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

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| **Name of the Finished Pharmaceutical Product** | [MA165 trade name][*] |
| **Manufacturer of Prequalified Product** | Guilin Pharmaceutical Co., Ltd<br>Oral Solid Dosage Workshop 1<br>No. 43, Qilidian Road, Guilin 541004<br>Guangxi, China |
| **Active Pharmaceutical Ingredient(s) (API)** | Artemether and Lumefantrine |
| **Pharmaco-therapeutic group (ATC Code)** | Antimalarials, blood schizontocide (P01BF01) |
| **Therapeutic indication** | [MA165 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above. |

## 1. Introduction

[MA165 trade name] is indicated in the treatment of malaria, as detailed in the summary of product characteristics.

## 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 assurance that these APIs, used in the manufacture of [MA165 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 microcrystalline cellulose, polysorbate 80, hypromellose, croscarmellose sodium, colloidal silicon dioxide, crospovidone, 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, biconvex, capsule-shaped tablet, debossed with a score line on one side. The tablets are presented in clear PVC/PVDC-Alu blisters.

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

Two strengths of artemether/lumefantrine tablets proportionally similar in composition were developed: 20mg/120mg and 80mg/480mg. The higher strength was used in the bioequivalence study against the WHO recommended comparator product, Coartem® tablets (artemether/lumefantrine 20mg/120mg).

The aim of the product development was to obtain a stable and robust formulation of artemether/lumefantrine 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, talc was added as a lubricant to improve the poor flowability of the APIs. Wet granulation manufacturing process was used to further improve the flow properties of the APIs. 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 pharmacoeia-based finished product specifications include tests for description, identification of the APIs (TLC and HPLC), average tablet weight, friability, content uniformity, dissolution (detection: HPLC for artemether and UV for lumefantrine), loss on drying, related substances (TLC for artemether and HPLC for lumefantrine), 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 2019 according to internationally accepted guidelines.
Study title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single-dose, truncated (for lumefantrine), crossover bioequivalence study of artemether/lumefantrine 80/480mg tablets (1 tablet) of Guilin Pharmaceutical Co., Ltd. with Coartem (artemether 20 mg + lumefantrine 120 mg tablet) (4 tablets) of Zhejiang Medicine Co. Ltd; Xinchang Pharmaceutical Factory; 98 East Xinchang Dadao Road, Xinchang, Zhejiang, P.R. China 312500 in normal, healthy, adult, human subjects under non-fasting condition (study no. ARL/19/013).

The objective of the study was to compare the bioavailability of the stated artemether/lumefantrine 80mg/480mg FDC tablet manufactured for/by Guilin Pharmaceutical Co., Ltd (test drug) with the reference formulation Coartem® 20mg/120mg FDC tablet (Zhejiang Medicine Co. Ltd) 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 each of the following treatments in a randomized fashion:

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|---|---|
| Treatment T: | Test – 1 tablet artemether/lumefantrine 80mg/480 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. : AL190101 |
| Treatment R: | References – 4 tablets Coartem 20mg/120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. APCA338 |

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 53 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.
Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether and lumefantrine as well as statistical results are summarised in the following tables:

**Artemether**

| 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) | 2.76 ± 1.00 | 2.50 ± 0.79 | - | - |
| $C_{max}$ (ng/mL) | 146 ± 71 (128) | 147 ± 78 (128) | 100.3 | 90.1 – 111.6 |
| $AUC_{0-t}$ (ng.h/mL) | 483 ± 237 (418) | 505 ± 276 (439) | 95.2 | 86.2 – 105.2 |
| $AUC_{0-inf}$ (ng.h/mL) | 497 ± 242 -- | 522 ± 283 -- | - | - |

* geometric mean

**Lumefantrine**

| 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) | 5.69 ± 0.62 | 5.66 ± 0.65 | - | - |
| $C_{max}$ (µg/mL) | 6057 ± 1927 (5767) | 6755 ± 2218 (6438) | 89.6 | 83.0 – 96.7 |
| $AUC_{0-72h}$ (µg.h/mL) | 102402 ± 41417 (95057) | 114728 ± 47257 (106398) | 89.3 | 82.7 – 96.4 |

* geometric mean

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values, regarding artemether and lumefantrine. Accordingly, the test artemether/lumefantrine 80mg/480 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® 20mg/120 mg tablet (Zhejiang Medicine Co. Ltd.).

A biowaiver was granted for the additional 20mg/120 mg FDC tablet strength (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 20mg/120 mg FDC tablet was determined to be qualitative essential the same, the ratio of active ingredients 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

[MA165 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, [MA165 trade name] is pharmaceutically and therapeutically equivalent and thus

interchangeable with the comparator product Coartem® (Zhejiang Medicine Co. Ltd) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA165 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 [MA165 trade name] is used in accordance with the SmPC.

**Bioequivalence**
[MA165 trade name] has been shown to be bioequivalent with Coartem® (Zhejiang Medicine Co. Ltd).

**Efficacy and Safety**
Regarding clinical efficacy and safety, [MA165 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 [MA165 trade name] was acceptable for the following indication: '**the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above**', and would allow inclusion of [MA165 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.