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	[MA193 trade name][*]
Manufacturer of Prequalified Product	S Kant Healthcare Ltd. Plot No. 1802-1805 G.I.D.C. Phase III, Vapi 396 195 Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine, sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Pyrimethamine, combinations (P01BD51)
Therapeutic indication	[MA193 trade name] is indicated for intermittent preventive treatment of malaria in first or second pregnancy for perennial malaria chemoprevention of children at high risk of severe malaria

1. Introduction

[MA193 trade name] for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas and it is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission

[MA190 trade name] should be initiated by a health care provider experienced in the management of malaria 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*.

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

Active pharmaceutical Ingredients (APIs)

Pyrimethamine and sulfadoxine have been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [MA193 Trade name], are of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, maize starch, povidone, sodium starch glycolate, purified talc and magnesium stearate, all being pharmacopoeial controlled. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin, respectively. TSE/BSE free certificates from the suppliers have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has "525" debossed (stamped into) one side and a break line 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 packaged in either plastic (PVC/PVDC) on aluminium foil blister cards or in HDPE bottles containing a desiccant.

The aim of the product development was to obtain a stable multisource product, bioequivalent to the comparator product, G-Cospe^{TM} (pyrimethamine/ sulfadoxine 25mg/500mg) tablets. The selection of excipients was based on the qualitative composition of the comparator product, API-excipient compatibility studies and the manufacturer's previous formulation experience with [MA145 Trade name] which has been prequalified. Due to the poor flow of the APIs, a wet granulation process using micronized APIs were chosen for manufacturing of the tablets. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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 description, identification of APIs (TLC and HPLC), uniformity of weight, tablet dimensions (diameter and thickness), hardness, disintegration time, water content, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), uniformity of content (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging intended for marketing of the product. The product proved to be quite stable at these storage conditions. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

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.

A randomized, open label, balanced, two-treatment, single oral dose, parallel, truncated, bioequivalence study of Sulfadoxine 500 mg and Pyrimethamine 25 mg tablets of S KANT Healthcare Ltd, with G-Cospe (pyrimethamine /sulfadoxine 25mg/500mg tablets) of Guilin Pharmaceutical Co. Ltd, in normal, healthy, adult, human subjects under fasting condition (study no. ARL/20/027).

The objective of the study was to compare the bioavailability of the stated Pyrimethamine/Sulfadoxine 25/500 mg FDC tablet manufactured for/by S Kant Healthcare ltd., India (test drug) with the reference formulation G-Cospe™ (pyrimethamine/sulfadoxine tablets 25/500 mg, Guilin Pharmaceutical Co., Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, parallel study in healthy subjects under fasting conditions. Each subject was assigned to receive one of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet Pyrimethamine/Sulfadoxine 25/500 (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: WSH22004

Treatment R: References

– 1 tablet G-Cospe™ (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: SP201004

The tablets were administered with 240 ml water. There was no wash-out period as this was a parallel designed study. Serial blood samples (1 pre-dose sample and 19 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 pyrimethamine and sulfadoxine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/ml for pyrimethamine and about 1.2 µg/ml for sulfadoxine.

The study was performed with 24 participants; data generated from a total of 21 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Pyrimethamine

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)#	3.00 (2.00 – 9.00)	2.75 (2.00 – 6.00)	-	-
C_{max} (ng/ml)	188 ± 29 (186)	172 ± 25 (170)	109.5	97.8 – 122.5
AUC_{0-72h} (ng.h/ml)	9917 ± 1851 (9759)	9358 ± 1233 (9289)	105.1	93.0 – 118.7

* geometric mean; #median (range)

Sulfadoxine

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)[#]	3.00 (1.00 – 4.50)	2.00 (1.00 – 4.00)	-	-
C_{max} (µg/ml)	72.0 ± 7.1 (71.6)	66.8 ± 7.1 (66.4)	107.9	99.8 – 116.6
AUC_{0-72h} (µg.h/ml)	4123 ± 455 (4101)	3670 ± 474 (3644)	112.5	103.1 – 122.8

* geometric mean; 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 pyrimethamine and sulfadoxine. Accordingly, the test Pyrimethamine/Sulfadoxine 25/500 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference G- Cospe™ 25/500 mg tablet (Guilin Pharmaceutical Co., Ltd.).

4. Summary of product safety and efficacy

[MA193 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, [MA193 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product G- Cospe™ tablets manufactured by Guilin Pharmaceutical Co., Ltd. China for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA193 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 [MA193 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA193 trade name] has been shown to be bioequivalent with G- Cospe™ tablets manufactured by Guilin Pharmaceutical Co., Ltd. China

Efficacy and Safety

Regarding clinical efficacy and safety, [MA193 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 [MA193 trade name] was acceptable for the following indication: for intermittent preventive treatment of malaria in first or second pregnancy and in infants aged less than 12 months in areas of moderate-to high malaria transmission ., and would allow inclusion of [MA193 trade name], manufactured at S Kant Healthcare Vapi 396 195,Gujarat, India in the list of prequalified medicinal products.