### SCIENTIFIC DISCUSSION

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>Falcimon 100/270 B/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of Prequalified Product:</td>
<td>Cipla Limited</td>
</tr>
<tr>
<td></td>
<td>Unit II, A-42, MIDC</td>
</tr>
<tr>
<td></td>
<td>Patalganga, District: Raigad</td>
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<tr>
<td></td>
<td>Maharashtra state</td>
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<tr>
<td></td>
<td>India</td>
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<tr>
<td>Active Pharmaceutical Ingredients (APIs):</td>
<td>artesunate, amodiaquine (as hydrochloride)</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Artemisinin and derivatives, combinations; (P01BF03)</td>
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<tr>
<td>Therapeutic indication:</td>
<td>Falcimon 100/270 B/L is indicated for the treatment of uncomplicated cases of malaria due to <em>Plasmodium falciparum</em> strains which are susceptible to amodiaquine as well as to artesunate.</td>
</tr>
</tbody>
</table>

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
1. Introduction

Falcimon 100/270 B/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 Falcimon 100/270 B/L.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

**Active pharmaceutical Ingredients (APIs)**

**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) 100mg/270mg 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 (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 artemesunate 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 352.66 mg amodiaquine hydrochloride equivalent to 270 mg amodiaquine and 100 mg artemesunate. The product is a capsule shaped, uncoated, bilayered, biconvex tablet with one white to light yellowish layer and the other yellow layer debossed with ‘100’ 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: 100mg/270mg, 50mg/135mg and 25/67.5mg.

**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°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 artemesunate 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.

**Conclusions:**
The quality part of the dossier is accepted.

3. **Assessment of Bio-Equivalence**
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:
Artesunate/Amodiaquine (as hydrochloride) 100mg/270mg Tablets (Cipla Ltd), MA104

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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, $C_{\text{max}}$ and $t_{\text{max}}$ 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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD</th>
<th>Reference (R) arithmetic mean ± SD</th>
<th>log-transformed parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.38 ± 0.30</td>
<td>0.50 ± 0.49</td>
<td>-</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>185 ± 131 (149)</td>
<td>169 ± 94 (146)</td>
<td>102.6 90.4 – 116.5</td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>114 ± 57 (101)</td>
<td>114 ± 51 (103)</td>
<td>98.4 92.5 – 104.7</td>
</tr>
<tr>
<td>AUC$_{0-inf}$ (ng.h/ml)</td>
<td>121 ± 56 (110)</td>
<td>120 ± 52 (111)</td>
<td>98.8 92.8 – 105.2</td>
</tr>
</tbody>
</table>

* geometric mean

### Amodiaquine

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithmetic mean ± SD</th>
<th>Reference (R) arithmetic mean ± SD</th>
<th>log-transformed parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.70 ± 0.26</td>
<td>0.80 ± 0.34</td>
<td>-</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>9.3 ± 4.5 (8.5)</td>
<td>9.5 ± 4.3 (8.6)</td>
<td>99.7 90.1 – 110.3</td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>72 ± 24 (69)</td>
<td>81 ± 35 (74)</td>
<td>93.3 86.0 – 101.1</td>
</tr>
<tr>
<td>AUC$_{0-inf}$ (ng.h/ml)</td>
<td>88 ± 30 (84)</td>
<td>100 ± 47 (91)</td>
<td>92.5 85.5 – 100.1</td>
</tr>
</tbody>
</table>

* geometric mean
Conclusions:
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 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).

4. Summary of Product Safety and Efficacy

Falcimon 100/270 B/L has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability Falcimon 100/270 B/L 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 Falcimon 100/270 B/L is used in accordance with the SmPC.

Bioequivalence

Falcimon 100/270 B/L has shown to be bioequivalent with Artesunate + Amodiaquine Winthrop® 100 mg /270 mg tablet (Sanofi-Aventis Maroc, Morocco).

Efficacy and Safety

Regarding clinical efficacy and safety, Falcimon 100/270 B/L is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 Falcimon 100/270 B/L was acceptable for the following indication: “treatment of malaria due to Plasmodium falciparum” and has advised that the quality, efficacy and safety of Falcimon 100/270 B/L allow inclusion of Falcimon 100/270 B/L, manufactured at Cipla Limited, Unit II, A-42, MIDC, Patalganga, District Raigad, Maharashtra state, India in the list of prequalified medicinal products.