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	[HA736 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block N2, Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174 101 India
Active Pharmaceutical Ingredient(s) (API)	Sulfamethoxazole/trimethoprim
Pharmaco-therapeutic group (ATC Code)	Combinations of sulfonamides and trimethoprim, incl. derivatives ATC-Code: J01EE01
Therapeutic indication	Treatment of susceptible infections in HIV/AIDS patients; prophylaxis in HIV/AIDS patients of *P. jiroveci* pneumonitis (PJP), toxoplasmosis encephalitis, *Plasmodium falciparum* malaria, and susceptible bacterial infections

1. Introduction

[HA736 trade name] is indicated for the treatment and prophylaxis of opportunistic infections in patients with human immunodeficiency virus-1 (HIV-1) weighing at least 8 kg (see Part 4 summary of products characteristics (SmPC) for full indications).

[HA736 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 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 test for related substances, residual solvents 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 pregelatinised starch, docusate sodium, sodium starch glycolate 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, round, biconvex, uncoated tablet with break line on one 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 clear PVC/PVdC-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 focussed on the higher strength and once the formula was optimised, it was scaled linearly for the lower strength.

The objective of the development of the multisource product was to formulate a stable product bioequivalent to the WHO recommended comparator product, Bactrim™ DS 800 mg/160 mg 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. Sulfamethoxazole and trimethoprim APIs have very poor flow properties; hence the prototype development was initiated by a wet granulation process to improve blend flow and provide uniform distribution of the APIs in the formulation. The dried granules are lubricated and compressed into tablets. 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 include tests for description, identification (TLC and HPLC), uniformity of dosage units (by content uniformity), hardness, water content (KF), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), subdivision of tablet 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 6 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

The following bioequivalence study has been performed in 2018 according to internationally accepted guidelines.

Study title: Single-dose fasting in-vivo bioequivalence study of fixed-dose combination of Sulfamethoxazole and Trimethoprim tablets 800 mg/160 mg (Macleods Pharmaceuticals Ltd, India) to Bactrim™ DS [sulfamethoxazole and trimethoprim (double strength)] tablets USP 800 mg/160 mg

(Sun Pharmaceuticals Industries Inc, USA) in healthy, adult, human subjects (study no. BEQ-2216-SuTr (F)-2017).

The objective of the study was to compare the bioavailability of the stated Sulfamethoxazole/Trimethoprim 800/160 mg FDC tablet manufactured for/by Macleods Pharmaceuticals Ltd, India (test drug) with the reference formulation BactrimTM 800/160 mg (Sun Pharmaceuticals Industries 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. BSA8702A

Treatment R: Reference – 1 tablet Bactrim™ 800/160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg) Batch no. 6851001

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1009 ng/mL for sulfamethoxazole and about 30 ng/mL for trimethoprim.

The study was performed with 24 participants; data generated from a total of 23 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)	2.26 ± 0.72	2.40 ± 0.68	–	–
C_{max} (µg/mL)	51.5 ± 6.4 (51.1)	50.1 ± 6.6 (49.7)	103.0	100.6–105.3
AUC_{0-t} (µg·h/mL)	679 ± 87 (674)	669 ± 98 (662)	101.7	100.3–103.2
AUC_{0-inf} (µg·h/mL)	700 ± 90 –	691 ± 99 –	–	–

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)	1.63 ± 1.09	1.46 ± 0.96	–	–
C_{max} (ng/mL)	1666 ± 332 (1636)	1794 ± 367 (1757)	93.1	87.7–98.9

$AUC_{0\text{-}t}$ (ng·h/mL)	23261 ± 5926 (22516)	23282 ± 6019 (22537)	99.9	97.0–102.9
$AUC_{0\text{-}inf}$ (ng·h/mL)	23990 ± 6207 –	24090 ± 6269 –	–	–

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 Bactrim™ (Sun Pharmaceuticals Industries Inc).

4. Summary of product safety and efficacy

[HA736 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, [HA736 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Bactrim™ (Sun Pharmaceuticals Industries Inc) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA736 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 [HA736 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA736 trade name] has been shown to be bioequivalent with Bactrim™ (Sun Pharmaceuticals Industries Inc).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA736 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 [HA736 trade name] was acceptable for the following indication: **'treatment and prophylaxis of opportunistic infections in patients with human immunodeficiency virus-1 (HIV-1) weighing at least 8 kg'**, and would allow inclusion of [HA736 trade name], manufactured at Macleods Pharmaceuticals Limited, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174 101 India in the list of prequalified medicinal products.