

## 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

Impavido capsules are for oral use.

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:

<b>Body weight</b>	<b>Daily Dosage</b>	<b>Number of Capsules</b>
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.

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 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 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**

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.

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.

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, alkaline phosphatase) 3 times and kidney values (serum creatinine, BUN) 1.5 times above the normal range were excluded from the clinical study.

Toxicological studies have shown an impairment of the reproductive function in male rats (see section 5.3). Data 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 effect on fertility.

Treatment with Impavido may lead to an increase in serum creatinine and liver enzymes. 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.

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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ocular changes such as keratitis are well-known symptoms of leishmaniasis. However, in a few case reports, particularly in the treatment of post-kala-azar dermal leishmaniasis (PKDL), ocular complications occurred after miltefosine had been administered for several weeks. In most of these cases, miltefosine had been administered for longer than the recommended therapy duration of 28 days. In published case reports, patients who developed ocular complications under miltefosine and who were therefore treated with topical glucocorticoids showed an improvement of symptoms.<sup>1,2,3</sup> 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.

<sup>1</sup> <https://dx.doi.org/10.1136/bjophthalmol-2020-317325>

<sup>2</sup> <https://doi.org/10.1371/journal.pntd.0006781>

<sup>3</sup> <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.

### 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.

### **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 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.

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

<b>Organ systems</b>	<b>Very common (≥ 1/10)</b>	<b>Common (≥ 1/100 to &lt; 1/10)</b>	<b>Unommon (≥ 1/1.000 to &lt; 1/100)</b>	<b>Rare (≥ 1/10.000 to &lt; 1/1.000)</b>	<b>Very rare (&lt; 1/10.000)</b>	<b>Not known (cannot be estimated from the available data)</b>
Immune system disorders					Stevens Johnson Syndrome	
Blood and lymphatic system disorders					Thrombocytopenia	
Eye disorders						Keratitis, keratopathy, acute scleritis (see section 4.4)
Gastro-intestinal disorders	Vomiting, diarrhea, nausea	Anorexia	Abdominal pain			
Hepato-biliary disorders	Increase in liver enzymes (AST, ALT, AP)					
Renal and urinary disorders		Increase of BUN and creatinine				

### 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](http://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

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<sub>50</sub> 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 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<sub>max</sub> 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
t <sub>max</sub>	8 – 24 hours	(not determined)
Plasma concentration after repeated dosing	C <sub>max, day 23</sub> = 70 µg/ml (Dosage: 100 mg/day)	C <sub>min, day 26 – 28</sub> = 24 µg/ml *) (Dosage: 2.5 mg/kg/day)
t <sub>1/2</sub>	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 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.

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.

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:

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 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.

### **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

## **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 renewal of authorisation: 14 March 2013

## **10. DATE OF REVISION OF THE TEXT**

December 2020

## **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.