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	[MA154 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co., Ltd Oral Solid Dosage Workshop I No. 43, Qilidian Road, Guilin 541004 Guangxi China
Active Pharmaceutical Ingredient(s) (API)	Artemether and Lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA154 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 kg and above.

1. Introduction

[MA154 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 kg and above.

[MA154 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)

Artemether and lumefantrine 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 [MA154 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:

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

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 microcrystalline cellulose, polysorbate, hypromellose, croscarmellose sodium, colloidal silicon dioxide, crospovidone, orange flavour, sucralose, talc and magnesium stearate. Magnesium stearate is of vegetable origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round tablet, plain on both sides with bevelled edges. The tablets are presented in clear PVC/PVDC-Alu blisters.

Three strengths of artemether/lumefantrine dispersible tablets proportionally similar in composition were developed: 20 mg/120 mg, 40 mg/240 mg and 60 mg/360 mg. The formulation development was first realized on the 20 mg/120 mg dispersible tablet and subsequently the formulation for the 40/240 mg and 60 mg/360 mg strengths were obtained using dose-proportionality approach. The highest strength was used in the BE study against the WHO recommended comparator product, Coartem® dispersible tablets (artemether/lumefantrine 20 mg/120 mg).

The aim of the product development was to obtain a stable and robust formulation of artemether/lumefantrine 40 mg/240 mg dispersible tablets, bioequivalent to the comparator product. The comparator product was characterized to define a quality target product profile. The excipients selected were based on the comparator product information, suitability to achieve the desired quality target product profile and API-excipient compatibility studies. Additionally, a sweetener and a flavouring agent were included in the formulation of the dispersible tablets. To improve the flow properties a wet granulation manufacturing process was used for the manufacture of lumefantrine granules. Artemether was incorporated in the extra granular stage to avoid any undue exposure to heat during drying of the wet granules. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the biobatch. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (TLC and HPLC), loss on drying, disintegration time, uniformity of dosage units (by weight variation), related substances (TLC for artemether and HPLC for lumefantrine), average tablet weight, fineness of dispersion, dissolution (HPLC for artemether and UV for lumefantrine), friability, assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated condition in the packaging proposed for marketing of the product. Some degradation was noted for artemether at the long-term storage condition in the proposed packaging configuration. 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 2018 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study of Artemether/Lumefantrine 60 mg/360 mg dispersible tablets (1 tablet) of Guilin Pharmaceutical Co., Ltd. with Coartem (artemether 20 mg + lumefantrine 120 mg dispersible tablet, Novartis) (3 tablets) of Novartis Saglik, Switzerland, in normal, healthy, adult, male and female human subjects under non-fasting condition (ARL/16/099).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 60 mg/360 mg FDC dispersible tablet manufactured for/by Guilin Pharmaceutical Co., Ltd, China (test drug) with the reference formulation Coartem® 20 mg/120 mg dispersible tablet (Novartis) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet Artemether/Lumefantrine 60 mg/360 mg (artemether 60 mg + lumefantrine 360 mg) Batch no. : DL170201

Treatment R: References – 3 tablets Coartem® 20 mg/120 mg (artemether 60 mg + lumefantrine 360 mg) Batch no. K0172B

A 21-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 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 artemether and lumefantrine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/mL for artemether and about 100 ng/mL for lumefantrine.

The study was performed with 60 participants. Data generated from a total of 60 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables artemether and lumefantrine as well as statistical results are summarised in the following tables:

Artemether

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)	3.47 ± 1.11	3.30 ± 1.10	–	–
C_{max} (ng/mL)	141 ± 70 (121)	129 ± 64 (111)	109.0	100.8 – 117.9
AUC_{0-t} (ng·h/mL)	410 ± 194 (350)	377 ± 166 (328)	106.9	100.6 – 113.6
AUC_{0-inf} (ng·h/mL)	431 ± 193 --	390 ± 171 --	–	–

Lumefantrine

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)	6.16 ± 1.16	6.43 ± 1.79	–	–
C_{max} (µg/mL)	11.1 ± 3.7 (10.4)	9.71 ± 3.3 (9.2)	113.8	107.5 – 120.5
AUC_{0-72} (µg·h/mL)	198 ± 80 (183)	182 ± 83 (165)	111.4	105.3 – 117.9

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding artemether and lumefantrine. Accordingly, the test artemether/lumefantrine 60 mg/360 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 Coartem 20 mg/120 mg dispersible tablet (Novartis).

A biowaiver was granted for the additional 20 mg/120 mg and 40 mg/240 mg FDC tablet strengths (Guilin Pharmaceutical Co. Ltd) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Artemether/Lumefantrine 20 mg/120 mg and 40 mg/240 mg FDC tablets were 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 APIs were determined the same.

4. Summary of product safety and efficacy

[MA154 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [MA154 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 [MA154 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA154 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [MA154 trade name] and Coartem® (artemether/lumefantrine 20 mg /120 mg dispersible tablets), of Novartis Saglik, Switzerland, can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA154 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 teamBased on WHO's assessment of data on quality, bioequivalence, safety and efficacy, the team of assessors considered that the benefit-risk profile of [MA154 trade name] was acceptable for the following indication: “treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* patients weighing 15 kg to less than 25 kg or 35 kg and above.” and would allow inclusion of [MA154 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.