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	[HA686 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No. 11,12 & 13 Special Economic Zone, Pharma Zone Phase-II, Sector-III, Pithampur-454775 Dist. Dhar, Madhya Pradesh India
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	[HA686 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include *pneumocystis jiroveci* pneumonitis, toxoplasmosis encephalitis, *plasmodium falciparum* malaria, norcardiosis, brucellosis and certain bacterial infections.

1. Introduction

[H686 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include pneumocystis jiroveci pneumonitis, toxoplasmosis encephalitis, plasmodium falciparum malaria, norcardiosis, brucellosis and certain bacterial infections.

[HA686 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 particle size distribution, the limits of which were set on the data obtained for the API batches used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the tablet formulation include maize starch, sodium starch glycolate,

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

docusate sodium, hydroxypropyl cellulose 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, bevelled edge tablet debossed with **"M"** above the break line on one side of the tablet and **"ST1"** 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 PVC/PVdC-Aluminium blisters.

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.

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 direct compression process was not considered. The prototype development was initiated by a wet granulation process to improve blend flow and uniform distribution of the APIs in the formulation. The dried granules are compressed into tablets. Various experiments were performed to select and optimize 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 (TLC and HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF), uniformity of mass 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. Data submitted showed that light protection is not needed. 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 2016 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Sulfamethoxazole and Trimethoprim tablets USP 800 mg/160 mg of Mylan Laboratories Limited with that of Bactrim™ DS sulfamethoxazole and trimethoprim (double strength) tablets USP 800/160 mg of AR Scientific, Inc., Philadelphia, PA 19124 USA in healthy adult, human subjects under fasting conditions (study no. 327/14).

The objective of the study was to compare the bioavailability of the stated sulfamethoxazole /trimethoprim 800/160 mg FDC tablet manufactured for/by Mylan Laboratories Limited, India (test

drug) with the reference formulation Bactrim™ 800/160 mg (Mutual Pharmaceutical Co.) 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. 2011738
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 22 samples within 48 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 1002 ng/mL for sulfamethoxazole and about 30 ng/mL for trimethoprim.

The study was performed with 40 participants; data generated from a total of 38 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) #	2.33 (0.67 – 4.5)	2.67 (1.67 – 5.0)	–	–
C_{max} (µg/mL)	57.6 ± 9.7 (56.8)	54.6 ± 8.1 (54.0)	105.1	101.7 – 108.6
AUC_{0-t} (µg·h/mL)	735 ± 104 (728)	724 ± 95 (718)	101.4	99.1 – 103.7
AUC_{0-inf} (µg·h/mL)	758 ± 107 (751)	749 ± 101 (742)	101.2	99.0 – 103.5

median (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) #	2.33 (1.0 – 8.0)	2.33 (0.67 – 8.0)	–	–
C_{max} (ng/mL)	1638 ± 330 (1603)	1665 ± 343 (1629)	98.4	93.9 – 103.1
AUC_{0-t} (ng·h/mL)	24227 ± 4734 (23696)	24402 ± 4907 (23827)	99.4	96.9 – 102.1
AUC_{0-inf} (ng·h/mL)	25195 ± 5309 (24589)	25502 ± 5594 (24831)	99.0	96.4 – 101.7

median (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 800/160 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 Co.).

A biowaiver was granted for the additional 400/80 mg FDC tablet strength (Mylan Laboratories Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the [H686 trade name] 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

[HA686 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, [HA686 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Bactrim™ DS (Mutual Pharmaceutical Co.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA686 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 [HA686 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA686 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, [HA686 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 [HA686 trade name] was acceptable for the following indication: 'for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection', and would allow inclusion of [HA686 trade name], manufactured at Mylan Laboratories Limited, Plot No. 11, 12 & 13, Special Economic Zone, Pharma Zone, Phase-II Sector-III, Pithampur-454775, Dist. Dhar, Madhya Pradesh, India in the list of prequalified medicinal products.