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:	[MA058 trade name][*]
Manufacturer of Prequalified Product:	Maphar, Km 10, Route Côtière 111 Quartier Industriel Zenata, Aïn Sebaâ 20250 Casablanca Morocco
Active Pharmaceutical Ingredient (API):	Artesunate + amodiaquine (as hydrochloride)
Pharmaco-therapeutic group (ATC Code):	Artesunate, combinations (P01BE53)
Therapeutic indication:	[MA058 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and to artesunate.

1. Introduction

[MA058 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and to artesunate.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with [MA058 trade name].

[MA058 trade name] should not be used in regions where amodiaquine resistance is widespread because such use significantly increases the risk of developing resistance to artesunate.

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 (APIs)

Amodiaquine

Amodiaquine hydrochloride is official in the Ph.Int., USP and Ph.Eur. and well established, Amodiaquine hydrochloride manufactured by the API supplier meets pharmacopoeial specifications. Additional specifications include residual solvents and related substances with HPLC.

Long-term stability data at 30°C/65%RH and accelerated stability data provided for three full scale batches of Amodiaquine hydrochloride API showed neither visible variability nor change over time, confirming the stability of the API. A 36-month retest period was approved for Amodiaquine hydrochloride API when stored not above 30°C.

Artesunate

Artesunate is manufactured via dihydroartemisinin (artenimol) from artemisinin and is controlled by the API manufacturer by an in-house set of specifications. The specifications and test procedures are

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

considered adequate for control of the quality of the API, providing at least the same level of control than the Ph.Int. monograph for Artesunate. Assay and related substances are determined by a validated HPLC method. The limits of the related substances were set according to the requirements of ICH Q3A(R2).

Stress testing conducted under various conditions confirmed the instability of artesunate, particularly towards hydrolysis. Based on the long-term stability data generated in the proposed packaging configuration at 25°C/60%RH and 30°C/70%RH, as well as at accelerated conditions for six months, a 36-month retest period has been approved for Artesunate API when stored not above 30°C.

Other ingredients

Other ingredients used in the tablet formulation include calcium carbonate, croscarmellose sodium, magnesium stearate, maize starch, microcrystalline cellulose, povidone and colloidal anhydrous silica. Magnesium stearate is from plant origin.

Finished pharmaceutical product (FPP)

The uncoated bilayered tablet is an immediate release formulation with amodiaquine hydrochloride formulated in one layer and artesunate formulated in the other.

The development of the [MA058 trade name] was essentially directed towards obtaining a formulation of this fixed-dose combination that would accommodate the physico-chemical properties of the two APIs, in particular the instability of artesunate. Extensive compatibility and formulation studies lead to the development of a bilayered tablet, allowing minimal contact between artesunate and amodiaquine, with good manufacturability properties and stability.

With respect to the manufacturing process, appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented for three production scale batches demonstrated the consistency of the process and the quality of the product. The release and shelf-life specifications are considered adequate to control for the quality of the product.

During pilot stability studies is was demonstrated that the tablets have to be protected from moisture. Based on these studies an aluminium blister pack, composed of a three-layer blister film (OPA/Alu/PVC) and aluminium lidding foil, was selected for marketing purposes.

Stability studies have been performed on primary stability batches stored at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. Bracketing was applied to the three different strengths submitted for prequalification ([MA058 trade name], [MA058 trade name] and [MA058 trade name]). Several supportive studies were conducted. At the time of prequalification of the product a shelf-life of 24 months has been allowed for the tablets packed in aluminium/aluminium blister packs and stored at or below 30°C.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

Pharmacokinetic data have only been submitted for the 100/270 mg tablet strength. In summary, the available bioequivalence studies indicate an overall comparable bioavailability to (WHO accepted) reference products containing the individual compounds. These data are considered also relevant for this (lower) strength of the fixed dose combination, based upon the fact that the formulations are dose-proportionally composed, are manufactured by the same manufacturer and manufacturing process, and have shown comparable dissolution. The pharmacokinetic data are ancillary to the clinical data (see section 4).

4. Summary of Product Safety and Efficacy

[MA058 trade name] has been shown to conform to relevant standards of quality, efficacy and safety as required by WHO. According to the submitted data on quality, safety and efficacy, [MA058 trade name] have been proven.

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 [MA058 trade name] is used in accordance with the SmPC.

Bioequivalence

Therapeutic efficacy and safety data constituted the mainstay of this dossier and pharmacokinetic information was ancillary. They were generated with the 100/270 mg tablet strength only and indicated overall comparable bioavailability with WHO accepted reference products.

Efficacy and Safety

[MA058 trade name] is considered safe and effective when used in accordance with the guidance and restrictions presented in the Summary of Product Characteristics. Further important information on safety and efficacy will be gathered with the measures as defined in the Risk Management Plan.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, safety and efficacy the team of assessors considered that the benefit–risk profile of [MA058 trade name] was acceptable for the following indication: **"treatment of uncomplicated malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and to artesunate."**, and has advised that the quality, efficacy and safety of [MA058 trade name] allow inclusion of [MA058 trade name], manufactured at Maphar Km 10, Route Côtière 111 Quartier Industriel Zenata, Aïn Sebaâ, 20250 Casablanca, Morocco, in the list of prequalified medicinal products.