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 excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of visceral Leishmaniasis caused by Leishmania donovani.

4.2 Posology and method of administration

Impavido capsules are for oral use.

The dosage of Impavido capsules depends on body weight. The daily dose for children aged 3 years and older, adolescence and adults is 1.5 – 2.5 mg/kg bodyweight as outlined in the following table:

Bodyweight	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 bodyweight lower 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 bodyweight above 67 kg under monitoring of the tolerability

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 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 4.4 " Special Warnings and Precautions for use").

- Sjögren-Larsson-Syndrome.

- Pregnancy and women of childbearing potential 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 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.

Patients with severe damage of liver and kidney functions were not investigated (see also 4.3 "Contra-indications").

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.

Toxicological studies have shown an impairment of reproductive function in male rats (see 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 clinically significant abnormality in kidney function monitoring should be continued until normalisation.

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 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 5.3).

Impavido is contraindicated in pregnancy (see 4.3). Women of childbearing potential have to use effective contraception during and up to 3 months after treatment.Vomiting and diarrhoea are very common side effects of therapy with Impavido and can compromise the efficacy of oral contraception. The patient must be informed accordingly by her physician. 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.

Lactation

It is not known whether miltefosine is excreted in the milk. Impavido must not be used during lactation; otherwise breast feeding must be stopped.

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, diarrhoea, 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 the following undesirable effects were observed in 475 patients who were treated at the recommended dosages:

Organ systems	**Very common side effects ≥ 10% of patients**	**Common side effects 1 - 10% of patients**	**Unommon side effects 0.1 - 1% of patients**
Gastrointestinal disorders	Vomiting Diarrhoea	Anorexia Nausea	Abdominal pain
Hepato biliary disorders	Increase in liver enzymes (SGOT, SGPT, AP)		
Renal and urinary disorders		Increase of BUN, Creatinine	

In addition one patient was observed with Steven Johnson Syndrome.

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 the 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.

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 into 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 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)	$C_{min,day26-28}$ = 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 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-Larrson syndrome, which is caused by a genetic defect in fatty aldeyhde 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

Collodial anhydrous silica, microcrystalline cellulose, lactose monohydrate, talc, magnesium stearate, gelatin, titanium dioxide, ferric oxide, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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 stripes, each containing 7 capsules.

Impavido 50 mg

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

6.6 Instructions for use and handling, and disposal

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

7. MARKETING AUTHORISATION HOLDER

Zentaris GmbH
Weismüllerstraße 45
D-60314 Frankfurt
Germany

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

19th November 2004

10. DATE OF REVISION OF THE TEXT

January 2005