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

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|---|---|
| **Name of the Finished Pharmaceutical Product** | [MA103 trade name]* |
| **Manufacturer of Prequalified Product** | Cipla Limited<br>Unit II, A-42, MIDC<br>Patalganga, District: Raigad<br>Maharashtra state<br>India |
| **Active Pharmaceutical Ingredient(s) (API)** | artesunate, amodiaquine (as hydrochloride) |
| **Pharmaco-therapeutic group (ATC Code)** | Artemisinin and derivatives, combinations; (P01BF03) |
| **Therapeutic indication** | [MA103 trade name] is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum strains which are susceptible to amodiaquine as well as to artesunate. |

## 1. Introduction

[MA103 trade name] L is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum.

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 [MA103 trade name].

## 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*

Amodiaquine hydrochloride (reference number WHOAPI-134) 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 amodiaquine hydrochloride, used in the manufacture of Artesunate/Amodiaquine (as hydrochloride) 50mg/135mg Tablets, 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

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

(APIMF) to verify compliance with WHO norms and standards and inspection of the site of API manufacture to verify compliance with WHO GMP requirements.

*Artesunate*

Artesunate API is described in the Ph.Int. It is manufactured in a two-step process from artemisinin via dihydroartemisinin (artenimol), followed by a purification step. 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 Ph.Int. based artesunate specifications include tests for description, solubility, identification, specific optical rotation, heavy metals, water content, residue on ignition, pH, related substances (HPLC), assay (HPLC), residual organic solvents and particle size distribution.

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**

Other ingredients used in the tablet formulation include lactose anhydrous, lactose monohydrate, croscarmellose sodium, magnesium stearate, calcium carbonate DC 95S with 5% corn starch, and colloidal anhydrous silica. Magnesium stearate is from vegetable origin. A TSE/BSE free declaration has been provided for lactose.

**Finished pharmaceutical product (FPP)**

*Pharmaceutical development and manufacture*

Each tablet contains 176.33 mg amodiaquine hydrochloride equivalent to 135 mg amodiaquine and 50 mg artesunate. The product is a circular, uncoated, bilayered, flat bevelled tablet with one white to light yellowish layer and the other yellow layer debossed with ‘50’ on one side and with central break-line on the white to light yellowish layer. The break-line is to facilitate breaking of the tablet for ease of swallowing. The tablets are packaged in Alu-Alu blisters.

The objective of the development programme was to obtain a robust, stable, immediate-release FDC tablet, pharmaceutically equivalent and bioequivalent to the WHO comparator product, Artesunate + Amodiaquine Winthrop® tablets of the same strength. The selection of the excipients was based on prior knowledge with respect to their physicochemical and functional properties, prior experience with similar products, available information of the comparator product and compatibility studies. Characterization of the comparator product identified a quality target product profile.

Similar to the comparator product a bilayered tablet, allowing minimal contact between artesunate and amodiaquine HCl, was developed. Artesunate is known to be sensitive to high temperature, moisture and acidic conditions. Thus the dry granulation technique was selected for both layers, whilst calcium carbonate DC granules were included as a pH regulator in order to neutralize the effect of the possible release of HCl from amodiaquine HCl. The primary packaging (Alu/Alu blisters) was selected to protect the tablets against moisture and light. Optimization of the manufacturing process has been described in detail. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Three strengths, proportionally similar in composition, were developed: 100 mg/270 mg, 50 mg/135 mg and 25/67.5 mg.

*Specifications*

The FPP specifications include tests for description, identification of the APIs, average weight, friability, hardness, disintegration time, water content, uniformity of dosage units (by content uniformity), dissolution (artesunate: HPLC detection and amodiaquine: UV/VIS detection), assay (HPLC), degradation products (HPLC) and microbiological examination of non-sterile products. The test procedures have been adequately validated.

*Stability testing*

Stability studies have been conducted at $30^0$C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was noted for artesunate at both storage conditions, though well within the agreed specification limits. The data support the proposed shelf-life and storage conditions as stated in the SmPC.

**Conclusion**

The quality part of the dossier is accepted.

## 3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines:

A randomized, open label, two treatment, two period, two sequence, single dose, truncated, crossover, bioequivalence study of Artesunate + Amodiaquine 100/270 mg bilayered tablets of Cipla Ltd., India with Artesunate + Amodiaquine Winthrop® 100 mg /270 mg of Sanofi – Aventis Maroc, Morocco, in normal, healthy, adult, human subjects under fasting condition (study no. ARL/09/440).

The objective of the study was to compare the bioavailability of the stated Artesunate + Amodiaquine 100/270 mg bilayered tablet manufactured by Cipla Limited, India (test drug) with the same dose of the reference formulation (Artesunate + Amodiaquine Winthrop® 100 mg /270 mg tablet) 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 – 1 tablet Artesunate/Amodiaquine 100/270 mg (artesunate 100 mg + amodiaquine 270 mg) Batch no. KW2370. |
| Treatment R: | Reference – 1 tablet Artesunate + Amodiaquine Winthrop® 100 mg /270 mg (artesunate 100 mg + amodiaquine 270 mg) Batch no. 5284. |

A 53 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for artesunate and amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/mL for artesunate and 0.25 ng/mL for amodiaquine.

The study was performed with 72 participants; data generated from a total of 69 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 tables:

**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) | 0.38 ± 0.30 | 0.50 ± 0.49 | – | – |
| $C_{max}$ (ng/mL) | 185 ± 131 (149) | 169 ± 94 (146) | 102.6 | 90.4 – 116.5 |
| $AUC_{0-t}$ (ng·h/mL) | 114 ± 57 (101) | 114 ± 51 (103) | 98.4 | 92.5 – 104.7 |
| $AUC_{0-inf}$ (ng·h/mL) | 121 ± 56 (110) | 120 ± 52 (111) | 98.8 | 92.8 – 105.2 |

**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) | 0.70 ± 0.26 | 0.80 ± 0.34 | - | - |
| $C_{max}$ (ng/mL) | 9.3 ± 4.5 (8.5) | 9.5 ± 4.3 (8.6) | 99.7 | 90.1 – 110.3 |
| $AUC_{0-t}$ (ng.h/mL) | 72 ± 24 (69) | 81 ± 35 (74) | 93.3 | 86.0 – 101.1 |
| $AUC_{0-inf}$ (ng.h/mL) | 88 ± 30 (84) | 100 ± 47 (91) | 92.5 | 85.5 – 100.1 |

**Conclusions**

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding artesunate and amodiaquine. Accordingly, the test Artesunate + Amodiaquine 100/270 mg bilayered 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 (Sanofi – Aventis).

A biowaiver was granted for the additional tablet strengths Artesunate + Amodiaquine 25/67.5 mg and Artesunate + Amodiaquine 50/135 mg (Cipla Ltd., India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Artesunate + Amodiaquine 25/67.5 mg and Artesunate + Amodiaquine 50/135 mg tablet strengths 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 to be similar.

## 4. Summary of product safety and efficacy

According to the submitted data on quality [MA103 trade name] is a direct scale-down of [MA104 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with innovator 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 [MA103 trade name] is used in accordance with the SmPC.

### Bioequivalence

[MA103 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

### Efficacy and Safety

Regarding clinical efficacy and safety, [MA103 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 [MA103 trade name] was acceptable for the following indication: ***'treatment of malaria due to Plasmodium falciparum'***, and would allow inclusion of [MA103 trade name], manufactured at Cipla Limited, Unit II, A-42, MIDC, Patalganga, District Raigad, Maharashtra state, India in the list of prequalified medicinal products.