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	[MA194 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase I, Unit II Plot No 25-27, Survey No 366 Premier Industrial Estate Kachigam, Daman, 369 210, India
Active Pharmaceutical Ingredient(s) (API)	Artesunate
Pharmaco-therapeutic group (ATC Code)	Antimalarials: artemisinin and derivatives (P01BE03)
Therapeutic indication	[MA194 trade name] is indicated for the treatment of severe malaria caused by *Plasmodium falciparum,* in adults and children.

1. Introduction

[MA194 trade name], administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children.

[MA194 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 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 [MA194 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.

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

Other ingredients

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a sterile white powder, presented in a 15 mL clear glass vial (USP Type III.) The filled vial is closed with 20 mm grey bromobutyl rubber plug and sealed with 20mm dark green flip off aluminium seal. One vial of Artesunate powder for injection is packed in a carton, together with two ampoules of sodium bicarbonate injection (50 mg/mL; 1mL) as solvent, and two ampoules 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 aseptic filling of sterile artesunate API into sterilized vials followed by stoppering and sealing. The intermediate sterile artesunate is manufactured from artesunate API: non-sterile artesunate is dissolved in ethanol and the clear solution is passed through sterilizing grade filters. The sterile filtrate is then lyophilized. Milling and crimping are carried out to yield the final sterile powder. 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, bacterial endotoxins, particulate contamination (sub-visible particles), particle size and ethanol content.

The sodium bicarbonate injection and sodium chloride injection are manufactured according to standard aseptic filtration procedures and finally terminally sterilized. These injections are controlled by their respective monographs.

Specifications

The specifications for the Artesunate powder for injection are Ph.Int. based and include tests for description, identification (IR and HPLC), average fill weight, uniformity of mass, pH, water content (KF), clarity of solution, particulate contamination (sub-visible and visible particles), reconstitution time, related substances (HPLC), assay (HPLC), bacterial endotoxins and sterility. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed on the Artesunate powder for injection at 25°C/60%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.

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. The formulations contain comparable excipients.

As the proposed product meet the biowaiver requirements described above, a biowaiver can be granted.

4. Summary of product safety and efficacy

[MA194 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 [MA194 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Artesun, 60 mg powder for solution for injection (Guilin Pharmaceutical Co Ltd) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA194 trade name] is considered to be 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 [MA194 trade name] is used in accordance with the SmPC.

Bioequivalence

N/A

Efficacy and Safety

Regarding clinical efficacy and safety, [MA194 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 [MA194 trade name] was acceptable for the following indication: 'treatment of severe malaria caused by *Plasmodium falciparum'*, and would allow inclusion of [MA194 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase I, Unit II, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 369 210, India in the list of prequalified medicinal products.