SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[MA135 trade name] [1]
Manufacturer of Prequalified Product:	Ipca Laboratories Limited Sejavta, Ratlam Madhya Pradesh, 457002 India Fax: +91 7412 279083 :
Active Pharmaceutical Ingredient (API):	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarial: artemisinin derivative, ATC Code P01BE03
Therapeutic indication:	[MA135 trade name] is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults, adolescents and children

1 Introduction

[MA135 trade name] 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 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 (API)

The APIMF of artesunate has been accepted through WHO's APIMF procedure. Artesunate is manufactured in a two-step process from artemisinin via dihydroartemisinin, followed by purification. 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 pharmacopoeial based and include tests for description, solubility, identification (IR, TLC and colour reaction), water content (KF), sulfated ash, specific optical rotation, heavy metals, pH, loss on drying, related substances (HPLC), assay (HPLC), sterility, bacterial endotoxins, particle size distribution, residual solvents, reconstitution time, particulate matter and clarity of solution.

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

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 60mg powder for injection is a sterile, white crystalline powder, presented in a clear, transparent, tubular USP Type I glass vial (5 ml) with grey bromobutyl rubber stopper and flip off seal

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

and blue coloured Ipca on aluminium/plastic cover.One vial of Artesunate powder for injection is packed in a box, together with one ampoule of sodium bicarbonate injection (50 mg/ml; 1ml) as solvent, and one ampoule of sodium chloride injection (9 mg/ml; 5 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 Sterile artesunate is manufactured from artesunate API: non-sterile artesunate is sterilized by filtration.Sterile artesunate is isolated dried and micronized. All operations are carried out under aseptic conditions and satisfactory operating parameters and in-process controls have been defined. Sufficient validation data were provided.

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 Artesunate powder for injection are Ph.Int. based and include tests for description, identification (IR), uniformity of mass, water content (KF), assay, related substances (HPLC), sterility, bacterial endotoxins, sub-visible and visible particles, ease of reconstitution of solution, pH, completeness and clarity of solution. Ethanol is controlled at ≤ 5000 ppm in the intermediate sterile bulk powder.

Stability testing

Stability studies have been performed on 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 sodium bicarbonate injection and 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.

Conclusion

The quality part of the dossier is accepted.

3. **Assessment of Bioequivalence**

The applicant requested a biowaiver as per WHO Technical Report Series, No. 992 which indicates that 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 (artesunate 60 mg, Guilin Pharmaceutical Co Ltd.) powder for solution for injection. The proposed product is also a powder for solution for injection, i.e. [MA135 trade name] (artesunate 60 mg). The formulations contain comparable excipients.

As the proposed product meets the biowaiver requirements described above, a biowaiver has been granted.

4. Summary of Product Safety and Efficacy

Severe Plasmodium falciparum malaria is a medical emergency that requires prompt, effective treatment. The WHO guidelines for the treatment of malaria (2015) 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 [MA135 trade name] is used in accordance with the SmPC.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA135 trade name] 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 [MA135 trade name] 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 [MA135 trade name], manufactured at Ipca Laboratories Limited, Sejavta, Ratlam, Madhya Pradesh, India in the list of prequalified medicinal products.