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** | [MA132 trade name]* |
| **Manufacturer of Prequalified Product** | Micro Labs Limited<br>Plot No S-155 to S-159 & N1<br>Phase-III and Phase IV<br>Verna industrial estate, Verna<br>Goa - 403722, India |
| **Active Pharmaceutical Ingredient(s) (API)** | Amodiaquine (as hydrochloride) /Artesunate |
| **Pharmaco-therapeutic group (ATC Code)** | Artemisinin and derivatives, combinations; (P01BF03) |
| **Therapeutic indication** | [MA132 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

[MA132 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum.*

[MA132 trade.name] should be initiated by a health care provider experienced in the management of malaria infection.

## 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)

Amodiaquine hydrochloride and artesunate have 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 these APIs, used in the manufacture of [MA132 trade.name] are 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**

Other ingredients used in the tablet formulation include mannitol, hydroxypropylcellulose, colloidal anhydrous silica, magnesium stearate, pregelatinized starch, croscarmellose sodium and polysorbate 80. BSE/TSE compliance declarations were provided for all excipients. None of them are of human or animal origin.

**Finished pharmaceutical product (FPP)**

*Pharmaceutical development and manufacture*

The multisource product is a capsule shaped, biconvex, bilayer tablet; one layer is yellow coloured and the other one is white to slightly yellow coloured. One face plain which is yellow in colour and a break line on the other face which is white in colour. The face with the break line having engravings "AA" on one side and "25" on the other side of break line.

The break line is to facilitate breaking of the tablet for ease of swallowing and not to divide into equal doses. The tablets are presented in PVC/EVOH-Aclar and Alu-Alu blister packs, both being sufficiently protective against moisture permeation.

Three strengths of Amodiaquine (as hydrochloride)/Artesunate Tablets – proportionally similar in composition and manufactured from a common blend – were developed: 270mg/100mg, 135mg/50mg and 67.5mg/25mg. The development focussed on the highest strength, which was used in the BE study against the WHO recommended comparator product, Artesunate Amodiaquine Winthrop tablet of the same strength.

The aim of the product development was to obtain a stable and robust FDC tablet, bio-equivalent to the WHO comparator product. Similar to the comparator product a bilayer tablet, allowing minimal contact between artesunate and amodiaquine HCl, was developed. The excipients selected are well known and widely used in solid oral formulations. Compatibility studies were conducted to investigate and predict physicochemical interaction between each API and the excipients and consequently to ensure chemical compatibility.

For the artesunate layer, a wet granulation method (non-aqueous to protect the API from hydrolytic degradation) was selected since micronized artesunate is fluffy in nature and it contributes 25 % of the layer weight. Aqueous wet granulation is used in the manufacture of the layer containing amodiaquine hydrochloride. Studies were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired characteristics including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

*Specifications*

The finished product specifications include tests for appearance, identification of the APIs (IR, HPLC), average mass, uniformity of mass, tablet dimensions, disintegration time, resistance to crushing, friability, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), residual solvents (GC), related substances (HPLC) and microbial limits. The test procedures have been adequately validated.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH (zone IVb), 30°C/65%RH (zone IVa) and 25°C/60%RH (zone II) as long-term storage conditions and for six months at accelerated condition in the packaging proposed for marketing of the product. Degradation was noted for artesunate, though within the agreed specification limits at zone IVb storage condition. Based on the available stability data the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

**Conclusion**

The quality part of the dossier is accepted.

## 3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

An open-label, randomized, balanced, single-dose, two-treatment, four-period, two-sequence, fully replicate, crossover oral bioequivalence study of 2 tablets of Artesunate Amodiaquine bilayer 100mg / 270 mg (artesunate 200mg + amodiaquine 540mg) manufactured by Micro Labs Limited., India and 2 tablets of Artesunate/Amodiaquine Winthrop® 100mg/270mg (artesunate 200mg + amodiaquine 540mg) manufactured by Maphar, Km 10, route cotiere111, Zenata Ain Sebaa-Casablanca-Morocco and distributed by Sanofi- Aventis Maroc. in 36 healthy, adult, human subjects under fasting conditions (study no. 053-16-WHO).

The objective of the study was to compare the bioavailability of the stated Artesunate/Amodiaquine 100/270mg fixed dose combination tablet manufactured by/for Micro Labs Limited, India (test drug) with the reference formulation Artesunate/Amodiaquine Winthrop® (Sanofi- Aventis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 2 tablets Artesunate/Amodiaquine 100/270mg (artesunate 200mg + amodiaquine 540mg) Batch no. AQCG002.

Treatment R: Reference – 2 tablets Artesunate/Amodiaquine Winthrop® 100mg/270mg (artesunate 200mg + amodiaquine 540mg) Batch no. 3MA068.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, $C_{max}$ and $t_{max}$ for bioequivalence evaluation. Drug concentrations for artesunate and amodiaquine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 1.5 ng/mL for artesunate and about 1.0 ng/mL for amodiaquine.

The study was performed with 36 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate and amodiaquine as well as statistical results are summarised in the following table:

**Artesunate**

| **Pharmacokinetic Parameter** | **Test formulation (T)** arithmetic mean ± SD (geometric mean) | **Reference (R)** arithmetic mean ± SD (geometric mean) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90%CI (ANOVAlog) |
| $t_{max}$ (h) | 0.49 ± 0.27 | 0.46 ± 0.48 | - | - |
| $C_{max}$ (ng/mL) | 380 ± 265 (300) | 341 ± 209 (290) | 103.4 | 86.9 – 123.1 |
| $AUC_{0-t}$ (ng·h/mL) | 199 ± 86 (183) | 200 ± 93 (182) | 100.5 | 92.6 – 109.0 |
| $AUC_{0-inf}$(ng·h/mL) | 207 ± 84 (196) | 207 ± 92 (193) | 101.6 | 93.3 – 110.8 |

**Amodiaquine**

| **Pharmacokinetic Parameter** | **Test formulation (T)** arithmetic mean ± SD (geometric mean)) | **Reference (R)** arithmetic mean ± SD (geometric mean)) | **log-transformed parameters** | |
|---|---|---|---|---|
| | | | **Ratio** T/R (%) | **Conventional** 90%CI (ANOVAlog) |
| $t_{max}$ (h) | 1.32 ± 1.15 | 1.20 ± 1.12 | - | - |
| $C_{max}$ (ng/mL) | 20.6 ± 7.3 (19.6) | 20.3 ± 8.7 (19.0) | 102.9 | 95.6 – 110.7 |
| $AUC_{0-t}$ (ng·h/mL) | 188 ± 78 (173) | 189 ± 70 (179) | 96.7 | 91.0 – 102.8 |
| $AUC_{0-inf}$ (ng·h/mL) | 235 ± 104 (214) | 238 ± 101 (223) | 96.3 | 89.2 – 103.9 |

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and $C_{max}$ values regarding artesunate and amodiaquine. Accordingly, the test Artesunate/Amodiaquine 100/270 mg fixed dose combination tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Artesunate/Amodiaquine Winthrop® 100 mg/270 mg fixed dose combination tablet (Sanofi-Aventis).

A biowaiver was granted for the additional 25/67.5 mg and 50/135 mg FDC tablet strengths (Micro Labs Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Artesunate/Amodiaquine 25/67.5 mg and 50/135 mg FDC tablets were determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined the same.

## 4. Summary of product safety and efficacy

According to the submitted data on quality [MA132 trade.name] is a direct scale-down of Artesunate/Amodiaquine 100/270 mg FDC tablets. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Artesunate + Amodiaquine Winthrop® 100 mg /270 mg tablet (Sanofi-Aventis) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. 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 [MA132 trade name] is used in accordance with the SmPC.

### Bioequivalence

[MA132 trade.name] has fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

**Efficacy and Safety**

Regarding clinical efficacy and safety, [MA132 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 [MA132 trade name] was acceptable for the following indication: "treatment of malaria due to *Plasmodium falciparum*", and would allow inclusion of [MA132 trade name], manufactured at Micro Labs Limited, Plot No S-155 to S-159 & N1, Phase-III and Phase IV, Verna industrial estate, Verna Goa - 403722, India in the list of prequalified medicinal products.