 - 200 hours	180 hours
Excretion (urine, day 23)	< 0.2% of applied dose	(not determined)

*) The plasma concentrations were determined before dosing on days 26-28; only a small fluctuation of concentrations is expected after repeated dosing.

After repeated dosing accumulation of plasma concentration was lower in children than in adults. No relevant sex differences of pharmacokinetic parameters were observed.

Distribution studies in rats, using radioactively labelled miltefosine, showed highest uptake of radioactivity in kidney, liver and spleen. Slow elimination of radioactivity from tissues (half lives 8-16 days) is partially explained by metabolism of miltefosine and incorporation of the labelled choline fragment into physiological lipids.

No oxidative metabolism by 15 different cytochrome P450 isozymes was observed *in vitro*. No CYP3A induction by miltefosine was found *in vivo*, in rats. Thus, no interaction has to be expected between miltefosine and drugs, like contraceptive hormones, that are metabolised by CYP3A. 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.

Preclinical and clinical studies suggest that only a very minor part of the administered dose will be excreted as the unchanged drug substance. Instead, choline and choline-containing metabolites are the most likely excretion products.

5.3 Preclinical safety data

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 regressive and/or progressive lesions especially affecting the eyes (retinal degeneration), kidneys (acute resp. chronic nephropathy) and organs with rapidly dividing cell tissues (atrophy/hyperplasia), as well as reproductive organs (atrophy). These alterations were observed after 8 weeks treatment at doses of 10 mg/kg/day which led to plasma drug levels of about 52 µg/ml. Juvenile rats were more sensitive than adult rats to the miltefosine induced effects, especially on eyes and kidneys.

Reproduction toxicity

Testicular atrophy and impaired fertility were observed in rats following daily oral doses of 8.25 mg/kg. These findings were reversible within a recovery period of 10 weeks.

Reproductive toxicity studies in rats during the early embryonic development (up to day 7 of pregnancy) indicate an embryotoxic, fetotoxic and teratogenic risk following miltefosine dosages of 1.2 mg/kg/day and higher.

Embryo- and fetotoxic findings were also observed in rabbits after oral administration of miltefosine during the phase of organogenesis (2.4 mg/kg/day and higher).

Mutagenicity/Carcinogenicity

Miltefosine tested negative in 6 of 7 of mutagenicity tests (AMES-Salmonella test, DNA-amplification test, chromosomal aberration test in vitro, UDS-test in vivo/in vitro, 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.

The results of the mutagenicity tests ruled out a genotoxicity-mediated carcinogenic potential of miltefosine. Carcinogenicity studies were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule content:

Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, talc, magnesium stearate

Hard capsule shell:

Gelatin, titanium dioxide, ferric oxide, purified water

Printing ink:

Consisting of shellac, ethanol, propylene glycol, titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and content of container

Impavido 10 mg

Pack with 56 hard capsules sealed in 8 aluminium/aluminium blister strips, each containing 7 hard capsules.

Impavido 50 mg

Packs with 28 and 56 hard capsules sealed in 4 and 8 aluminium/aluminium blister strips, respectively, each containing 7 hard capsules.

6.6 Instructions for use and handling, and disposal

Any unused product or waste material should be disposed in accordance with local requirements.

The hard capsule should not be break, crush, dissolve, or chew Impavido before swallowing.

7. LICENSE HOLDER

Megapharm Ltd, P.O.Box 514, Hod Hasharon, 4510501 Israel

8. MANUFACTURER

Paesel + Lorei GmbH & Co. KG, Rheinberg, Germany.

9. MARKETING AUTHORISATION NUMBERS

Impavido 10 mg: 154-05-34311

Impavido 50 mg: 154-06-34313

The format of this leaflet was determined by the ministry of health and its content was checked and approved in June 2015.