# Summary of Product Characteristics

## 1. NAME OF THE MEDICINAL PRODUCT

Impavido 10 mg capsules
Impavido 50 mg capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule contains:

Impavido 10 mg capsules

10 mg Miltefosine.

Impavido 50 mg capsules

50 mg Miltefosine.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Capsules

Impavido 10 mg 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 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.
Treatment of cutaneous leishmaniasis caused by Leishmania brasiliensis complex or Leishmania mexicana complex.

### 4.2 Posology and method of administration

Posology
The dosage of Impavido capsules depends on the body weight.

*Visceral leishmaniasis*

The daily dose for children aged 3 years and older, adolescents and adults is 1.5 – 2.5 mg/kg body weight as outlined in the following table:

| Body weight | Daily Dosage | Number of Capsules |
|---|---|---|
| 9 – 11 kg | 20 mg | 2 capsules Impavido 10 mg |
| 12 – 16 kg | 30 mg | 3 capsules Impavido 10 mg |
| 17 – 20 kg | 40 mg | 4 capsules Impavido 10 mg |
| 21 – 25 kg | 50 mg | 5 capsules Impavido 10 mg |
| 26 – 31 kg | 60 mg | 6 capsules Impavido 10 mg |
| 32 – 39 kg | 80 mg | 8 capsules Impavido 10 mg |
| 40 kg and above | 100 mg | 2 capsules Impavido 50 mg |

No data from clinical studies are available for patients with a body weight less than 9 kg and higher than 67 kg. An increase of the daily dosage to 150 mg (3 capsules Impavido 50 mg) could be considered in patients with a body weight above 67 kg while monitoring 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 less than 45 kg is 100 mg miltefosine (2 capsules Impavido 50 mg).

Patients with a body weight more than 45 kg receive 150 mg miltefosine daily (3 capsules Impavido 50 mg).

No data from clinical studies are available for patients with a body weight less than 30 kg. A therapy may be considered using the dosages recommended for visceral leishmaniasis.

Method of administration
Impavido capsules are for oral use.

The capsules should be taken with meals. Dosages of 2 – 8 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 Contraindications

- 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 age who do not use a reliable contraception during and up to 3 months after treatment.

## 4.4 Special warnings and special precautions for use

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

In 39 HIV 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 leishmaniasis co-infection 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.

Cutaneous leishmaniasis caused by Leishmania brasiliensis
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 Leishmania species.

Liver and kidney function
Treatment with Impavido may lead to an increase in serum creatinine and liver enzymes (aspartate transaminase [ALT], alanine aminotransferase [AST], alkaline phosphatase [AP]). In a few cases, an increase in blood uric acid has been reported, sometimes with transient gout symptoms. Liver and kidney function must be controlled in weekly intervals. In patients with a clinically significant abnormality in the kidney function monitoring should be continued until normalization.

Patients with severe damage of liver and kidney function were not investigated (see also section 4.3).

Sufficient data of patients with mild and moderate impairment of liver and kidney function are not available. Patients with liver values (AST, ALT, AP) 3 times and kidney values (serum creatinine, blood urea nitrogen [BUN]) 1.5 times above the normal range were excluded from the clinical study.

Gastrointestinal disorders
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.

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

Male fertility

*Spermatogenesis*
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. (see section 4.6).

*Reproductive function*
The effects of these findings on male reproductive rate are not known. Limited data available to date on reproductive performance of 300 male patients who were treated in clinical studies with up to 200 mg Impavido per day for 4 weeks did not indicate an impairment of reproductive performance.

Ocular disorders
Ocular changes are well-known symptoms of leishmaniasis. However, in case reports mainly from South Asia, predominantly in the treatment of post-kala-azar dermal leishmaniasis (PKDL), ocular complications such as unilateral or bilateral keratitis and visual impairment, sometimes permanent, occurred after miltefosine had been administered for a few days or several weeks. In most of these cases, miltefosine had been administered for PKDL during 12 weeks, longer than the recommended therapy duration of 28 days in the treatment of visceral leishmaniasis. In published case reports, patients who developed ocular complications under miltefosine and who were therefore treated with topical glucocorticoids showed an improvement of symptoms.[1,2,3]
Before starting the treatment eyes examination should be considered and the history of ocular disorders should be collected. In case of current or past history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought if feasible. All patients should be informed before starting the treatment that in case of eye problems (e.g. red eyes, eye pain, blurred vision) they should discontinue miltefosine and contact their healthcare professional immediately.
If ocular complications occur and a connection with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since miltefosine has a very long half-life, it is possible that ocular changes will not heal without treatment even after discontinuation of miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid possible permanent damage. See also sections 4.8 and 4.9.

[1] https://dx.doi.org/10.1136/bjophthalmol-2020-317325
[2] https://doi.org/10.1371/journal.pntd.0006781
[3] https://doi.org/10.1177/0049475520929822

## 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 be excluded entirely.

## 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 age have to use effective contraception during and up to 3 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.

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.

Breast Feeding
It is not known whether miltefosine is excreted in the milk. Impavido must not be used during lactation; otherwise breast feeding must be stopped during treatment and for 3 months thereafter.

Fertility
Effects of miltefosine on spermatogenesis were evaluated in an open-label uncontrolled study in a total of 58 adult males with cutaneous or mucosal leishmaniasis who were treated with Impavido for 28 days at a target dose of 2.5 mg/kg/day.

Reductions in semen parameters (ejaculate volume, total sperm count, sperm concentration, sperm morphology, sperm motility) were observed. 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 (refer to section 4.8 and 5.3). No clinically meaningful changes were observed in serum testosterone or FSH concentrations.

Reductions in ejaculate volume, temporary absence of ejaculate, and scrotal tenderness were reported in an observational study with 33 male patients who received Impavido. These adverse reactions resolved in all patients upon completion of Impavido therapy (see section 4.8 and 5.3).

The effects of these findings on male reproductive rate are not known. Limited data available to date on reproductive performance of 300 male patients who were treated in clinical studies with up to 200 mg Impavido per day for 4 weeks did not indicate an impairment of reproductive performance.

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 (refer to section 5.3).

## 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

Most common adverse events
The most commonly reported adverse events are transient gastrointestinal disorders, vomiting, diarrhea, nausea 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.

Tabulated list of adverse events
In clinical trials and during therapeutic use the following adverse events were observed:

| **MedDRA System organ classes** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Uncommon (≥ 1/1.000 to < 1/100)** | **Rare (≥ 1/10.000 to < 1/1.000)** | **Very rare (< 1/10.000)** | **Not known (cannot be estimated from the available data)** |
|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | | | Thrombo-cytopenia | |
| Metabolism and nutrition disorders | | Anorexia | | | | Acute gout (see section 4.4) |
| Eye disorders* | | | | | | Keratitis, keratopathy, acute scleritis, uveitis, ocular hyperaemia (increased ocular vascularity) and visual impairment up to blindness (see section 4.4) |
| Gastro-intestinal disorders | Vomiting, diarrhea, nausea | | Abdominal pain | | | |
| Skin and subcutaneous tissue disorders | | | | | Stevens Johnson Syndrome | |
| Reproductive system and breast disorders | | | | | | scrotal pain, semen volume decreased, absent ejaculation, epididymitis (see section 4.6), |
| General disorders and administration site conditions | | | | | | Malaise, fatigue |
| Investigations | Elevated liver enzymes (AST, ALT, AP) | Increase of BUN and creatinine | | | | Blood uric acid increased (see section 4.4) |

*most cases have been reported for treatment of PKDL, see also section 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the German Federal Institute for Drugs and Medical Devices (BfArM), Pharmacovigilance Department, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany. Website: www.bfarm.de.

### 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoal, ATC code: P01CX

Antileishmanial activity
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 $ED_{50}$ concentrations around 1µmol/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.

Mechanism of action
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.

Cardiac Electrophysiology:
The effect of miltefosine 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.

### 5.2 Pharmacokinetic properties

Absorption
Due to the hemolytic nature of miltefosine after intravenous administration, studies in humans to assess the bioavailability after oral use cannot be performed. 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.

Distribution
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.

Pharmacokinetic parameters
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 |
|---|---|---|
| $t_{max}$ | 8 – 24 hours | (not determined) |
| Plasma concentration after repeated dosing | $C_{max,\ day\ 23}$ = 70 µg/ml (Dosage: 100 mg/day) | $C_{min,\ day\ 26-28}$ = 24 µg/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 and metabolism
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 6 – 8 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.

Elimination
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 or 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 (refer to section 4.6).

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 of no 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

Capsule content:
Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, talc, magnesium stearate

Capsule shell:
Gelatine, 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 in the original container in order to protect from moisture.

### 6.5 Nature and content of container

Impavido 10 mg

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

Impavido 50 mg

Packs with 28 and 56 capsules sealed in 4 and 8 aluminium/aluminium blister strips, respectively, each containing 7 capsules.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

## 7. MARKETING AUTHORISATION HOLDER

Paesel + Lorei GmbH & Co. KG
Nordring 11
47495 Rheinberg
Germany

**Sales & Distribution:**
Phone: +49 2843 90260
Email: info@paesel-lorei.de

**Medical Information & Drug Safety:**
Phone: +49 228 710027-73
Email: drugsafety@paesel-lorei.de

**Product information in multiple languages:**
www.miltefosine-impavido.de

## 8. MARKETING AUTHORISATION NUMBERS

Impavido 10 mg: 56589.00.00

Impavido 50 mg: 56589.01.00

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2004
Date of last renewal of authorisation: 14 March 2013

## 10. DATE OF REVISION OF THE TEXT

September 2024

## 11. PRESCRIPTION STATUS/PHARMACY REQUIREMENT

Prescription only.

This medicinal product contains a substance whose effect in the authorized indications is not yet generally understood in the medical science.