SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	Artesunate for Injection 60 mg
Manufacturer of Prequalified Product:	Guilin Pharmaceutical Co. Ltd. No. 17 Shanghai Road Guilin Guangxi, China Telephone: + 86 773 38 33 116 Fax: +86 773 38 33 812 Email: glpharma@public.glptt.gx.cn
Active Pharmaceutical Ingredient:	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarial: artemisinin derivative, ATC Code P01BE03
Therapeutic indication:	Artesunate for injection 60 mg is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults, adolescents and children

1. Introduction

Artesunate 60 mg/ml powder and solvent for solution for injection 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 is adequately controlled by the quality specifications which are Ph.Int. based, with additional tests including residual solvent, clarity and colour of solution 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 packaging material.

Other ingredients

The powder for injection contains no excipient. The solvent for reconstitution contains sodium bicarbonate and Water for Injections.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development

Artesunate 60 mg for injection is a sterile, white crystalline powder, presented in a colourless 7 ml, type I glass vial with grey-coloured type I rubber stopper and aluminium lid with a blue flip-off plastic cover. One vial of Artesunate 60 mg for injection is packed in a carton box, together with one ampoule (colourless, class 1 glass) of the solvent for reconstitution, 1 ml of sodium bicarbonate injection (50 mg/ml). The powder for injection is firstly dissolved in the solvent for reconstitution and then further diluted with either 5% glucose solution for injection or 0.9% sodium chloride solution for injection and immediately injected intravenously or intramuscularly. The pH of the final solutions is not higher than 8.0. Artesunate is poorly soluble in water, though it is sufficiently soluble in sodium bicarbonate injection (50 mg/ml) to prepare a clear solution.

Artesunate 60 mg for injection is manufactured by filling vials with sterile artesunate under aseptic conditions. Sterile artesunate is manufactured from artesunate API: A solution of the API in ethanol is sterile filtered and quenched in sterilised water, whereupon the precipitated sterile material is filtered, washed with sterilised water 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 5000 ppm), particle size distribution and clarity and colour of solution.

The specification for the Artesunate 60 mg for injection is based on the adopted Ph.Int. monograph for Artesunate for Injections and includes tests for description, identification, clarity of solution, pH, related substances (HPLC), water (KF), insoluble particulate matter, bacterial endotoxins, sterility, variation of fill mass and assay.

The quality of the solvent for reconstitution, sodium bicarbonate injection (50 mg/ml), terminally sterilised, is controlled by the BP monograph for Sodium Bicarbonate Intravenous Infusion.

Stability testing

Stability studies have been performed on the Artesunate 60mg for injection for 36 months at 30ºC/70%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 the storage conditions and support the proposed shelf life and storage conditions as defined in the SmPC.

The reconstituted, diluted solutions showed acceptable stability, chemically and physically (including particulate matter), for one hour at 30ºC.

Stability studies have been performed on the sodium bicarbonate injection (50 mg/ml) at 30ºC/70%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.

Conclusions

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

Artesunate for Injection 60 mg was subject to clinical assessment of efficacy and safety (see section 4). Bioequivalence data were not 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

The quality of this product is considered acceptable when it is used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Efficacy and Safety

Regarding clinical efficacy and safety, Artesunate for Injection 60 mg 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 assessment of data on quality, efficacy and safety, the team of assessors considered by consensus that the benefit–risk profile of Artesunate for Injection 60 mg 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 Artesunate for Injection 60 mg, manufactured at Guilin Pharmaceutical Co. Ltd., No. 43 Qilidian Road, Guilin, Guangxi, China in the list of prequalified medicinal products.