

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	[HA782 trade name]*
Manufacturer of Prequalified Product	Reyoung Pharmaceutical Co., Ltd. Solid Preparation Workshop (316) First Floor of Building B2 Plant B Reyoung Pharmaceutical Co., Ltd. No. 1, Ruiyang Road, Yiyuan County Shandong Province, 256100 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	[HA783 trade name] is indicated for the treatment of HIV related opportunistic <i>Pneumocystis jirovecii</i> pneumonia and toxoplasmosis in patients with HIV infection. It is also used for the prevention of <i>Pneumocystis jirovecii</i> pneumonia, toxoplasmosis, malaria and some severe bacterial infections in infants, children and adults with HIV infections.

1. Introduction

[HA782 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.

[HA782 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

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

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.

Other ingredients

Other ingredients used in the tablet formulation include pregelatinised starch, sodium starch glycolate, docusate sodium and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. Magnesium stearate is of vegetable origin. TSE/BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break line on one side and is plain on the other side. The break line is intended for subdivision of tablet when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in white plastic (HDPE) bottles with white plastic (polypropylene) caps.

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, Bactrim DS 800 mg/160 mg tablets. The excipients used in the multisource product were selected based on the excipients used in the comparator product and excipient compatibility studies. Sulfamethoxazole and trimethoprim 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 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 (TLC and HPLC), dissolution (HPLC detection), content uniformity of tablet halves, moisture content, uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), moisture content (KF) 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. 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 2022 according to internationally accepted guidelines:

An open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, cross over, oral bioequivalence study comparing sulfamethoxazole/trimethoprim tablet 800 mg / 160 mg manufactured by Reyoung Pharmaceutical Co., Ltd., No.1 Ruiyang Road, Yiyuan County, Shandong Province, China with BACTRIM™ DS tablet 800 mg/160 mg (containing 800 mg sulfamethoxazole and 160 mg trimethoprim) of Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512 in healthy, adult, human, subjects under fasting conditions (study no. 132-21).

The objective of the study was to compare the bioavailability of the stated sulfamethoxazole/trimethoprim 800 mg /160 mg FDC tablet manufactured for/by Reyoung Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Bactrim™ DS 800 mg/160 mg tablet (Sun Pharmaceutical Industries, Inc.) 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 mg /160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg)
Batch no.: 21110612

Treatment R: Reference – 1 tablet Bactrim™ DS 800/160 mg (sulfamethoxazole 800 mg + trimethoprim 160 mg)
Batch no. P2083

A 9-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 20 samples within 72 hours 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-MS/MS method. The limit of quantification was stated to be about 200 ng/mL for sulfamethoxazole and about 10 ng/mL for trimethoprim.

The study was performed with 26 participants; data generated from a total of 25 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t _{max} (h)	2.63 ± 1.32	2.13 ± 1.09	-	-
C _{max} (µg/mL)	58.3 ± 8.6 (57.6)	58.8 ± 7.9 (58.2)	98.9	94.3 – 103.8
AUC _{0-t} (µg·h/mL)	882 ± 153 (870)	885 ± 150 (872)	99.7	97.3 – 102.2
AUC _{0-inf} (µg·h/mL)	892 ± 154 --	892 ± 152 --	-	-

*geometric mean

Trimethoprim

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean $\pm$ SD (*)	Reference (R) arithmetic mean $\pm$ SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
$t_{\max}$ (h)	1.28 $\pm$ 0.94	1.49 $\pm$ 1.10	-	-
$C_{\max}$ (ng/ml)	1956 $\pm$ 528 (1894)	1894 $\pm$ 521 (1834)	103.3	94.4 – 113.0
AUC _{0-t} (ng.h/ml)	24173 $\pm$ 5514 (23555)	25242 $\pm$ 5070 (24754)	95.2	90.1 – 100.5
AUC _{0-inf} (ng.h/ml)	24433 $\pm$ 5504 --	25537 $\pm$ 5100 --	-	-

*geometric mean

The results of the study show that the pre-set 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™ DS 800/160 mg (Sun Pharmaceutical Industries, Inc.).

A biowaiver was granted for the additional 400 mg/80 mg FDC tablet strength (Reyoung Pharmaceutical Co., Ltd., China) in accordance with WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the sulfamethoxazole/trimethoprim 400 mg/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

[HA782 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [HA782 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance.

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 [HA782 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA782 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. Hence, [HA782 trade name] and Bactrim™ DS (Sun Pharmaceutical Industries, Inc.) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA782 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 [HA782 trade name] was acceptable for the following indication: ‘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’, and would allow inclusion of [HA782 trade name], manufactured at Reyoung Pharmaceutical Co., Ltd., Solid Preparation Workshop (316), First Floor of Building B2, Plant B Reyoung Pharmaceutical Co., Ltd., No. 1, Ruiyang Road, Yiyuan County, Shandong Province, 256100, China, in the list of prequalified medicinal products.