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	[MA084 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co. Ltd. OSD-I No. 43, Qilidian Road Guilin, Guangxi 541004 Guilin, China
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine (as hydrochloride) and artesunate
Pharmaco-therapeutic group(ATC Code)	Artemisinin and derivatives, combinations (P01BF03)
Therapeutic indication	[MA084 trade name]is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine as well as to artesunate.

1. Introduction

[MA084 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum.*

[MA084 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)

Amodiaquine hydrochloride

Amodiaquine hydrochloride API is described in the Ph.Int. and the USP and is considered well-established in the WHO Prequalification Programme.

The API specifications are pharmacopoeial based and include tests for appearance, identification, completeness of solution, water content, residue on ignition, chromatographic purity (HPLC), assay (HPLC), residual solvents and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

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

Artesunate

Artesunate API is described in the Ph.Int. Artesunate is manufactured in a two-step process from artemisinin via dihydroartemisinin (artenimol), followed by a purification step. The specifications for the starting material and the intermediate ensure adequate control thereof. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The Ph.Int. based API specifications include tests for description, identification, specific optical rotation, pH value, water content, particle size distribution, sulfated ash, heavy metals, related substances (HPLC), assay (HPLC), residual organic solvents, clarity and colour of solution and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the tablet formulation include calcium carbonate, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone and pregelatinised starch. Magnesium stearate is from vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 176.32 mg amodiaquine hydrochloride equivalent to 135 mg amodiaquine and 50 mg artesunate. The tablet is round, bilayered; the artesunate layer is white and the amodiaquine hydrochloride layer yellow, and the white side is engraved with "50".

The development of the final composition of the tablets has been described. The objective was to develop a robust, stable, immediate release fixed-dose combination product, bioequivalent to the WHO comparator product, Coarsucam® of the same strength. The design of the formulation was based on the characteristics of the APIs. Artesunate proved to be the more sensitive of the two APIs, being degraded at high temperature and humid conditions, especially in acidic environment which may be provided by amodiaquine hydrochloride. Thus it was decided to separate the APIs by developing a bilayered tablet, allowing minimal contact between artesunate and amodiaquine hydrochloride. Calcium carbonate was included in the artesunate layer to protect against a potentially acidic environment. Furthermore, the artesunate layer was obtained through a dry granulation process to protect artesunate against hydrolysis during manufacture.

The process parameters were optimised to obtain tablets of desired characteristics, with dissolution profiles similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data demonstrated the consistency of the process. The tablets are packaged in aluminium-PA/aluminium/PVC blisters to protect against moisture and light.

Three strengths, proportionally similar in composition, were developed: 270 mg/100 mg, 135 mg/50 mg and 67.5 mg/25 mg.

Specifications

The FPP specifications include tests for appearance, identification, average tablet weight, uniformity of dosage units, loss on drying, dissolution, assay (HPLC), related substances (HPLC) and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/70% RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was noted for both APIs, more pronounced for artesunate, though well within the accepted specification limits for assay and degradation products. The data support the proposed shelf-life and 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 2012 according to internationally accepted guidelines.

Artesunate/amodiaquine bioequivalence study (study no. CP1103).

The objective of the study was to compare the bioavailability of artesunate/amodiaquine 100 mg/270 mg fixed-dose combination tablets (Artesun-Plus®, Guilin Pharmaceutical Co., Ltd., China (test drug)) with the same dose of the reference fixed dose combination formulation (ASAQ Winthrop®, Sanofi-Aventis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, replicate, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 2 tablets artesunate/amodiaquine 100 mg/270 mg (artesunate 200 mg + amodiaquine 540 mg) Batch no. SH100701.
Treatment R:	Reference – 2 tablets ASAQ Winthrop® (artesunate 200 mg + amodiaquine 540 mg) Batch no. 5355.

A 7 day wash-out period was observed between each administration. Serial blood samples (1 pre-dose sample and 17 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 artesunate, dihydroartemisinin and amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1 ng/mL for artesunate, 3 ng/mL for its metabolite dihydroartemisinin and 1 ng/mL for amodiaquine.

The study was performed with 36 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 artesunate, dihydroartemisinin and amodiaquine as well as statistical results are summarised in the following tables:

Artesunate

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)**	0.33	0.33	-	-
C_{max} (ng/mL)	309 ± 178 (274)	336 ± 200 (286)	95.9	84.5 – 108.7
AUC_{0-t} (ng.h/mL)	168 ± 60 (157)	180 ± 66 (168)	93.9	87.2 – 101.1
AUC_{0-inf} (ng.h/mL)	177 ± 71 (165)	188 ± 66 (175)	94.2	87.2 – 101.8

* geometric mean; **median

Dihydroartemisinin

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)**	0.50	0.50	-	-

C_{max} (ng/mL)	633 ± 310 (569)	646 ± 275 (591)	96.2	86.8 – 106.6
AUC_{0-t} (ng.h/mL)	981 ± 306 (938)	1060 ± 274 (1021)	91.9	87.4 – 96.6
AUC_{0-inf} (ng.h/mL)	992 ± 305 (949)	1071 ± 272 (1033)	91.9	87.5 – 96.5

* geometric mean; **median

Amodiaquine

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)**	0.50	0.50	-	-
C_{max} (ng/mL)	40.2 ± 20.8 (36.1)	42.4 ± 19.9 (39.0)	95.0	86.7 – 104.1
AUC_{0-t} (ng.h/mL)	321 ± 131 (295)	322 ± 136 (295)	100.0	93.5 – 107.0
AUC_{0-inf} (ng.h/mL)	346 ± 132 (321)	347 ± 137 (321)	100.1	94.2 – 106.4

* geometric mean; **median

Conclusions

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding artesunate, dihydroartemisinin and amodiaquine. Accordingly, the test fixed dose combination tablet artesunate/amodiaquine 100 mg/270 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference ASAQ Winthrop® (Sanofi-Aventis).

A biowaiver was granted for the additional strengths artesunate/amodiaquine 25 mg/67.5 mg and 50 mg/135 mg fixed dose combination tablets (Guilin Pharmaceutical Co., Ltd., China) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the artesunate/amodiaquine 25 mg/67.5 mg and 50 mg/135 mg fixed dose combination tablet strengths were determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same, and the dissolution profiles between the formulations for the APIs were determined to be similar

4. Summary of product safety and efficacy

According to the submitted data on quality [MA084 trade name] is a direct scale-down of Artesun-Plus® (100 mg/270 mg). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with innovator product ASAQ Winthrop® (Sanofi-Aventis) 270 mg/100 mg fixed dose combination tablets (amodiaquine 270 mg + artesunate 100 mg) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this [MA084 trade name] 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 [MA084 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA084 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, [MA084 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [MA084 trade name] was acceptable for the following indication: “treatment of malaria due to *Plasmodium falciparum*” and has advised that the quality, efficacy and safety of [MA084 trade name] and would allow inclusion of [MA084 trade name], manufactured at Guilin Pharmaceutical Co. Ltd., OSD-I, No. 43 Qilidian Road, Guilin, Guangxi, 541004 Guilin, China in the list of prequalified medicinal products