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	[HA754 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited
Active Pharmaceutical Ingredient(s) (API)	Flucytosine
Pharmaco-therapeutic group (ATC Code)	Fluorinated cytosine analogue antifungal for systemic use (ATC code: J02AX01)
Therapeutic indication	Severe systemic fungal infections with susceptible pathogens, as an alternative or when switching from parenteral use, particularly: candidiasis, cryptococcosis, chromoblastomycosis and certain forms of aspergillosis.

1. Introduction

[HA754 trade name] is indicated for the treatment of severe systemic fungal infections with susceptible pathogens, as an alternative or when switching from parenteral use, particularly: candidiasis, cryptococcosis, chromoblastomycosis and certain forms of aspergillosis.

Combination with another antifungal agent:

Flucytosine must be used in combination, to avoid as much as possible the selection of resistant organisms, especially in the treatment of candidiasis and cryptococcosis.

Combination with amphotericin B is often synergistic and never antagonistic.

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)

A CEP (Certificate of Suitability) issued by the EDQM was submitted for flucytosine ensuring good manufacturing control and applicability of the respective Ph.Eur monograph to control the quality of the API. Additional user requirements for the BCS low soluble flucytosine include test for particle size distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the tablet formulation include corn starch (maize starch), povidone, partially pregelatinized maize starch, silicon dioxide, microcrystalline cellulose and magnesium stearate. All the excipients are conventional pharmaceutical ingredients included in the formulation at suitable

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

levels and for recognised purposes. None of the excipients are of animal or human origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, flat-faced, round edge tablet debossed with 'M' above the break-line on one side of the tablet and 'FU2' on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are packaged in white HDPE bottles.

Two tablet strengths, proportionally similar in composition and manufactured according to the same procedure, were developed; 500 mg and 250 mg. The development focused on the higher strength which was used in the bioequivalence study.

The goal of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Ancotil® 500mg Tablets (flucytosine). The selection of the excipients was primarily based on the literature search and characteristics of the comparator product, API-excipient compatibility studies and prior experience of manufacturing similar types of solid oral immediate release tablet dosage forms. Flucytosine has very poor flow property; therefore, in order to improve the blend flow, drug distribution and dissolution, a non-aqueous wet granulation was selected as the manufacturing process. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. The multisource product showed dissolution profiles similar to those of the comparator product. Satisfactory in-process controls have been established.

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

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (HPLC and UV), dissolution (UV detection), uniformity of dosage units (by mass variation), assay (HPLC), water content (KF), related substances (HPLC), uniformity of mass (subdivided tablets), residual solvent ethanol (GC) and microbial limits. The test procedures have been adequately validated.

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 package proposed for marketing of the product. The product proved to be stable at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

A randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of [HA754 trade name] (flucytosine tablets 500 mg of Mylan Laboratories Limited, India) with Ancotil 500 mg comprimé (flucytosine tablets) of Meda Pharma 4044 Rue Washington 75008 Paris in normal healthy adult human subjects under fasting conditions (study no. C17220).

The objective of the study was to compare the bioavailability of the stated flucytosine 500 mg tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulation Ancotil® (Meda Pharma) 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 [HA754 trade name]
(flucytosine 500 mg)
Batch no. 2017302.

Treatment R: Reference – 1 tablet Ancotil® 500 mg
(flucytosine 500 mg)
Batch no. 80155790.

A 5 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 24 h 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 100 ng/ml for flucytosine.

The study was performed with 48 participants; data generated from a total of 46 subjects were utilised 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)	1.30 ± 0.61	1.56 ± 1.49	_	_
C_{max} (ng/mL)	12379 ± 2647 (12096)	12743 ± 3547 (12291)	98.4	92.3 – 105.0
AUC_{0-t} (ng·h/mL)	82857 ± 13751 (81747)	83580 ± 15909 (82252)	99.4	96.5 – 102.4
AUC_{0-inf} (ng·h/mL)	88771 ± 14387 (87622)	89025 ± 16886 (87580)	100.1	96.9 – 103.3

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and C_{max} values regarding flucytosine. Accordingly, the test [HA754 trade name] 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).

A biowaiver was granted for the additional 250 mg tablet strength in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the 250 mg tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the API were determined the same.

4. Summary of product safety and efficacy

[HA754 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, [HA754 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Ancotil® (Meda Pharma) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA754 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 [HA754 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA754 trade name] has been shown to be bioequivalent with the comparator product Ancotil® (Meda Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA754 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 [HA754 trade name] was acceptable for the following indication: 'severe systemic fungal infections with susceptible pathogens, as an alternative or when switching from parenteral use, particularly: candidiasis, cryptococcosis, chromoblastomycosis and certain forms of aspergillosis', and would allow inclusion of [HA754 trade name], manufactured at Mylan Laboratories Limited, Pithampur – 454775, Dist. Dhar, Madhya Pradesh, India, in the list of prequalified medicinal products.