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	[MA113 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co. Ltd. No. 43 Qilidian Road Guilin Guangxi China, 541004
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine and Sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Pyrimethamine, combinations (P01BD51)
Therapeutic indication	[MA113 trade name] is indicated 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 in Africa.

1. Introduction

[MA113 trade name] is indicated for intermittent preventive treatment of malaria in pregnant women and in infants less than 12 months of age.

[MA113 trade name] should be initiated by a health care provider experienced in the management of malaria.

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)

Pyrimethamine

Pyrimethamine has 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 API, used in the manufacture of [MA113 trade name], is 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

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

(APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

The pharmacopoeial based specifications of this API include tests for description, melting range, identification, acidity/alkalinity, particle size distribution, loss on drying, residue on ignition, related substances (HPLC), residual solvents (GC), elemental impurities, assay (HPLC) and microbial limits.

Sulfadoxine

Sulfadoxine has 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 API, used in the manufacture of [MA113 trade name], is 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.

The pharmacopoeial based specifications of this API include tests for description, melting range, identification, particle size distribution, related substances (HPLC), loss on drying, residue on ignition, residual solvents (GC), heavy metals, assay (HPLC) and microbial limits.

Other ingredients

Other ingredients used in the tablet formulation include lactose monohydrate, hyprolose, sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulfate, magnesium stearate, corn starch and hypromellose. None of the materials are from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white round tablet, debossed with "SP" on both sides and a scoreline on one side. The tablets are packed in a PVC/Alu blister card.

The development of the final composition of tablets has been described. The selection of the excipients was based on the physico-chemical characteristics of the APIs and the target product profile. Sodium lauryl sulfate is included to facilitate the dissolution of the APIs, which show poor solubility in water. The wet granulation method is used in manufacture of the tablets. The critical steps of the manufacturing process were optimized to obtain tablets of desired characteristics – including hardness, friability and dissolution – and appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The specifications for [MA113 trade name] are pharmacopoeial based and include tests for description, identification (HPLC and TLC), loss on drying, friability, uniformity of dosage units (by content), dissolution (HPLC detection), related substances (HPLC), assay (HPLC) and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and at accelerated conditions for six months in the same packaging as proposed for marketing of the product. The product proved to be stable at both long term and accelerated storage conditions. 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 2009 according to internationally accepted guidelines.

Sulfadoxine/Pyrimethamine bioequivalence study (study no. C081117-B21).

The objective of the study was to compare the bioavailability of [MA113 trade name] fixed dose combination tablet manufactured by Guilin Pharmaceutical Co., Ltd., China (test drug) with the same dose of the reference fixed dose formulation Fansidar® (Hoffman-La Roche Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, single dose, parallel study in healthy male subjects under fasting conditions. Each subject was assigned to receive one of the following two treatments:

Treatment T: Test – 3 tablets [MA113 trade name]
(pyrimethamine 75 mg + sulfadoxine 1500 mg)
Batch no. SP090202.

Treatment R: Reference – 3 tablets Fansidar® 25mg/500mg
(pyrimethamine 75 mg + sulfadoxine 1500 mg)
Batch no. B1500-50.

Serial blood samples (1 pre-dose sample and 16 samples within 168 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for sulfadoxine and pyrimethamine were analyzed using a validated LC-MS/MS methods. The limit of quantification was stated to be about 500 ng/mLfor sulfadoxine and about 5 ng/mL for pyrimethamine.

The study was performed with 48 participants; data generated from a total of 46 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Sulfadoxine

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)	5.5 (4.0 – 48.0)	10.0 (3.5 – 77.2)	–	–
C_{max} (µg//mL)	183 ± 18 (182)	165 ± 17 (164)	110.9	105.4 – 116.6
$AUC_{0\text{-}72h}$ (µg·h/mL)	11037 ± 1142 (10977)	10537 ± 1137 (10477)	104.8	99.3 – 110.6

Pyrimethamine

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)	5.5 (1.0 – 10.0)	5.5 (2.0 – 10.0)	–	–
C_{max} (µg/mL)	0.55 ± 0.07 (0.54)	0.58 ± 0.08 (0.57)	94.6	88.8 – 100.9
AUC_{0-72h} (µg·h/mL)	29.8 ± 3.4 (29.7)	31.4 ± 4.2 (31.2)	95.1	89.5 – 101.0

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding sulfadoxine and pyrimethamine. Accordingly, the test [MA113 trade name] fixed dose combination tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Fansidar® (Hoffman-La Roche Ltd).

4. Summary of product safety and efficacy

[MA113 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, [MA113 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Fansidar® for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [MA113 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA113 trade name] has shown to be bioequivalent with Fansidar® (pyrimethamine/sulfadoxine 25 mg/500 mg tablets), Hoffman-La Roche Ltd, Switzerland.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA113 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 [MA113 trade name] was acceptable for the following indication: intermittent preventive treatment of malaria in pregnant women and in infants less than 12 months of age, and would allow inclusion of [MA113 trade name], manufactured at Guilin Pharmaceutical Co. Ltd, Oral solid dosage workshop (OSD-I), No. 43 Qilidian Road, Guilin Guangxi, China, 541004 in the list of prequalified medicinal products.