WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[NT017 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 50mg Miltefosine.

Excipients with potential clinical effect

Each hard gelatin capsule contains 85mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

[NT017 trade name] is a hard gelatin capsules with an opaque blue cap and opaque grey body. They are plain with no markings. They contain white to off-white granular powder. The capsules are to be swallowed whole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[NT017 trade name] is indicated either alone or in combination with other drugs for the treatment of:

- Visceral leishmaniasis due to *Leishmania donovani*
- Cutaneous leishmaniasis due to *L. braziliensis*, *L. guyanensis*, *L. panamensis* or *L. mexicana*

There may be geographic variation in the response of the same *Leishmania* species to [NT017 trade name]. Treatment regimens should take into account the most recent official treatment guidelines (e.g., those of the WHO/PAHO) and local information on infecting species and the likelihood of resistance to Miltefosine.

4.2 Posology and method of administration

Posology

Therapy should be initiated by a health care provider experienced in the treatment of leishmaniasis.

Patients should be advised to take [NT017 trade name] exactly as prescribed and to complete the full course.

Visceral leishmaniasis due to *L. donovani*

[NT017 trade name] is used either alone or in combination with amphotericin B or paromomycin.

The dose of [NT017 trade name] depends on body weight as follows:

Weight	**Dose**
30 to less than 45 kg	One capsule (50 mg) twice daily for 28 consecutive days
45 kg or greater	One capsule (50 mg) three times daily for 28 consecutive days

For children weighing less than 30 kg an alternative product may be needed in order to supply an appropriate dose of Miltefosine.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Visceral leishmaniasis due to *L.donovani*, in HIV-coinfected patients

[NT017 trade name] is used with liposomal amphotericin B. The dose of [NT017 trade name] depends on the geographic location, as shown below:

Patients in East Africa co-infected with HIV

Adults

The dose is one capsule twice a day, for 28 consecutive days.

Children aged 12 years and older

The dose for children weighing less than 25 kg is one capsule once a day for 28 consecutive days.
The dose for children weighing 25-50 kg is one capsule twice daily for 28 consecutive days.

For children aged 2 to 11 years, an alternative product may be needed in order to supply an appropriate dose of Miltefosine.

Patients in South-East Asia co-infected with HIV

Adults

The dose is one capsule twice a day for 14 consecutive days.

Children aged 12 years and older

The dose for children weighing less than 25 kg is one capsule once a day for 14 consecutive days. The dose for children weighing 25-50 kg is one capsule twice daily for 14 consecutive days.

For children aged 2 to 11 years, an alternative product may be needed in order to supply an appropriate dose of Miltefosine.

Cutaneous leishmaniasis

Adults infected with *L. braziliensis, L. guyanensis, L. panamensis or L. mexicana*

The dose of [NT017 trade name] is one capsule taken three times daily for 28 consecutive days.

Children weighing over 45 kg infected with *L. panamensis, L. guyanensis or L. braziliensis.*

The dose of [NT017 trade name] is one capsule taken three times daily for 28 consecutive days.

Miltefosine has also been suggested as an alternative in the treatment of mucosal (mucocutaneous) spread in patients who cannot be given pentavalent antimonials.

Renal impairment

Miltefosine pharmacokinetics have not been studied in patients with renal impairment. Miltefosine is not excreted in urine in significant amounts (see section 5.2), so renal impairment would not be expected to have an important effect on exposure.

Hepatic impairment

Miltefosine pharmacokinetics have not been studied in patients with hepatic impairment.

Missed dose

If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.

Method of administration

[NT017 trade name] should be taken with or directly after meals to reduce gastrointestinal side effects.

4.3 Contraindications

- Hypersensitivity to Miltefosine or any of its excipients
- Pregnancy (see section 4.6)
- Sjögren-Larsson syndrome

4.4 Special warnings and precautions for use

Patients with cutaneous lesions should be advised on how to care for them and how to recognise superinfections of the lesions.

For patients with visceral leishmaniasis hospitalisation and supportive treatment, including rehydration or nutritional supplementation may be required.

Limitations of use

The effectiveness of Miltefosine against some *Leishmania* species has not been established. There may be geographic variation in the response of the same *Leishmania* species to [NT017 trade name].

[NT017 trade name] is not recommended for use in visceral leishmaniasis due to *L. infantum*.

Renal effects

Treatment with [NT017 trade name] may lead to an increase in serum creatinine (see section 4-8). Serum creatinine should be monitored regularly during therapy and for 4 weeks after end of therapy. In patients who develop clinically significant abnormalities in kidney function monitoring should be continued until kidney function returns to normal.

There are no data on the use of [NT017 trade name] in patients with severe renal impairment.

Hepatic effects

Raised liver enzymes may occur during treatment (see section 4-8). Transaminases and bilirubin should be monitored during therapy. (See section 4-8).

Gastrointestinal effects

Vomiting and/or diarrhoea commonly occur during Miltefosine administration and may result in volume depletion. The importance of an adequate fluid intake, especially if such symptoms are prolonged or severe, should be explained to patients so as to reduce their risk of dehydration and renal impairment. Fluid intake should be encouraged to avoid volume depletion.

Effects on the eyes

Ocular changes such as keratitis are well-known symptoms of leishmaniasis. However, there have been some case reports of ocular complications occurring after Miltefosine had been administered for several weeks, particularly in the treatment of post-kala-azar dermal leishmaniasis (PKDL). In most of these cases, Miltefosine had been administered for longer than the recommended therapy duration of 28 days, and symptoms responded to treatment with topical corticosteroids.

If ocular complications occur and a connection with Miltefosine cannot be excluded, Miltefosine treatment should be stopped immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since Miltefosine has a very long half-life, ocular changes may not heal without treatment even after stopping Miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid possible permanent damage. See also sections 4.8 and 4.9.

Thrombocytopenia

Thrombocytopenia may result from therapy with Miltefosine. Platelet count should be monitored during therapy for visceral leishmaniasis.

Stevens-Johnson syndrome

Stevens-Johnson syndrome has been reported during Miltefosine therapy. Discontinue [NT017 trade name] if an exfoliative or bullous rash is noted during therapy.

Excipients

[NT017 trade name] contains lactose. Lactose is a source of glucose and galactose. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients. If, however, you have one of the rare genetic disorders galactosaemia, glucose-galactose intolerance or congenital lactase deficiency you must talk to your health care provider before taking this medicine.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been performed.

Miltefosine is not metabolised by CYP450 enzyme systems, and no pharmacokinetic interactions are expected with medicines that are metabolised by this route.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential/Contraception in females

Women of childbearing age have to use effective contraception during and up to 5 months after treatment. Vomiting and diarrhoea are very common side effects of therapy with [NT017 trade name] and can compromise the efficacy of oral contraception.

The patient must be informed by her health care provider accordingly. If necessary, suitable alternative methods of contraception must be used.

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). Fetal death and teratogenicity, occurred in animals administered Miltefosine at doses lower than the recommended human dose.

[NT017 trade name] is contraindicated in pregnancy (see section 4.3).

Obtain a urine or serum pregnancy test in females of reproductive potential prior to prescribing

The patient has to be advised to immediately contact her health care provider 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. [NT017 trade name] is not recommended during lactation. Discontinue drug or breast feeding depending on importance of drug to mother. Avoid breastfeeding for 5 months after [NT017 trade name] therapy.

Fertility

Studies in rats revealed toxicity (see section 5.3). The potential effects on human fertility have not been adequately evaluated.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for gastrointestinal adverse events (e.g., vomiting, diarrhoea) while taking [NT017 trade name] (see section 4.8), and should be advised not to drive or operate machines if either of these symptoms occur.

4.8 Undesirable effects

The most commonly reported adverse drug reactions with Miltefosine are transient gastrointestinal disorders, vomiting, diarrhoea, 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.

The most serious adverse reactions thought to be associated with Miltefosine use include hyperbilirubinemia (≥10 times the upper limit), diarrhoea (≥10 stools per day), Stevens-Johnson syndrome, and thrombocytopenia. These occurred at the normal recommended doses. In the case of Stevens-Johnson syndrome, therapy with [NT017 trade name] should immediately be stopped (see section 4.4).

The adverse reactions reported in patients treated with Miltefosine are listed below by body system or organ class and frequency. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Gastrointestinal disorders

Very common	Nausea, vomiting, diarrhoea
Common	Decreased appetite
Uncommon	Abdominal pain

Eye disorders

Frequency unknown	Keratitis, keratopathy, acute scleritis

Skin and subcutaneous tissue disorders

Very rare	Stevens-Johnson syndrome

Blood and lymphatic system disorders

Very rare	Thrombocytopenia

Hepatobiliary disorders

Very common	Increased liver enzymes (AST, ALT, AP)
Frequency unknown	Hyperbilirubinemia

Renal and urinary disorders

Very common	Increased BUN and creatinine

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

The common adverse effects of vomiting, diarrhoea, and abdominal pain are likely in case of overdose with [NT017 trade name]. Adequate hydration should be instituted to prevent the risk of impaired renal function, and electrolytes replaced as necessary.

A specific antidote to treat Miltefosine overdose is not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other agents against leishmaniasis and trypanosomiasis, ATC code: P01CX04

Pharmacodynamic effects
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 ED50 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*.

Sensitivity of different *Leishmania* species as well as different strains of a *Leishmania* species to Miltefosine may vary in different geographic regions.

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.

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.

Clinical efficacy: visceral leishmaniasis
The efficacy of Miltefosine was evaluated for the treatment of visceral leishmaniasis, in an area where *L. donovani* was known epidemiologically to be the prevalent infecting species (Bihar, India). Patients ≥ 12 years of age 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 Miltefosine or intravenous amphotericin B deoxycholate.

Patients weighing ≥ 25 kg received one Miltefosine 50-mg capsule with meals twice a day. Patients weighing < 25 kg received one Miltefosine 50-mg capsule with meals once a day in the morning. 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.

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 Miltefosine 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%) Miltefosine 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 Miltefosine 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 Miltefosine and amphotericin B were 94% and 97%, respectively. The results are presented in the table below:

Clinical efficacy results: visceral leishmaniasis

	Miltefosine n = 299	**Amphotericin B deoxycholate n = 99**
End of therapy		
Initial care	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 – Miltefosine) in final cure is (-3.0%, 6.8%).

Clinical efficacy: 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 mm^2.

Patients were randomized to receive Miltefosine or placebo in a 2:1 allocation. Patients who weighed < 45 kg received one Miltefosine 50 mg capsule twice a day, and patients who weighed ≥45 kg received one Miltefosine 50 mg capsule three times a day.

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 Miltefosine was statistically significantly higher than the cure rate for placebo.

Clinical efficacy results: cutaneous leishmaniasis

	Miltefosine	**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 Miltefosine 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 Miltefosine orally for 28 days. Miltefosine 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 > 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 was 27/40 (67.5%) for Manaus, Brazil and 34/40 (85%) for Bahia, Brazil.

5.2 Pharmacokinetic properties

Absorption of [NT017 trade name]

The absorption characteristics of [NT017 trade name] have been determined after administration of a single dose capsule in healthy volunteers in the fed state as follows:

Pharmacokinetic variable'	**Mean value* (± standard deviation)**
	Miltefosine
Maximum concentration (C_{max})	2783 ± 431 ng/mL (2744)
Area under the curve (AUC_{0-t}), a measure of the extent of absorption	151 ± 24 ng.h/mL (149)
Time to attain maximum concentration (t_{max})	13.4 ± 3.9 h

* arithmetic mean

Pharmacokinetics of Miltefosine

General	
	The below data were obtained from leishmaniasis patients.
Absorption	
Oral bioavailability	NA
Food effect	NA
Distribution	
Volume of distribution (mean)	NA
Plasma proteinbinding *in vitro*	98%
Tissue distribution	NA

Metabolism	
	Metabolized by phospholipase D to choline, which is incorporated into tissues, and hexadecanol, which is oxidized to palmitic acid.
Active metabolite(s)	None.
Elimination	
Elimination half life	150 – 200 hours
Mean systemic clearance (Cl/F)	NA
% of dose excreted in urine	< 0.2 %
% of dose excreted in faeces	NA
Drug interactions *(in vitro*)	
Metabolizing enzymes	In vitro studies showed that Miltefosine did not markedly induce or inhibit the activity of the major human cytochrome P450 enzymes.

Renal impairment
Miltefosine pharmacokinetics have not been studied in patients with renal impairment.

Hepatic impairment
Miltefosine pharmacokinetics have not been studied in patients with hepatic impairment.

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.

Reproductive 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 fill : Microcrystalline cellulose
Lactose monohydrate
Colloidal silicon dioxide
Talc and
Magnesium stearate

Capsule shell: Titanium dioxide
Gelatin
Sodium lauryl sulfate
FD&C blue #2/indigo carmine
Iron oxide yellow
Iron oxide red and
Iron oxide black

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *capsule*.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

6.5 Nature and contents of container

Alu/Alu foil blister
[NT017 trade name] is provided in an aluminium on aluminium foil blister cards, each containing 10 capsules. Available in cartons of 10 x 10 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

Zydus Lifesciences Limited
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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

NT017

9. DATE OF PREQUALIFICATION

22 February 2024

10. DATE OF REVISION OF THE TEXT

May 2024

References

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products