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	[MA180 trade name][*]
Manufacturer of Prequalified Product	Swiss Pharma Nigeria Ltd 5 Dopemu Road Agege-Lagos Ikeja 463 Nigeria
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine / sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarials, pyrimethamine combinations (P01BD51)
Therapeutic indication	[MA180 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas. {DotWP-ProductName} is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine/pyrimethamine is effective. Moderate to high perennial malaria transmission settings are defined as areas with *Plasmodium falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

1. Introduction

[MA180 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas.

{DotWP-ProductName} is also indicated for perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine/pyrimethamine is effective. Moderate to high perennial malaria transmission settings are defined as areas with Plasmodium falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

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

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 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 API, used in the manufacture of [MA180 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients include maize starch, lactose monohydrate, hydroxypropyl cellulose, sodium lauryl sulfate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and colloidal anhydrous silica, all being pharmacopoeial controlled. TSE / BSE free certificate has been provided for lactose monohydrate and magnesium stearate. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has 'SWIPHA SP' debossed (stamped into) one side and a break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies. The tablets are packaged in clear PVC-Alu blisters.

The aim of the product development was to obtain a stable and robust, immediate release solid oral dosage form, bioequivalent to the WHO recommended comparator product, G-COSPE™ pyrimethamine/sulfadoxine 25mg/500mg tablets (Guilin Pharmaceutical Co., Ltd.). The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility data. To ensure compressibility of the high API load of sulfadoxine, blend and content uniformity of the low API load of pyrimethamine, wet granulation is used in manufacture 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. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has 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 (TLC and HPLC), disintegration time, friability, average mass, uniformity of content, subdivision of tablets, water content, assay (HPLC), dissolution (HPLC detection), related substances (HPLC) and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The tablets

showed increasing trend although within limits with respect to water content. 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 2021 according to internationally accepted guidelines.

Comparative, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, open-label bioequivalence study on healthy subjects was adopted to evaluate the bioequivalence of the test product SWIDAR (sulfadoxine / pyrimethamine) 500/25 mg immediate release tablet and the reference product GCOSPE 500/25 mg immediate release tablet, after oral administration to healthy male and non-pregnant female adults under fasting conditions (study no. SUPY-T0121/13).

The objective of the study was to compare the bioavailability of the stated pyrimethamine/sulfadoxine 25 mg/500 mg FDC tablet manufactured for/by Swiss Pharma Nigeria Ltd., Nigeria (test drug) with the reference formulation G-Cospe™ (pyrimethamine/sulfadoxine) 25 mg /500 mg tablets (Guilin Pharmaceutical Co., Ltd.) 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 pyrimethamine/sulfadoxine 25 mg/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: L219164
Treatment R:	Reference – 1 tablet G-Cospe™ 25/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: SP190301

A 45-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 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 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 1.0 µg/mL for sulfadoxine.

The study was performed with 32 participants; data generated from a total of 31 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)	3.41 ± 4.20	3.02 ± 2.29	-	-
C_{max} (ng/mL)	153 ± 30 (149)	144 ± 30 (141)	105.9	101.2 – 110.8
AUC_{0-72h} (ng.h/mL)	8000 ± 1570 (7840)	7620 ± 1470 (7460)	105.0	103.3 – 106.8

* geometric mean

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)	4.09 ± 1.97	3.20 ± 1.46	-	-
C_{max} (µg/mL)	56.3 ± 6.8 (56.0)	56.0 ± 6.1 (55.7)	100.6	98.2 – 103.0
AUC_{0-72h} (µg.h/mL)	3304 ± 468 (3272)	3262 ± 522 (3225)	101.4	99.4 – 103.5

* 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 pyrimethamine and sulfadoxine. Accordingly, the test pyrimethamine/sulfadoxine 25 mg/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

[MA180 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, [MA180 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, G-Cospe™ 25/500 mg tablet (Guilin Pharmaceutical Co., Ltd.), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA180 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 [MA180 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA180 trade name] has been shown to be bioequivalent with G-Cospe™ 25/500 mg tablet (Guilin Pharmaceutical Co., Ltd.).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA180 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 [MA180 trade name] was acceptable for the following indications: ‘intermittent preventive treatment of malaria as part of antenatal care for women in pregnancy in malaria-endemic areas and perennial malaria chemoprevention of children at high risk of severe malaria in areas of moderate to high perennial malaria transmission, where sulfadoxine/pyrimethamine is effective’', and would allow inclusion of [MA180 trade name], manufactured at Swiss Pharma Nigeria Ltd, 5 Dopemu Road, Agege-Lagos, Ikeja 463, Nigeria, in the list of prequalified medicinal products.