This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Artesun® 120mg*
Manufacturer of Prequalified Product:	Guilin Pharmaceutical Co., Ltd. No. 43 Qilidian Road Guilin, Guangxi, China
Active Pharmaceutical Ingredient (API):	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarial: artemisinin derivative, ATC Code P01BE03)
Therapeutic indication:	Artesun® 120 mg is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults, adolescents and children

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Artesun® 120mg is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults, adolescents and children.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Artesunate is manufactured in a two-step process from artemisinin via dihydroartemisinin (artenimol), followed by a purification step. The specifications for the starting material and the intermediate ensure adequate control thereof. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The API specifications are Ph.Int. based and include tests for description, identification, related substances (HPLC), assay (HPLC), specific optical rotation, heavy metals, sulfated ash, water content, particle size distribution, pH, clarity and colour of solution, residual solvents, bacterial endotoxins and microbial limits.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

The Artesunate powder for injection contains no excipient. The solvent for reconstitution contains sodium bicarbonate and water for injection, while the diluent contains sodium chloride and water for injection.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
Artesunate 120mg powder for injection is a sterile, white crystalline powder, presented in a colourless transparent type I glass vial with grey halogenated butyl rubber stopper, crimped with aluminium-plastic cap. One vial of Artesunate powder for injection is packed in a carton box, together with one ampoule of sodium bicarbonate injection (50 mg/ml; 2ml) as solvent, and one ampoule of sodium chloride injection (9 mg/ml; 10 ml) as diluent. The powder for injection is firstly dissolved in the solvent for reconstitution and then further diluted with saline solution and immediately injected intravenously or intramuscularly. The pH of the diluted solution is not higher than 8.0. Artesunate is poorly soluble in water, though it is sufficiently soluble in 5% sodium bicarbonate 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 specifications of the intermediate sterile artesunate are Ph.Int. based and similar to that of the API, including tests for sterility and ethanol content.

The sodium bicarbonate injection and sodium chloride injection are manufactured according to standard procedures, applying terminal sterilization. These injections are controlled by their respective BP monographs.

Specifications
The specifications for the Artesunate powder for injection are Ph.Int. based and include tests for description, identification, clarity and colour of solution, pH, sub-visible and visible particles, water content, bacterial endotoxins, content uniformity, related substances (HPLC), sterility and assay (HPLC). Ethanol is controlled at ≤ 500 ppm in the intermediate sterile bulk powder.

Stability testing
Stability studies have been performed on the Artesunate powder for injection at 30°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 injection and the sodium chloride injection at 30°C/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 and diluted solutions showed acceptable stability, chemically and physically (including visible and sub-visible particles), for a total 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.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The product Artesunate 120mg sterile powder for injection from Guilin Pharmaceutical Co., Ltd., Guilin, China, is the same to Artesunate 60 mg/vial sterile powder for injection from the same manufacturer (reference number MA051), except a difference in strength/volume. Since the 120 mg sterile powder for injection is additional strength/volume to the product already prequalified, no additional data is required.

4. Summary of Product Safety and Efficacy

Severe *Plasmodium falciparum* malaria is a medical emergency that requires prompt, effective treatment. Recommendations in the second edition of WHO guidelines for the treatment of malaria (2010), together with the April 2011 update reflect data from clinical trials, systematic reviews, observational studies, and expert opinion. The guidelines recommend intravenous or intramuscular artesunate for severe *P. falciparum* malaria in adults and in children.

Evidence from large trials in Southeast Asia and in Africa indicates that intravenous artesunate is more efficacious and better tolerated than intravenous quinine. In particular, a large randomised controlled trial, the South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT), which compared intravenous artesunate and quinine in 1461 Asian patients, showed increased survival on artesunate treatment, with a mortality rate of 22% with quinine compared to 15% with artesunate, a risk reduction of 34.7%. Intravenous artesunate had a relatively benign side-effect profile compared to quinine. In addition, a Cochrane review of six randomised trials comparing intravenous quinine with intravenous artesunate (five trials, including SEAQUAMAT) and intramuscular artesunate (one trial), demonstrated the overall superiority of artesunate, with significant reduction in the risk of death (relative risk 0.62; 95% CI 0.51–0.75), lower incidence of hypoglycaemia, and shorter parasite clearance time, compared to quinine. Three of the six Cochrane-reviewed safety and efficacy trials, including the SEAQUAMAT trial, used Guilin artesunate product.

A further trial involving 5425 children aged under 15 years in 9 African countries—African Quinine Artesunate Malaria Trial (AQUAMAT)—compared artesunate and quinine, both given either by intravenous or by intramuscular injection. The mortality rate of children treated with artesunate was lower by 22.5% (95% CI 8.1–36.9%) compared to quinine. Although the risk of neurological sequelae in survivors in both groups did not differ significantly, coma, convulsions, and deterioration of coma were all less frequent in artesunate-treated children. The trial found no serious artesunate-related adverse effects. The AQUAMAT trial used Guilin artesunate product.

The clinical safety of this product is considered acceptable when guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration. 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 Artesun® 120mg is used in accordance with the SmPC.

Efficacy and Safety

Regarding clinical efficacy and safety, Artesun® 120mg 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of Artesun® 120mg was acceptable for the following indication: **"for the treatment of severe malaria caused by *Plasmodium falciparum* in adults, adolescents and children",** and has advised to include Artesun® 120mg , manufactured at Guilin Pharmaceutical Co. Ltd., No. 43 Qilidian Road, Guilin, Guangxi, China in the list of prequalified medicinal products.