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	[HA769 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited
Active Pharmaceutical Ingredient (API)	Macleods Pharmaceuticals Limited
Pharmaco-therapeutic group (ATC Code)	Fluorinated cytosine analogue antifungal for systemic use (J02AX01)
Therapeutic indication	[HA769 trade name] is indicated together with other systemic antifungals in the treatment of susceptible severe or systemic fungal infections such as candidiasis, cryptococcosis (including cryptococcal meningitis), chromoblastomycosis and certain forms of aspergillosis.

1. Introduction

[HA769 trade name] is indicated together with other systemic antifungals in the treatment of susceptible severe or systemic fungal infections such as candidiasis, cryptococcosis (including cryptococcal meningitis), chromoblastomycosis and certain forms of aspergillosis. It is given for the oral continuation of parenteral treatment or as an alternative where the parenteral route is not appropriate.

Flucytosine must be used in combination, to minimise the selection of resistant organisms, especially in the treatment of candidiasis and cryptococcosis.

Treatment regimens should take into account the most recent official treatment guidelines (where available) and the susceptibility of the infection.

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 flucytosine, is a white or almost white crystalline powder. Solubility data provided indicate that the API is BCS highly soluble. Flucytosine exhibits polymorphism. The manufacturer of the API consistently produces the polymorphic form-I, which is routinely controlled by p-XRD in the specifications of the API.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and HPLC), clarity and colour of solution, sulfated ash, loss on drying, fluorides, related substances (HPLC), assay (potentiometry), N, N-dimethylaniline content (HPLC; ≤ 1.6ppm), residual solvents (GC), polymorphism (p-XRD) and particle size (laser diffraction).

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

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 tablet formulation include maize starch, povidone, microcrystalline cellulose, crospovidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. TSE/BSE free certificates have been provided for the excipients. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a bevelled edge. The tablet has "K" and "24" debossed (stamped into) and separated by a break line on one side and is plain on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in either plain aluminium foil (laminated with polyethylene film) strip packs or HDPE bottles with childproof plastic (polypropylene) screw caps.

The objective of the product development was to obtain a stable and robust formulation of [HA769 trade name] which is bioequivalent to the WHO recommended comparator product, Ancotil® (flucytosine) tablets 500 mg (Meda Pharma, France). The composition was based on the properties of the API and the excipients that are used in the comparator product. Compatibility studies showed that the API is compatible with the selected excipients. Due to poor flowability and high amount of API in formulation, a wet granulation process was selected for the manufacture of the FFP to improve the flow of the final blend. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

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), water content (KF), hardness, disintegration time, dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC), subdivision of tablets and microbial limits.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data did not show any obvious trend or significant variability for any of the stability indicating parameters. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2020 according to internationally accepted guidelines.

Single dose fasting in-vivo bioequivalence study of [HA769 trade name] (Macleods Pharmaceuticals Ltd., India) to Ancotil® (flucytosine) tablets 500 mg (Meda Pharma, France) in healthy, adult, human subjects (study no. BEQ-2531-FLUC-2019).

The objective of the study was to compare the bioavailability of the stated [HA769 trade name] manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Ancotil® (Meda Pharma, France) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet [HA769 trade name] (flucytosine 500 mg) Batch no. RFA2001B.
Treatment R:	Reference – 1 tablet Ancotil® 500 mg (flucytosine 500 mg) Batch no. 80182617.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for flucytosine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 253 ng/mL for flucytosine.

The study was performed with 24 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Flucytosine

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)	1.38 ± 0.61	1.32 ± 0.60	–	–
C_{max} (ng/mL)	11410 ± 1545 (11307)	11304 ± 2214 (11090)	102.0	95.0 – 109.5
AUC_{0-t} (ng·h/mL)	82351 ± 10570 (81649)	81946 ± 10494 (81264)	100.5	99.0 – 102.0
AUC_{0-inf} (ng·h/mL)	85405 ± 10646 --	84962 ± 10571 --	–	–

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding flucytosine. Accordingly, the test Flucytosine 500 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Ancotil® (Meda Pharma).

4. Summary of product safety and efficacy

[HA769 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, [HA769 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Ancotil® tablets (Meda Pharma) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA769 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 [HA769 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA769 trade name] has been shown to be bioequivalent with Ancotil® tablets (Meda Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA769 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 [HA769 trade name] was acceptable for the following indication: 'susceptible severe or systemic fungal infections such as candidiasis, cryptococcosis (including cryptococcal meningitis), chromoblastomycosis and certain forms of aspergillosis', and would allow inclusion of [HA769 trade name], manufactured at Macleods Pharmaceuticals Limited, Plot No.50 to 54A, SEZ, Phase II, Pithampur, Dhar, Madhya Pradesh, 454774, India in the list of prequalified medicinal products.