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	[HA744 trade name][*]
Manufacturer of Prequalified Product	Ipca Laboratories Limited Plot No.255/1, Village Athal Silvassa 396 230 U.T of Dadra and Nagar Haveli and Daman and Diu,() India
Active Pharmaceutical Ingredients (API)	Sulfamethoxazole/trimethoprim
Pharmaco-therapeutic group (ATC Code)	Antibacterials for systemic use, combinations of sulfonamides and trimethoprim (sulfamethoxazole and trimethoprim: J01EE01)
Therapeutic indication	[HA744 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection.

1. Introduction

[HA744 trade name] is indicated for the treatment of *Pneumocystis jiroveci* pneumonitis (PJP), toxoplasmosis encephalitis, acute otitis media, uncomplicated urinary tract infections, acute exacerbation of chronic bronchitis, nocardiosis or (in combination with another antibacterial) brucellosis, when caused by susceptible organisms in patients with HIV/AIDS. It may also be used for prophylaxis of PJP, toxoplasmosis encephalitis, *Plasmodium falciparum* malaria and susceptible bacterial infections in patients with advanced HIV infection.

Treatment should be prescribed by a health care provider experienced in the management of HIV.

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)

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 tests for polymorphic form and 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 pregelatinized starch, sodium starch glycolate, docusate sodium (mixed with sodium benzoate), and magnesium stearate. All the excipients are conventional pharmaceutical ingredients included in the formulation at suitable 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 coloured, round shaped, uncoated tablet debossed with 'CC' and '7' on either side of break line on one side and plain 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 HDPE bottles and PVdC/PVC-Aluminium blister cards.

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 and once the formula was optimised, 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, Bactrim™ DS 800mg/160mg Tablets. The selection of the excipients was primarily based on the qualitative composition of the comparator product. API-API and API-excipient compatibility studies did not reveal any incompatibilities.

The manufacturing process was by wet granulation using a combination of intra and extra disintegrant quantity with optimum use of solubiliser. Various experiments were performed to select and optimise the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification (HPLC and TLC), disintegration time, average weight, weight of 20 tablets, uniformity of dosage units (by weight variation for sulfamethoxazole and content uniformity for trimethoprim), hardness, friability, assay (HPLC), dissolution (HPLC detection), related substances (HPLC), loss on drying 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 conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with little degradation observed. 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

A biowaiver was granted for the 400 mg/80 mg FDC tablet strength (Ipca Laboratories Limited, India) in accordance with WHO guidelines. In comparison with the strength of the 800 mg/160 mg test product used in the bioequivalence study, the sulfamethoxazole/trimethoprim 400 mg/80 mg FDC tablet was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be the same.

The following bioequivalence study for the 800 mg/160 mg product was performed in 2018 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study of Sulfamethoxazole and Trimethoprim tablets 800 mg + 160 mg of Ipca Laboratories Limited, India with Bactrim™ DS (sulfamethoxazole and trimethoprim) tablets 800 mg/160 mg of Mutual Pharmaceutical Company, Inc. Philadelphia, PA 19124 USA, in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/17/328).

The objective of the study was to compare the bioavailability of the stated sulfamethoxazole/trimethoprim 800 mg/160 mg FDC tablet manufactured for/by Ipca Laboratories Ltd., India (test drug) with the reference formulation Bactrim™ 800 mg/160 mg (Mutual Pharmaceutical Company, Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, 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. HFT0270049
Treatment R: Reference – 1 tablet Bactrim™ 800/160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no. 6751401

A 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 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 a validated LC-MS/MS method. The limit of quantification was stated to be about 1 µg/mL for sulfamethoxazole and about 35 ng/mL for trimethoprim.

The study was performed with 38 participants; data generated from a total of 35 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)#	2.85 ± 0.93	3.02 ± 1.26	–	–
C_{max} (µg/mL)	57.8 ± 11.8 (56.3)	54.9 ± 8.8 (54.3)	103.7	95.6 – 112.4
AUC_{0-t} (µg·h/mL)	787 ± 182 (760)	770 ± 150 (758)	100.3	92.2 – 109.1
AUC_{0-inf} (µg·h/mL)	811 ± 185 --	795 ± 154 --	–	–

Mean range

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)#	2.62 ± 2.47	2.22 ± 0.92	–	–

C_{max} (ng/mL)	1999 ± 455 (1940)	2006 ± 381 (1973)	98.3	90.3 – 107.1
AUC_{0-t} (ng·h/mL)	28556 ± 7458 (27421)	27106 ± 5395 (26605)	103.1	95.3 – 111.5
AUC_{0-inf} (ng·h/mL)	29350 ± 7664 --	27853 ± 5530 --	–	–

Mean range

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 mg/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 Bactrim™ (Mutual Pharmaceutical Company, Inc).

4. Summary of product safety and efficacy

[HA744 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, [HA744 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Bactrim™ (Mutual Pharmaceutical Company, Inc) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA744 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 [HA744 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA744 trade name] is considered to be bioequivalent with Bactrim™ (Mutual Pharmaceutical Company, Inc).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA744 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 [HA744 trade name] was acceptable for the following indication: 'for the treatment of *Pneumocystis jiroveci* pneumonitis (PJP), toxoplasmosis encephalitis, acute otitis media, uncomplicated urinary tract infections, acute exacerbation of chronic bronchitis, nocardiosis or (in combination with another antibacterial) brucellosis, when caused by susceptible organisms in patients with HIV/AIDS, and for prophylaxis of PJP, toxoplasmosis encephalitis, *Plasmodium falciparum* malaria and susceptible bacterial infections in patients with advanced HIV infection.', and would allow inclusion of [HA744 trade name], manufactured at Ipca Laboratories Limited, Silvassa 396 230, India, in the list of prequalified medicinal products.