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:	[MA157 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 30 mg/240 mg
Pharmaco-therapeutic group (ATC Code):	Artemisinin and derivatives, combinations (artenimol and piperaquine, P01BF05)
Therapeutic indication:	Indicated for the treatment of uncomplicated malaria in children. [MA157 trade name] is active against all *Plasmodium* parasites that cause malaria in humans

1. Introduction

[MA157 trade name] is indicated for the treatment of uncomplicated malaria in children. [MA157 trade name] is active against all *Plasmodium* parasites that cause malaria in humans.
[See Part 4 Summary of Products Characteristics (SmPC), for full indications].
[MA157 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 [MA157 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 tablet formulation include pregelatinized starch, microcrystalline cellulose, dextrin, croscarmellose sodium, sucralose and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. Magnesium stearate is of vegetable origin. The commercially sourced proprietary sweet and orange flavours which are included in the tablet formulation are supported by appropriate declarations and controlled by

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

acceptable specifications. 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 white or pale yellow, round, tablet debossed with "D" on one side and a score line on the other side. The score-line is not to divide the tablet into equal doses. The tablets are presented in PA/Alu/PVC-Alu blisters.

Three strengths of dihydroartemisinin/piperaquine phosphate dispersible tablets proportionally similar in composition and manufactured from a common blend were developed: 20mg/160mg 30mg/240mg and 40mg/320mg. The development focused on the highest 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 30mg/240mg 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. Sweet and orange flavours were used to improve the taste of the dispersible tablet. Sucralose was used to enhance the sweet taste by masking the bitterness of the APIs. 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 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.

Specifications

The finished product specifications include tests for description, identification of the APIs (LC-MS, HPLC and UV), loss on drying, friability, uniformity of dosage units (by content),disintegration time limit (3 min.), fineness of dispersion, 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 dispersible tablet, 2 bioequivalence studies have been performed according to internationally accepted guidelines, 1 study analysing only dihydroartemisinin and 1 study analysing only piperaquine.

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 dispersible 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/16/074).

The objective of the study was to compare the bioavailability of the stated Dihydroartemisinin/ Piperaquine Tetraphosphate 40/320 mg FDC dispersible 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. The comparison was performed as a single centre, open label, randomized, fully 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 dispersible tablet Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg
(dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg)
Batch no. DS160201.

Treatment R: Reference – 1 tablet Eurartesim®
(dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg)
Batch no. 150246

At least a 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 47 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)	1.27 ± 0.58	1.35 ± 0.75	-	-
C_{max} (ng/ml)	107 ± 54 (93)	119 ± 68 (99)	93.9	86.2 – 102.2
AUC_{0-t} (ng.h/ml)	233 ± 122 (200)	237 ± 127 (202)	99.3	93.8 – 105.0
AUC_{0-inf} (ng.h/ml)	236 ± 122 --	240 ± 128 --	-	-

* 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.

The following bioequivalence study have been carried out in 2016:

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover study to evaluate bioequivalence for PPQ component of the FDC of Dihydroartemisinin 40 mg and Piperaquine Tetraphosphate 320 mg dispersible 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/16/075).

The objective of the study was to compare the bioavailability of the stated Dihydroartemisinin/ Piperaquine Tetraphosphate 40/320 mg FDC dispersible 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 piperaquine. 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 dispersible tablet Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg
(dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg)
Batch no. SQ160702.

Treatment R: Reference – 1 tablet Eurartesim®
(dihydroartemisinin 40 mg + piperaquine tetraphosphate 320 mg)
Batch no. 150246

A 103 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 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 piperaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.3 ng/ml for piperaquine.

The study was performed with 100 participants; data generated from a total of 93 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	3.65 ± 1.97	3.86 ± 1.77	-	-
C_{max} (ng/ml)	28 ± 12 (25)	30 ± 17 (26)	94.7	87.5 – 102.4
AUC_{0-72h} (ng.h/ml)	718 ± 284 (664)	735 ± 281 (679)	97.7	91.9 – 103.9
AUC_{0-inf} (ng.h/ml)	1474 ± 912 --	1460 ± 673 --	-	-

* 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.

Accordingly, the test Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 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 formulation Eurartesim® (Sigma-tau Industrie Farmaceutiche Riunite S.p.A.).

A biowaiver was granted for [MA157 trade name] in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence studies, [MA157 trade name] was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the API were determined the same.

4. Summary of Product Safety and Efficacy

[MA157 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [MA157 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance.
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 [MA157 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA157 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, [MA157 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 [MA157 trade name] was acceptable for the following indication: “for the treatment of malaria in children”, and has advised that the quality, efficacy and safety of [MA157 trade name] allow inclusion of [MA157 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.