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	[HA774 trade name]*
Manufacturer of Prequalified Product	Shouguang Fukang Pharmaceutical Company Limited No. 999, Wensheng East Street Shouguang City Shandong- 262700 China
Active Pharmaceutical Ingredient(s) (API)	Sulfamethoxazole/trimethoprim
Pharmaco-therapeutic group (ATC Code)	Antibacterials for systemic use, combinations of sulfonamides and trimethoprim (sulfamethoxazole and trimethoprim: J01EE01)
Therapeutic indication	[HA774 trade name] is indicated for the treatment of HIV related opportunistic *Pneumocystis jirovecii* pneumonia and toxoplasmosis in patients with HIV infection. It is also used for the prevention of Pneumocystis *jirovecii* pneumonia, toxoplasmosis, malaria and some severe bacterial infections in infants, children and adults with HIV infections.

1. Introduction

[HA774 trade name] is indicated for the treatment of HIV related opportunistic *Pneumocystis jirovecii* pneumonia and toxoplasmosis in patients with HIV infection. It is also used for the prevention of Pneumocystis *jirovecii* pneumonia, toxoplasmosis, malaria and some severe bacterial infections in infants, children and adults with HIV infections.

[HA774 trade name] should be initiated by a health care provider experienced in the management of HIV 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 Ingredients (APIs)

CEPs (Certificates of Suitability) issued by the EDQM were submitted for sulfamethoxazole and trimethoprim ensuring good manufacturing control and applicability of the respective Ph.Eur monographs to control the quality of the APIs. Additional user requirements for the BCS low soluble sulfamethoxazole 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.

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

Other ingredients

Other ingredients used in the tablet formulation include maize starch, lactose monohydrate, hypromellose, sodium starch glycolate, silica colloidal hydrated and magnesium stearate. All the excipients are conventional pharmaceutical ingredients included in the formulation at suitable levels and for recognised purposes. TSE/BSE free certificates have been provided for the excipients. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has 'FULKON 480' debossed (stamped into) on one side and a break line 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 presented in either plastic (PVC) on aluminium foil blister cards or white plastic (HDPE) bottles. Each bottle has a white plastic (HDPE) screw cap.

Two sulfamethoxazole/trimethoprim tablet strengths, proportionally similar in composition, were developed: 800 mg/160 mg and 400 mg/80 mg. The development focused on the higher strength which was used in the bioequivalence study and once the formula was optimized, it was scaled linearly for the lower strength.

The goal of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product, Bactrimel® 800 mg/160 mg tablets. The excipients used in the multisource product were selected based on the excipients used in the comparator product, excipient compatibility studies and use in the finalized manufacturing process i.e, wet granulation. The wet granulation manufacturing process was selected to achieve uniform distribution of the APIs with excipients for the desired compressibility of the tablets. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. 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 are pharmacopoeial based and include tests for appearance, identification of the APIs (IR and HPLC), moisture content, uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), dissolution (HPLC detection), elemental impurities and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The HDPE bottle was shown photoprotective and the blister pack has additional statement to keep tablets in the provided carton. The in-use storage period after first opening of the HDPE 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 2020 according to internationally accepted guidelines:

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of sulfamethoxazole and trimethoprim 800 mg/160 mg tablets of Shouguang Fukang Pharmaceutical Co. Ltd., China and Bactrimel® 800 mg/160 mg (sulfamethoxazole + trimethoprim) tablets of Roche (Hellas) AE, Alamanas 4 & Delphi151 25 Marousi, Attica in healthy, adult, human subjects under fasting condition (study no. 20-VIN-0126).

The objective of the study was to compare the bioavailability of the stated sulfamethoxazole/trimethoprim 800/160 mg FDC tablet manufactured for/by Shouguang Fukang Pharmaceutical Company Limited, China (test drug) with the reference formulation Bactrimel® 800/160 mg tablet (Roche) 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 treatments in a randomized fashion:

Treatment T:	Test – 1 tablet Sulfamethoxazole/trimethoprim 800/160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no.: 21811004
Treatment R:	References – 1 tablet Bactrimel® 800/160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no. R0360B01

A 10-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 22 samples within 72 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 sulfamethoxazole and trimethoprim were analyzed using validated LC-ESI-MS/MS method. The limit of quantification was stated to be about 500 ng/mL for sulfamethoxazole and about 25 ng/mL trimethoprim.

The study was performed with 34 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for sulfamethoxazole and trimethoprim as well as statistical results are summarised in the following tables:

Sulfamethoxazole

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)	2.46 ± 0.84	3.17 ± 0.91	–	–
C_{max} (µg/mL)	46.8 ± 6.3 (46.4)	44.1 ± 8.3 (43.3)	107.0	102.5 – 111.8
AUC_{0-t} (µg·h/mL)	593 ± 83 (587)	578 ± 84 (571)	102.7	100.5 – 105.0
AUC_{0-inf} (µg·h/mL)	608 ± 85 --	593 ± 87 --	-	-

Trimethoprim

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)	1.41 ± 0.81	1.76 ± 1.03	-	-
C_{max} (ng/mL)	1720 ± 395 (1681)	1565 ± 354 (1521)	110.5	103.4 – 118.1
AUC_{0-t} (ng·h/mL)	23396 ± 4561 (22990)	23176 ± 5468 (22627)	101.6	98.5 – 104.8
AUC_{0-inf} (ng·h/mL)	24196 ± 4691 --	23831 ± 5552 --	-	-

The results of the study show that preset acceptance limits of 80 -125% are met by both AUC and C_{max} values regarding sulfamethoxazole and trimethoprim. Accordingly, the test Sulfamethoxazole/ trimethoprim 800/160 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Bactrimel® 800/160 mg (Roche).

A biowaiver was granted for the additional 400/80 mg FDC tablet strength (Shouguang Fukang Pharmaceutical Company Limited China) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Sulfamethoxazole/trimethoprim 400/80 mg FDC 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 APIs were determined the same.

4. Summary of product safety and efficacy

[HA774 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, [HA774 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Bactrimel® 800/160 mg (Roche) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA774 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 [HA774 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA774 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA774 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 [HA774 trade name] was acceptable for the following indication: 'for the treatment and prevention of infections in infants, children and adults with HIV infection', and would allow inclusion of [HA774 trade name], manufactured at Shouguang Fukang Pharmaceutical Company Limited, No. 999, Wensheng East Street place, Shouguang City, Shandong-262700, China in the list of prequalified medicinal products.