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	[MA202 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co Ltd No. 43, Qilidian Road, Guilin Guangxi – 541 004 China
Active Pharmaceutical Ingredient(s) (API)	Primaquine (as phosphate)
Pharmaco-therapeutic group (ATC Code)	Aminoquinoline anti-protozoal agent (P01BA03)
Therapeutic indication	[MA202 trade name] is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria. [MA202 trade name] is also used in combination with an artemisinin-based combination therapy (ACT) to reduce the transmissibility of *Plasmodium falciparum* infections in low-transmission areas.

1. Introduction

[MA202 trade name] is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria.

Primaquine is used in conjunction with an effective blood schizonticide: either artemisinin-based combination therapy (ACT) or chloroquine for *P. vivax* or *P. ovale* malaria.

Testing for glucose-6-phosphate-dehydrogenase (G6PD) deficiency is needed beforehand to guide appropriate treatment.

[MA202 trade name] is also used in combination with an ACT to reduce the transmissibility of *Plasmodium falciparum* infections in low-transmission areas.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

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 Ingredient (API)

Primaquine phosphate is an orange-red crystalline powder. Solubility data provided indicate that the API is highly soluble according to the BCS. Primaquine phosphate possesses a chiral carbon in the diamine side chain and hence shows stereoisomerism. It exists as both R and S enantiomers, but only preparations containing the racemic mixture, which is also the pharmaceutical form, are commercially available. Polymorphism has not been reported in the literature for primaquine phosphate. The manufacturer of the API consistently produces the racemic mixture (RS).

The API specifications are pharmacopoeial based and include tests for description, identification (IR, HPLC) and pyrophosphate, loss on drying, heavy metals, organic impurities (HPLC), hydrazine hydrate content (GC; ≤ 400ppm), residual solvents, assay (HPLC) and particle size distribution.

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 core tablet formulation include pregelatinized starch, saccharin sodium, orange flavour (containing glucose), microcrystalline cellulose and magnesium stearate, all being controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol- partially hydrolysed, talc, titanium dioxide, glyceryl monocaprylocaprate, sodium lauryl sulfate, iron oxide red, black iron oxide and iron oxide yellow. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break line on one side and is plain 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 data. The tablets are packaged in aluminium foil on aluminium foil blister cards.

Two strengths of Primaquine (as phosphate) dispersible tablets proportionally similar in composition were developed: 5 mg and 2.5 mg. The higher strength was used in the BE study against the WHO recommended comparator product, Primaquine phosphate 15 mg tablets.

The development of the final composition of the multisource product has been described. The objective was to develop a stable, robust, dispersible tablet, bioequivalent to the WHO recommended comparator product. The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The selection of excipients was based on the excipients used in the comparator product, suitability to achieve the desired characteristics of the multisource product and API-excipient compatibility data. Sweetener and flavouring agents were included to make the dispersible tablets more palatable. Since primaquine phosphate has poor flow properties with relatively low concentration in the multisource product, highly soluble, direct compression was selected to manufacture the dispersible tablets. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

A risk assessment has been performed and a risk for nitrosamine impurities has been identified within the FPP manufacture. Confirmatory testing has been performed and N-nitroso-primaquine impurity was identified. A test for this impurity has been included in the FPP specifications.

Specifications

The finished product specifications include tests for description, identification of API (HPLC and UV), content uniformity, fineness of dispersion, disintegration, dissolution (HPLC detection), loss on

drying, N-nitroso-primaquine (LC-MS), 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 storage conditions in the packaging intended for marketing of the product. The data provided indicate that all the tested parameters remained within acceptable limits at both storage conditions, with no obvious trend or variability. 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 2024 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Primaquine (as phosphate) 5 mg dispersible tablets (3 tablets) of Guilin Pharmaceutical Co Ltd, compared to Primaquine (as phosphate) 15 mg tablets of Sanofi-Aventis, in normal, healthy, adult, male and female participants under fasting conditions (study no. ARL/21/196).

The objective of the study was to compare the bioavailability of the stated Primaquine Phosphate 5 mg dispersible tablet manufactured by/for Guilin Pharmaceutical Co Ltd, China (test drug) with the reference formulation Primaquine Phosphate 15 mg tablet, USP (Sanofi-Aventis U.S. LLC) 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 two treatments in a randomized fashion:

Treatment T:	Test – 3 tablets [MA202 trade name] (primaquine 15 mg) Batch no. MB230701.
Treatment R:	Reference – 1 tablet Primaquine phosphate 15 mg USP (primaquine 15 mg) Batch no. 8125520.

The Test tablets were dispersed in 10 mL water (+ 40 mL of rinsing water) and administered. The Reference tablet was administered with 240 mL water. A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 24h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for primaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1 ng/mL for primaquine.

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

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

Primaquine

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)#	2.00 (1.25 – 4.00)	2.00 (1.50 – 4.00)	–	–
C_{max} (ng/mL)	71 ± 22 (68)	75 ± 25 (71)	95.3	88.3 – 103.0
AUC_{0-t} (ng·h/mL)	602 ± 179 (578)	654 ± 210 (623)	92.8	87.8 – 98.0
AUC_{0-inf} (ng·h/mL)	634 ± 186 --	693 ± 222 --	-	-

#median (range)

The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and Cmax values regarding primaquine. Accordingly, the test [MA202 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Primaquine 15 mg tablet USP (Sanofi-Aventis U.S. LLC).

4. Summary of product safety and efficacy

[MA202 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, [MA202 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Primaquine phosphate 15 mg tablet, USP (Sanofi-Aventis U.S. LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA202 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 [MA202 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA202 trade name] has been shown to be bioequivalent with Primaquine phosphate 15 mg tablet, USP (Sanofi-Aventis U.S. LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA202 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 [MA202 trade name] was acceptable for the following indication: 'for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria and in combination with an ACT to reduce the transmissibility of

Plasmodium falciparum infections in low-transmission areas', and would allow inclusion of [MA202 trade name], manufactured at Guilin Pharmaceutical Co Ltd, No. 43, Qilidian Road, Guilin, Guangxi – 541 004 China in the list of prequalified medicinal products.