This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[NT017 trade name][*]
Manufacturer of Prequalified Product	Zydus Lifesciences Limited Kundaim Industrial Estate, OSD Block – II, Plot No.203-213, Kundaim, Goa-403 115, India
Active Pharmaceutical Ingredient(s) (API)	Miltefosine
Pharmaco-therapeutic group (ATC Code)	Agents against leishmaniasis and trypanosomiasis (P01CX04)
Therapeutic indication	[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.*

1. Introduction

[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.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

Data provided in the dossier show that miltefosine, is a white to an off-white crystalline solid. Solubility data provided indicate that the API is highly soluble according to the BCS. The manufacturer of the API consistently produces an anhydrous crystalline form.

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

The API specifications include tests for description, solubility, identification (IR and HPLC), water content (KF), solubility, pH, assay (HPLC), related substances (HPLC), residual solvents (GC and HSGC) and particle size distribution.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the capsule fill formulation include microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, talc and magnesium stearate. The capsule shell contains titanium dioxide, gelatin, sodium lauryl sulfate, FD&C blue #2/indigo carmine, iron oxide yellow, iron oxide red and iron oxide black. Lactose monohydrate and gelatin are of bovine origin. Magnesium stearate is of vegetable origin. TSE/BSE free certificates from the suppliers have been provided with regard to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[NT017 trade name] are hard gelatin capsules with an opaque blue cap and opaque grey body. They contain white to off-white granular powder. The capsules are packaged in aluminium on aluminium foil blister cards.

The development of the final composition of the capsules has been described. The objective was to develop an immediate release solid oral dosage form, bioequivalent to the WHO recommended comparator product, Impavido® (miltefosine) 50mg capsules. Based on the clinical, pharmacokinetic and physicochemical characteristics as well as in vitro dissolution profiles of the comparator product a quality target product profile was defined and the critical quality attributes were identified. The prototype formulation selection was based on the literature of the comparator product and API-excipient compatibility study; therefore, qualitatively similar excipients were used for development of the multisource product. Due to the API content in the formulation, a dry mixing/blending, lubrication and capsule-filling process which is more convenient and well known to the manufacturer was adopted for manufacturing of the product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and IR), moisture content (KF), average net content, disintegration time, dissolution (HPLC detection), uniformity of dosage units (by weight variation), assay (HPLC), related substances (HPLC) and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. No significant change was observed and all parameters remained well within the agreed limits at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are regarded acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2022 according to internationally accepted guidelines.

Single dose oral bioequivalence study of Miltefosine capsules 50 mg and 'IMPAVIDO®' (miltefosine) capsules 50 mg in healthy adult male subjects under fed conditions (study C1B00193).

The objective of the study was to compare the bioavailability of the stated Miltefosine 50 mg capsule manufactured by Zydus Lifesciences Limited, India (test drug) with the reference formulation Impavido® 50 mg capsule (Paesel + Lorei GmbH & Co. KG) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, parallel study in healthy subjects under fed conditions. Each subject was assigned to receive one of the following treatments in a randomized fashion:

Treatment T:	Test – 1 capsule Miltefosine 50 mg (miltefosine 50 mg) Batch no. GE20082.
Treatment R:	Reference – 1 capsule Impavido® 50 mg (miltefosine 50 mg) Batch no. 0L2153.

Serial blood samples (1 pre-dose sample and 20 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for miltefosine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for miltefosine.

The study was performed with 36 participants; data generated from a total of 36 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for miltefosine as well as statistical results are summarised in the following table:

Miltefosine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	13.4 ± 3.9	15.8 ± 5.9	–	–
C_{max} (ng /mL)	2783 ± 431 (2744)	2861 ± 449 (2826)	97.1	88.1 – 107.1
AUC_{0-t} (µg·h/mL)	151 ± 24 (149)	157 ± 24 (155)	95.9	87.0 – 105.7

The results of the study show that preset acceptance limits of 80 – 125% are met by AUC and C_{max} values regarding miltefosine. Accordingly, the test Miltefosine 50 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Impavido® 50 mg capsule (Paesel + Lorei GmbH & Co. KG).

4. Summary of product safety and efficacy

[NT017 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [NT017 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Impavido® 50 mg capsule (Paesel + Lorei GmbH & Co. KG) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [NT017 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [NT017 trade name] is used in accordance with the SmPC.

Bioequivalence

[NT017 trade name] has been shown to be bioequivalent with Impavido® 50 mg capsule (Paesel + Lorei GmbH & Co. KG).

Efficacy and Safety

Regarding clinical efficacy and safety, [NT017 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [NT017 trade name] was acceptable for the following indication: ' either alone or in combination with other drugs for the treatment of visceral leishmaniasis and cutaneous leishmaniasis', and would allow inclusion of [NT017 trade name], manufactured at Zydus Lifesciences Limited, Kundaim Industrial Estate, OSD Block – II, Kundaim, Goa-403 115, India in the list of prequalified medicinal products.