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	[MA200 trade name][*]
Manufacturer of Prequalified Product	Guilin Pharmaceutical Co., Ltd No. 43, Qilidian Road, Guilin 541004 Guangxi, China.
Active Pharmaceutical Ingredient(s) (API)	Artesunate
Pharmaco-therapeutic group (ATC Code)	Antimalarial: artemisinin derivative, ATC Code P01BE03
Therapeutic indication	[MA200 trade name] is indicated for the treatment of severe malaria.

1. Introduction

[MA200 trade name] is indicated for the treatment of severe malaria.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

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)

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 manufacture of [MA200 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 arginine, sodium bicarbonate, phosphoric acid (for pH adjustment) and water for injection.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a sterile, white crystalline powder, presented in a clear colourless type I glass vial with grey halogenated butyl rubber stopper, crimped with a purple aluminium-plastic cap. One vial of Artesunate powder for injection is packed in a carton box, together with one ampoule of arginine and sodium bicarbonate injection (6mL, arginine 20mg/mL and sodium bicarbonate 8.4mg/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 (WFI), 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 visible particles, organic residual solvents (ethanol ≤ 2000 ppm; benzene ≤2ppm), particle size distribution and clarity and colour of solution.

The arginine and sodium bicarbonate 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 is pharmacopoeial-based and include tests for description, identification, pH, reconstitution time, clarity and colour of solution, related substances (HPLC), water content (KF), sub-visible and visible particles, bacterial endotoxins, sterility, filling quantity variation and assay (HPLC). The test procedures have been adequately validated.

Stability testing

Stability studies have been performed on the Artesunate powder for injection at 30ºC/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 arginine and sodium bicarbonate injection at 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

According to the WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products, no bioequivalence study is necessary when the

pharmaceutical product is to be administered parenterally (e.g. intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

The appropriate comparator product is Artesun, 60 mg powder for solution for injection (Guilin Pharmaceutical Co., Ltd). The proposed product is also a powder for solution for injection, i.e., Artesunate 120 mg.

This 120 mg strength is the higher strength of the prequalified Argesun® 60 mg (artesunate) solution for injection, which is co-packaged with sodium bicarbonate and arginine injection (sodium bicarbonate 8.4 mg/ml, arginine 20 mg/ml, 6 ml) (see MA168).

The recommended dose for [MA200 trade name] solution for injection is the same as for Argesun® 60 mg solution for injection. Both will have the same end concentration after reconstitution, i.e., 20 mg/ml. No bioequivalence study is submitted to support this application. As both formulations are solutions for injection, and the final concentrations of the solutions for injection is the same, a biowaiver is applicable and acceptable.

4. Summary of product safety and efficacy

[MA200 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, [MA200 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Artesun® 60 mg (artesunate) solution for injection for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA200 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 [MA200 trade name] is used in accordance with the SmPC.

Bioequivalence

NA

Efficacy and Safety

Regarding clinical efficacy and safety, [MA200 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 [MA200 trade name] was acceptable for the following indication: 'for the treatment of severe malaria', and would allow inclusion of [MA200 trade name], manufactured at Guilin Pharmaceutical Co., Ltd., No. 43, Qilidian Road, Guilin 541004, Guangxi, China in the list of prequalified medicinal products.