SCIENTIFIC DISCUSSION

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.

Name of the Finished Pharmaceutical Product:	[MA131 trade name] *
Manufacturer of Prequalified Product:	Guilin Pharmaceutical Co., Ltd Oral Solid Dosage Workshop 1 No. 43, Qilidian Road, Guilin 541004 Guangxi, China
Active Pharmaceutical Ingredient (API):	Dihydroartemisinin /piperaquine phosphate
Pharmaco-therapeutic group (ATC Codes):	Artemisinin and derivatives, combinations (artenimol and piperaquine, P01BF05)
Therapeutic indication:	Indicated for the treatment of uncomplicated malaria in adults, children and infants. [MA131 trade name] is active against all *Plasmodium* parasites that cause malaria in humans

1. Introduction

[MA131 trade name] is indicated for the treatment of uncomplicated malaria in adults, children and infants. [MA131 trade name] is active against all *Plasmodium* parasites that cause malaria in humans. [MA131 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 Ingredients (APIs)

Dihydroartemisinin and piperaquine phosphate (piperaquine tetraphosphate tetrahydrate) 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 [MA131 trade name], 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.

Other ingredients

Other ingredients used in the core tablet formulation include pregelatinized starch, hypromellose, dextrin, croscarmellose sodium and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc and FD& C Blue #2/Indigo carmine aluminium lake. Magnesium stearate is of vegetable

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

origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a blue round, film-coated tablet debossed with a score line on one side. The tablets are presented in PA/Alu/PVC-Alu blisters.

Two strengths of dihydroartemisinin/piperaquine (as phosphate) Tablets proportionally similar in composition were developed: 40mg/320mg and 80mg/640mg. The development focused on the lower strength, which was used in the BE study against the WHO comparator product Eurartesim®, (dihydroartemisinin/piperaquine tetraphosphate 40mg/320mg tablets). Once the formulation for the 40mg/320mg strength was finalized, the 80mg/640mg strength was pursued using dose-proportionality approach.

The aim of the development was to formulate a stable fixed dose combination tablet, which is bioequivalent to the WHO comparator product Eurartesim®. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility studies. Due to the high dose, low solubility, poor flowability of the APIs and thermolability of dihydroartemisinin, the manufacturing process was developed by wet granulation of piperaquine phosphate together with some of the excipients whereafter a mixture of dihydroartemisinin with the remaining excipients was added before the final blend was compressed into tablets. Based on 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.

Specifications

The finished product specifications include tests for description, identification of the APIs (LC-MS, HPLC and UV), loss on drying, uniformity of dosage units (by content), dissolution of dihydroartemisinin (HPLC detection), dissolution of piperaquine phosphate (UV detection), related substances (LC-MS, TLC and HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions. Degradation was observed for dihydroartemisinin at long term storage conditions, with significant changes for assay and degradation products observed at accelerated condition. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable. The tablets must be protected from light and moisture.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

For the 40/320 mg tablet, 2 bioequivalence studies have been performed according to internationally accepted guidelines instead of 1 study, as in 1 of the studies bioequivalence could not be proven for dihydroartemisinin, which necessitated a second study.

The following bioequivalence study have been carried out in 2015:

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, truncated, crossover, bioequivalence study of FDC of Dihydroartemisinin 40 mg and Piperaquine Tetraphosphate 320 mg film-coated tablets of Guilin Pharmaceutical Co., Ltd., with Eurartesim Dihydroartemisinin 40 mg and Piperaquine Tetraphosphate 320 mg film coated tablets, manufactured by Sigma-tau Industrie

Farmaceutiche Riunite S.p.A., Italy in normal, healthy, adult, male human subjects under fasting condition (study no. ARL/14/734).

The objective of the study was to compare the bioavailability of the stated Dihydroartemisinin/ Piperaquine Tetraphosphate 40/320 mg FDC tablet manufactured by/for Guilin Pharmaceutical Co., Ltd, China (test drug) with the reference formulation Eurartesim® (Sigma-tau Industrie Farmaceutiche Riunite S.p.A.) 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–1 tablet Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg (dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg) Batch no. SQ140901.

Treatment R: Reference – 1 tablet Eurartesim® (dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg) Batch no. 130877

A 100 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for dihydroartemisinin and piperaquine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 1.0 ng/ml for dihydroartemisinin and about 0.30 ng/ml for piperaquine.

The study was performed with 120 participants; data generated from a total of 107 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dihydroartemisinin and piperaquine as well as statistical results are summarised in the following tables:

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)	1.45 ± 0.67	1.30 ± 0.71	-	-
C_{max} (ng/ml)	119 ± 58 (107)	102 ± 53 (89)	119.2	109.0 – 130.4
AUC_{0-t} (ng.h/ml)	238 ± 107 (216)	217 ± 100 (198)	109.4	102.3 – 116.9
AUC_{0-inf} (ng.h/ml)	241 ± 108 --	222 ± 100 --	-	-

* geometric mean

Piperaquine

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)	4.17 ± 2.66	4.21 ± 2.69	-	-
C_{max} (ng/ml)	23 ± 13 (21)	23 ± 12 (21)	98.0	91.9 – 104.6
AUC_{0-72h} (ng.h/ml)	678 ± 282 (620)	690 ± 281 (632)	98.1	93.3 – 103.1

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding piperaquine and for AUC values regarding dihydroartemisinin. However for the Cmax values of dihydroartemisinin bioequivalence could not be proven as the results were outside the preset limits of 80 – 125%.

The following bioequivalence study have been carried out in 2016:

A randomized, open label, balanced, two-treatment, four-period, two-sequence, single dose, full replicate crossover study to evaluate bioequivalence for DHA component of the FDC of Dihydroartemisinin 40 mg and Piperaquine Tetraphosphate 320 mg film-coated tablets of Guilin Pharmaceutical Co.,Ltd., and Eurartesim Dihydroartemisinin 40 mg and Piperaquine Tetraphosphate 320 mg film coated tablets, manufactured by Sigma-tau Industrie Farmaceutiche Riunite S.p.A., Italy in normal, healthy, adult, male human subjects under fasting condition. (study no. ARL/15/408).

The objective of the study was to compare the bioavailability of the stated Dihydroartemisinin/ Piperaquine Tetraphosphate 40/320 mg FDC tablet manufactured by/for Guilin Pharmaceutical Co., Ltd, China (test drug) with the reference formulation Eurartesim® (Sigma-tau Industrie Farmaceutiche Riunite S.p.A.) and to assess bioequivalence for dihydroartemisinin only. The comparison was performed as a single centre, open label, randomized, full replicate 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–1 tablet Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg (dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg) Batch no. SQ140901.
Treatment R:	Reference – 1 tablet Eurartesim® (dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg) Batch no. 150246

An at least 3 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 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 dihydroartemisinin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1.0 ng/ml for dihydroartemisinin.

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 dihydroartemisinin as well as statistical results are summarised in the following table:

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)	1.36 ± 0.65	1.30 ± 0.70	-	-
C_{max} (ng/ml)	150 ± 78 (135)	157 ± 70 (141)	95.7	88.1 – 103.8
AUC_{0-t} (ng.h/ml)	282 ± 120 (260)	296 ± 117 (275)	94.5	89.6 – 99.7
AUC_{0-inf} (ng.h/ml)	287 ± 121 --	300 ± 117 --	-	-

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dihydroartemisinin.

Taking into account the results of study ARL/14/734 and ARL/15/408, the overall results indicate that bioequivalence can be considered for dihydroartemisinin. Accordingly, the test Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Eurartesim® (Sigma-tau Industrie Farmaceutiche Riunite S.p.A.).

4. Summary of Product Safety and Efficacy

[MA131 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, [MA131 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, Eurartesim® 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 [MA131 trade name] is used in accordance with the SmPC.

Bioequivalence
[MA131 trade name] has shown to be bioequivalent with Eurartesim® (Sigma-tau Industrie Farmaceutiche Riunite S.p.A.).

Efficacy and Safety
Regarding clinical efficacy and safety, [MA131 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [MA131 trade name] was acceptable for the following indication: “for the treatment of uncomplicated malaria in adults, children and infants”, and has advised that the quality, efficacy and safety of [MA131 trade name] allow inclusion of [MA131 trade name], manufactured at Guilin Pharmaceutical Co., Ltd, Oral Solid Dosage Workshop 1, No. 43, Qilidian Road, Guilin 541004 Guangxi, China, in the list of prequalified medicinal products.