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:	[MA168 trade name][1]
Manufacturer of Prequalified Product:	Guilin Pharmaceutical Co., Ltd No. 43, Qilidian Road, Guilin 541004 Guangxi, China.
Active Pharmaceutical Ingredients (APIs):	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarials: artemisinin and derivatives (P01BE03)
Therapeutic indication:	[MA168 trade name] is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children.

1. Introduction

[MA168 trade name], administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children.

[MA168 trade name] should be initiated by a healthcare 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)

Artesunate has 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 the API, used in the

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

manufacture of [MA168 trade name], is 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

The artesunate powder for injection contains no excipient. The solvent for reconstitution contains sodium bicarbonate, arginine, phosphoric acid (for pH adjustment) and water for injection.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a sterile, white crystalline powder, presented in a colourless transparent type I glass vial with grey halogenated butyl rubber stopper, crimped with a blue aluminium-plastic cap. One vial of artesunate powder for injection is packed in a carton box, together with one ampoule of sodium bicarbonate and arginine injection (6mL, sodium bicarbonate 8.4mg/mL and arginine 20mg/mL) as solvent. The powder for injection is dissolved in the solvent for reconstitution and immediately injected intravenously or intramuscularly. The pH of the diluted solution is not higher than 8.5. Artesunate is poorly soluble in water, though it is sufficiently soluble in the solvent to prepare a clear solution.

Artesunate powder for injection is manufactured by dry filling of vials with sterile artesunate. The intermediate sterile artesunate is manufactured from artesunate API: A solution of the API in ethanol is sterile filtered and quenched in sterile filtered water for injection, whereupon the precipitated sterile material is filtered, washed with WFI and freeze dried. All operations are carried out under aseptic conditions and satisfactory operating parameters and in-process controls have been defined. Sufficient validation data were provided. The specification of the intermediate sterile artesunate is Ph.Int. based with additional tests for bacterial endotoxins, sterility, residual ethanol (not more than 2000 ppm), residual benzene (not more than 2 ppm), visible particles, particle size distribution and clarity and colour of solution.

The sodium bicarbonate and arginine injection is manufactured according to standard procedures, applying refined filtration.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The specifications for the artesunate powder for injection include tests for description, identification, clarity and colour of solution, reconstitution time, pH, sub-visible and visible particles, water content, filling quantity variation, content uniformity, related substances (HPLC), bacterial endotoxins, sterility and assay (HPLC). The test procedures have been adequately validated.

Stability testing

Stability studies have been performed on the artesunate powder for injection at 25^{o}C/65%RH, 30^{o}C/75%RH as long-term storage conditions and at accelerated conditions for six months. The data showed little to no change for all attributes at both storage conditions and support the proposed shelf-life and storage conditions

as defined in the SmPC. The product should be protected from light. Stability data supported the proposed hold period for the bulk intermediate sterile artesunate.
Stability studies have been performed on the sodium bicarbonate and arginine injection at 25ºC/65%RH, 30ºC/75%RH as long-term storage conditions and at accelerated conditions for six months. The data support the proposed shelf life and storage conditions as defined in the SmPC.
The reconstituted solution showed acceptable stability, chemically and physically (including visible and sub-visible particles), for an in-use period of one hour at 30ºC. The pH of the diluted solution showed little variation during this period and remained below 8.0.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2028 according to internationally accepted guidelines.

Randomized, open-label, single-dose, cross-over study to evaluate the bioequivalence of a new parenteral formulation of artesunate with the currently used formulation in healthy adult Thai subjects (study no. PHARMA1702 [TCTR20170907002]).

The objective of the study was to compare the bioavailability of a new parenteral formulation of artesunate (artesunate 60 mg for solution for injection, co-packed with diluent arginine 20 mg/mL and sodium bicarbonate 8.4 mg/mL) manufactured by/for Guilin Pharmaceutical Co Ltd., China (test drug) with the reference formulation Artesun® 60 mg, solution for injection (co-packed with diluent sodium bicarbonate 50 mg/mL) (Guilin Pharmaceutical Co Ltd., China). The only difference between the artesunate formulations is the diluent. Bioequivalence was assessed after intramuscular and intravenous administration. The comparison was performed as a single centre, open label, randomized, 4-sequence 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 – artesunate 60 mg, for solution for injection (intravenous injection: artesunate 20 mg/mL; intramuscular injection: 20 mg/mL) Batch no. ZA1170619.
Treatment R:	Reference – Artesun® 60 mg, for solution for injection (intravenous injection: artesunate 10 mg/mL; intramuscular injection: 20 mg/mL) Batch no. ZA1170619.

The test is diluted with sodium bicarbonate (8.4 mg/mL) and arginine (20 mg/mL) to a final concentration of 20 mg/mL for intramuscular and intravenous administration. The reference is diluted with sodium bicarbonate (50 mg/mL) and sodium chloride (9 mg/mL) to a final concentration of 20 mg/mL for intramuscular administration and 10 mg/mL for intravenous administration.
Bolus intramuscular and intravenous injections of artesunate of 2.4 mg/kg were administered.

A 7-day wash-out period was observed between the administrations. Serial blood samples (1 pre-dose sample and 14 samples within 24 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 artesunate and dihydro-artemisinin were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1.2 ng/mL for artesunate and 2.0 ng/mL for dihydro-artemisinin.

The study was performed with 75 participants. Data generated from a total of 72 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.
Arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate and dihydro-artemisinin as well as statistical results are summarised in the following table:

Artesunate after intramuscular administration

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)	0.24 ± 0.12	0.27 ± 0.11	-	-
C_{max} (ng/mL)	1393 ± 347 (1345)	1260 ± 347 (1215)	110.7	104.5 – 117.4
AUC_{0-t} (ng.h/mL)	1044 ± 188 (1026)	978 ± 166 (964)	106.5	103.8 – 109.2
AUC_{0-inf} (ng.h/mL)	1046 ± 188 (1029)	981 ± 167 (966)	106.4	103.8 – 109.1

*geometric mean

Artesunate after intravenous administration

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)	0.080 ± 0.001	0.081 ± 0.004	-	-
C_{max} (ng/mL)	5934 ± 2191 (5568)	7388 ± 3386 (6832)	81.5	74.7 – 88.9
AUC_{0-t} (ng.h/mL)	653 ± 216 (622)	769 ± 297 (725)	85.9	80.1 – 92.0
AUC_{0-inf} (ng.h/mL)	654 ± 216 (623)	770 ± 297 (725)	85.9	80.1 – 92.1

*geometric mean

Dihydro-artemisinin after intramuscular administration

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)	0.67 ± 0.19	0.72 ± 0.20	-	-
C_{max} (ng/mL)	780 ± 192 (756)	724 ± 157 (705)	107.3	102.4 – 112.5
AUC_{0-t} (ng.h/mL)	1795 ± 350 (1760)	1706 ± 332 (1674)	105.1	102.2 – 108.1
AUC_{0-inf} (ng.h/mL)	1815 ± 359 (1779)	1725 ± 339 (1692)	105.1	102.2 – 108.1

*geometric mean

Dihydro-artemisinin after intravenous administration

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)	0.21 ± 0.10	0.21 ± 0.09	-	-
C_{max} (ng/mL)	1892 ± 1107 (1729)	1817 ± 586 (1726)	100.2	92.6 – 108.4
AUC_{0-t} (ng.h/mL)	1964 ± 408 (1922)	1997 ± 436 (1950)	98.6	95.4 – 101.8
AUC_{0-inf} (ng.h/mL)	1985 ± 420 (1942)	2019 ± 447 (1971)	98.5	95.4 – 101.8

*geometric mean

After intramuscular administration, the results of the study show that the acceptance limits of 80 -125% are met by both AUC and C_{max} values regarding artesunate and dihydro-artemisinin.

After intravenous administration, the results of the study show that the acceptance limits of 80 -125% are met by AUC regarding artesunate and AUC and C_{max} values regarding dihydro-artemisinin. Cmax after intravenous administration was lower after administration of the test formulation, which can be attributed to the fact that the test formulation is administered as a bolus injection with a concentration of 20 mg/mL, while the reference formulation is administered as a bolus injection with a lower concentration of 10 mg/mL. Moreover, the test formulation is administered with half the volume as that for the comparator and with the same administration time, which will have also an impact on Cmax. However, the artesunate test and reference vials are similar, only the diluents and dilution factor are different. After intravenous administration, for both products artesunate will be 100% available. The lower Cmax observed for the test formulation after intravenous administration will not have an impact on efficacy as the artesunate reference formulation can also be administered as an intramuscular injection, resulting in a much lower Cmax.

4. Summary of Product Safety and Efficacy

[MA168 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, [MA168 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Artesun® (co-packed with solvent sodium bicarbonate solution and diluent sodium chloride solution) manufactured by Guilin Pharmaceutical Co Ltd., China.

The clinical safety of this product is considered to be acceptable when guidance and restrictions presented 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 clinical performance of the product 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 [MA168 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA168 trade name] has shown to be bioequivalent with Artesun® (co-packed with solvent sodium bicarbonate solution and diluent sodium chloride solution) manufactured by Guilin Pharmaceutical Co Ltd., China.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA168 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics is taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of [MA168 trade name] was acceptable for the following indication: **"for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children"** and has advised that quality, efficacy and safety of [MA168 trade name] allow inclusion of [MA168 trade name], manufactured at Guilin Pharmaceutical Co., Ltd, No. 43, Qilidian Road, Guilin 541004, Guangxi, China, in the list of prequalified medicinal products.