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	[MA186 trade name][*]
Manufacturer of Prequalified Product	Ipca Laboratories Limited P.O. Sejavta, Ratlam 457001 (Madhya Pradesh), India
Active Pharmaceutical Ingredient(s) (API)	Artesunate
Pharmaco-therapeutic group (ATC Code)	Antimalarial: artemisinin derivative, ATC Code(P01BE03)
Therapeutic indication	[MA186 trade name] is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults, adolescents and children

1. Introduction

[MA186 trade name] is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults 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 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 [MA186 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

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.

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

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Artesunate 120 mg powder for injection is a sterile, white crystalline powder, presented in a clear, 15-mL USP type I glass vial, sealed with a grey bromobutyl rubber stopper and an aluminium seal closed with a red-flip-off plastic cap embossed with "Ipca".

One vial of artesunate powder for injection is packed in a 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 the 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 dissolved in ethanol and the clear solution is passed through sterilizing grade filters. The sterile filtrate is then chilled to crystalize out the sterile API. Removal of the mother liquor and drying at low controlled temperature and further on micronisation yields 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.

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 include tests for description, identification (IR), uniformity of mass, water content (KF), assay (HPLC), 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

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 meets the biowaiver requirements described above, a biowaiver was granted.

4. Summary of product safety and efficacy

[MA186 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, [MA186 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 [MA186 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 [MA186 trade name] is used in accordance with the SmPC.

Bioequivalence

NA

Efficacy and Safety

Regarding clinical efficacy and safety, [MA186 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 [MA186 trade name] was acceptable for the following indication: for the treatment of severe malaria caused by *Plasmodium falciparum*', and would allow inclusion of [MA186 trade name], manufactured at Ipca Laboratories Limited P.O. Sejavta, Ratlam 457001(Madhya Pradesh), India in the list of prequalified medicinal products.