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** | [MA155 trade name][*] |
| **Manufacturer of Prequalified Product** | Guilin Pharmaceutical Co., Ltd<br>Oral Solid Dosage Workshop I<br>No. 43, Qilidian Road, Guilin 541004<br>Guangxi, China. |
| **Active Pharmaceutical Ingredient(s) (API)** | Artemether and Lumefantrine |
| **Pharmaco-therapeutic group (ATC Code)** | Artemisinin and derivatives, combinations (P01BF01 |
| **Therapeutic indication** | [MA155 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in children weighing 25 to less than 35 kg. |

## 1. Introduction

[MA155 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing children weighing 25 to less than 35 kg.

[MA155 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 [MA155 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.

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

**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 oval 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 20mg/120mg dispersible tablet and subsequently the formulation for the 40 mg/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 60mg/360mg 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 |
| $AUC_{0-72h}$ (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

[MA155 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, [MA155 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem 20 mg/120 mg dispersible tablet (Novartis) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA155 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 [MA155 trade name] is used in accordance with the SmPC.

### Bioequivalence

[MA155 trade name] has been shown to be bioequivalent with Coartem® of Novartis Saglik.

### Efficacy and Safety

Regarding clinical efficacy and safety, [MA155 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 [MA155 trade name] was acceptable for the following indication: 'treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in in children weighing 25 to less than 35 kg ', and would allow inclusion of [MA155 trade name], manufactured at Guilin Pharmaceutical Co., Ltd, Oral Solid Dosage Workshop I, No. 43 Qilidian Road, Guilin 541004, Guangxi, China in the list of prequalified medicinal products.