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	[MA116 trade name]*
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co. Ltd. No. 43 Qilidian Road Guilin Guangxi, China, 541004
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine hydrochloride, pyrimethamine, sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarial: P01BA06
Therapeutic indication	Seasonal malaria chemoprevention in the sub-sahel region of Africa for children aged 3 to 11 months

1. Introduction

[MA116 trade name] is indicated for the seasonal malaria chemoprevention in the sub-sahel region of Africa for children aged 3 to 11 months.

[MA116 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.*

Active pharmaceutical Ingredient (API)

Amodiaquine hydrochloride, 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 these APIs, used in the manufacture of Amodiaquine (as hydrochloride) 76.5mg dispersible tablets + Pyrimethamine/Sulfadoxine 12.5mg/250mg dispersible tablets (co-blistered), 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

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

Other ingredients

Other ingredients used in Amodiaquine (as hydrochloride) 76.5mg dispersible tablets include povidone, sodium bicarbonate, microcrystalline cellulose, crosslinking carboxymethyl cellulose sodium, sucralose and magnesium stearate. Other ingredients used in Pyrimethamine/Sulfadoxine 12.5mg/250mg dispersible tablets include hypromellose, low-substituted hydroxypropyl cellulose, sucralose and magnesium stearate.

The supplier of magnesium stearate provided written attestation that this excipient is of plant origin and is free from herbicides/insecticides and aflatoxins.

Finished pharmaceutical product (FPP)

The FPP is a co-blistered product, consisting of three Amodiaquine (as hydrochloride) 76.5 mg dispersible tablets and one dosage unit of Pyrimethamine/Sulfadoxine 12.5 mg/250 mg dispersible tablets per PVC/aluminium blister card.

Amodiaquine (as hydrochloride) 76.5 mg dispersible tablets

Pharmaceutical development and manufacture

Amodiaquine Hydrochloride 76.5 mg dispersible tablets are yellow and round, debossed with "AQ" on one side and a score line on the other side.

The development of the final composition of the dispersible tablets has been described. Since rapid dispersion in water is required – without occurrence of large particles – excipients with good disintegration and dissolution properties have been selected. Due to the bitterness and strong acidic properties of amodiaquine hydrochloride a suitable flavouring agent (sucralose) and a pH adjusting agent (sodium bicarbonate) were included in the formula. Acceptable API-excipient compatibility has been demonstrated by stress testing on binary mixtures.

Amodiaquine HCl exhibits poor flow properties and the bulk density data show that the API has poor compressibility. Therefore, an aqueous wet granulation process was selected for manufacture of the tablets. The composition and process parameters were optimised to get tablets of the desired characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The specifications for Amodiaquine (as hydrochloride) 76.5 mg dispersible tablets include tests for description, identification (HPLC, UV), weight variation, content uniformity, disintegration time (≤ 3 min.), fineness of dispersion, dissolution, friability, loss on drying, related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Pyrimethamine/Sulfadoxine 12.5 mg/250 mg dispersible tablets

Pharmaceutical development and manufacture

The tablets are white and round, debossed with "SP" on one side and a score line on the other side.

The development of the final composition of the dispersible tablets has been described. The selection of the excipients was based on the physico-chemical characteristics of the APIs and the target product profile. Sucralose is included to mask the mildly bitter taste of sulfadoxine. 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 disintegration and dissolution – and appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The specifications for Pyrimethamine/Sulfadoxine 12.5 mg/250 mg dispersible tablets include tests for description, identification (HPLC, TLC), uniformity of dosage units (by content), disintegration

time (≤ 3 min.), fineness of dispersion, friability, loss on drying, dissolution (HPLC detection), related substances (HPLC), assay (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 condition and for six months at 40°C/75%RH as accelerated condition in the same packaging as proposed for marketing of the co-blistered product. A slight increase in degradation products were observed, though these stayed well within the agreed limits. The data support the proposed shelf-life and storage conditions as stated in the SmPC for the co-blistered product.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence studies have been performed in 2014 according to internationally accepted guidelines.

Study 1: A randomized, open label, balanced, one period, two treatment, single dose, parallel, truncated, bioequivalence study of FDC dispersible tablets of Sulfadoxine 500 mg and Pyrimethamine 25 mg of Guilin Pharmaceutical Co., Ltd., with Fansidar (sulfadoxine 500 mg and pyrimethamine 25 mg tablets, manufactured by F. Hoffmann-La Roche Ltd. Basel, Switzerland) in normal, healthy, adult, male and female human subjects under fasting condition (study no. ARL/13/487).

The objective of the study was to compare the bioavailability of the stated Sulfadoxine/Pyrimethamine 500 mg/25 mg FDC dispersible tablet manufactured by/for Guilin Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Fansidar® (F. Hoffmann-La Roche Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, parallel study in healthy subjects under fasting conditions. Subjects were assigned to receive one of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 FDC dispersible tablet Sulfadoxine/Pyrimethamine 500 mg/25 mg (sulfadoxine 500 mg + pyrimethamine 25 mg) Batch no. SP131106.
Treatment R:	Reference – 1 tablet Fansidar® (sulfadoxine 500 mg + pyrimethamine 25 mg) Batch no. Z0110.

Serial blood samples (1 pre-dose sample and 19 samples within 72h post dose) were taken during each study treatment period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for sulfadoxine and pyrimethamine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1208 ng/mL for sulfadoxine and 10 ng/mL for pyrimethamine.

The study was performed with 32 participants; data generated from a total of 32 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 tables:

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)	4.16 ± 1.33	11.5 ± 15.	–	–
C_{max} (µg/mL)	70.2 ± 9.2 (69.7)	65.5 ± 4.8 (65.3)	106.7	100.3-113.6
AUC_{0-72}(µg·h/mL)	4125 ± 507 (4096)	3935 ± 212 (3930)	104.2	98.5-110.3

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)	3.84 ± 1.47	4.47 ± 1.77	–	–
C_{max} (µg/mL)	193 ± 29 (191)	178 ± 20 (177)	107.9	99.8-116.5
AUC_{0-72}(ng·h/mL)	9922 ± 1238 (9852)	9323 ± 782 (9292)	106.0	99.6-112.9

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 Sulfadoxine/Pyrimethamine 500 mg/25 mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Fansidar® (F. Hoffmann-La Roche Ltd.).

Study 2: A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Amodiaquine dispersible tablets containing 153 mg amodiaquine base (3×153 mg) manufactured by Guilin Pharmaceutical Co., Ltd., with Amodiaquine tablets 150 mg (3×150 mg) of Guilin Pharmaceutical Co., Ltd., in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/13/485).

The objective of the study was to compare the bioavailability of the stated Amodiaquine 153 mg dispersible tablets manufactured for/by Guilin Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Amodiaquine 150 mg tablets (Guilin Pharmaceutical Co., Ltd.) 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 – 3 tablets Amodiaquine 153 mg (amodiaquine 459 mg)
Batch no. AQ130808

Treatment R: Reference – 3 tablets Amodiaquine 150 mg (amodiaquine 450 mg)
Batch no. AQ130902

A 17-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 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 amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.25 ng/mL for amodiaquine.

The study was performed with 56 participants; data generated from a total of 53 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Amodiaquine

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)	0.81 ± 0.27	1.29 ± 0.64	–	–
C_{max} (µg/mL)	14.7 ± 6.7 (13.4)	13.2 ± 5.9 (12.1)	110.7	102.1-119.9
AUC_{0-72}(ng·h/mL)	104 ± 26 (101)	104 ± 24 (101)	100.3	95.8-105.0
AUC_{0-inf} (ng·h/mL)	116 ± 29 --	113 ± 25 --		

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding amodiaquine. Accordingly, the test Amodiaquine 153 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Amodiaquine 150 mg tablet (Guilin Pharmaceutical Co., Ltd.).

A biowaiver was granted for the additional 250/12.5 mg sulfadoxine/pyrimethamine FDC dispersible tablet strength and the 76.5 mg amodiaquine dispersible tablet strength (Guilin Pharmaceutical Co., Ltd., China) in accordance to WHO guideline. In comparison with the strengths of the test products used in the bioequivalence studies, the Sulfadoxine/Pyrimethamine 250mg/12.5 mg FDC dispersible tablet and the Amodiaquine 76.5 mg dispersible tablet were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths were considered essentially the same and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

According to the submitted data on quality, [MA116 trade name] is a direct scale down of Amodiaquine 153 mg dispersible tablet + Sulfadoxine/Pyrimethamine 500mg/25 mg FDC dispersible tablet. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Fansidar® (F. Hoffmann-La Roche Ltd.) and Amodiaquine 150mg Tablets (Guilin Pharmaceuticals Co., Ltd) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product 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 [MA116 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA116 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, [MA116 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 [MA116 trade name] was acceptable for the following indication: 'for the seasonal malaria chemoprevention in the sub-sahel region of Africa for children aged 3 to 11 months', and would allow inclusion of [MA116 trade name], manufactured at Guilin Pharmaceutical Co. Ltd, No. 43 Qilidian Road, Guilin, Guangxi, China, 541004 in the list of prequalified medicinal products.