## SCIENTIFIC DISCUSSION

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product:</th>
<th>Amodiaquine Hydrochloride (150mg base) Tablets*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of the Prequalified Product:</td>
<td>Guilin Pharmaceutical Co., Ltd. - China</td>
</tr>
<tr>
<td>Active Pharmaceutical Ingredient (API):</td>
<td>Amodiaquine hydrochloride</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>Antimalarial (P01BA06)</td>
</tr>
<tr>
<td>Therapeutic indication:</td>
<td>Amodiaquine is indicated for the treatment of uncomplicated cases of malaria.</td>
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</tbody>
</table>

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
1. Introduction

Amodiaquine Hydrochloride tablets * contains 150 mg amodiaquine (equivalent to 196mg of amodiaquine hydrochloride). It is indicated for the treatment of uncomplicated cases of malaria. It should be used in combination with another antimalarial medicine.

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 amodiaquine. Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and public health authorities’ guidelines.

Amodiaquine Hydrochloride Tablets must not be used for malaria prophylaxis, since it may result in agranulocytosis and severe hepatotoxicity.

2. Assessment of Quality

The dossier was assessed according to WHO’s Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis and other relevant WHO and/or ICH guidance documents.

Active pharmaceutical Ingredient (API)

Amodiaquine hydrochloride API is described in the Ph.Int. and the USP and is considered well-established.

The API, which is manufactured by Guilin, is adequately controlled by the quality specifications which are pharmacopoeial based, with additional in-house specifications including residual solvents. Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 36 months was approved for amodiaquine hydrochloride.

Other ingredients

The core tablets contain dextrin, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polysorbate-80, sodium starch glycolate and corn starch. The film-coat contains methacrylic acid-ethyl acrylate copolymer. Magnesium stearate is from plant origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The development of the final composition of the amodiaquine tablets has been described. Critical process variables were optimized during the pharmaceutical R&D stage. The ingredients are typical for wet granulated tablets; alcohol is used as a film-coating solvent. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The proposed specifications for the amodiaquine tablets, which are pharmacopoeial based, include related substances and residual solvents and are adequate to ensure consistent quality for this finished pharmaceutical product.

Product specification

The amodiaquine tablets are film-coated tablets, with yellow cores, marked “AM150” on both sides and a score line on one side. The tablets are packed in PVC/Aluminium blister cards.
Stability testing

Stability studies have been performed on the FPP (co-blistered tablets) at 30°C/70%RH as long-term conditions and at accelerated conditions. At the time of the prequalification, a shelf-life of 36 months has been allowed for the FPP when stored below 30°C.

Conclusion

The quality part of the dossier is accepted.

2. Bioequivalence

The following bioequivalence study has been performed in 2006 according to internationally accepted guidelines.

Bioequivalence study of Amodiaquine Hydrochloride tablets in healthy subjects (study no. 20060625).

The objective of the study was to compare the bioavailability of the stated amodiaquine tablet manufactured by Guilin Pharmaceutical Co., Ltd, China (test drug) with the same dose of reference tablet and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

- **Treatment T:** Test – Amodiaquine 200 mg tablets, 3 tablets
  (amodiaquine hydrochloride 200 mg, amodiaquine [as hydrochloride] 150 mg)
  Batch No. AQ060602

- **Treatment R:** Reference – Flavoquine® 200 mg tablets (Aventis Laboratoire), 3 tablets
  (amodiaquine hydrochloride 200 mg, amodiaquine [as hydrochloride] 150 mg)
  Batch No. 418

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 samples within 96 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 amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be 0.150 ng/ml.

The study was performed with 24 participants, data generated from a total of 23 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Geometric means (AUC, C\text{max}) and arithmetic means (t\text{max}) for amodiaquine as well as statistical results are summarised in the following tables:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T) arithm. mean ± SD (*</th>
<th>Reference (R) arithm. mean ± SD (*)</th>
<th>log-transformed parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>t\text{max} (h)</td>
<td>0.91 ± 1.13</td>
<td>0.92 ± 0.52</td>
<td></td>
</tr>
<tr>
<td>C\text{max} (ng/ml)</td>
<td>30.3 ± 12.6 (28.1)</td>
<td>29.9 ± 15.0 (26.8)</td>
<td>105.0 * 92.5 – 119.2</td>
</tr>
<tr>
<td>AUC\text{0-t} (ng.h/ml)</td>
<td>309.4 ± 76.0 (300.0)</td>
<td>309.5 ± 105.3 (202.7)</td>
<td>102.5 * 93.7 – 112.1</td>
</tr>
<tr>
<td>AUC\text{0-inf} (ng.h/ml)</td>
<td>324.0 ± 78.8 (314.9)</td>
<td>323.1 ± 110.0 (305.6)</td>
<td>103.0 * 93.9 – 113.0</td>
</tr>
</tbody>
</table>

* geometric mean
The results of the study show that preset acceptance limits of 80 - 125 % are met by both AUC and $C_{\text{max}}$ values regarding amodiaquine. Accordingly, the test product Amodiaquine hydrochloride 200 mg tablets (Guilin Pharmaceutical Co., Ltd, China), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Flavoquine® (200 mg tablets, Aventis Laboratoire).

### 4. Summary of Product Safety and Efficacy

Amodiaquine Hydrochloride Tablets 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 Amodiaquine Hydrochloride Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Flavoquine 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 considered. 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 Amodiaquine Hydrochloride Tablets is used in accordance with the conditions as stated in the SmPC.

#### Bioequivalence

Amodiaquine Hydrochloride Tablets has shown to be bioequivalent with the innovator, Flavoquine, from Aventis Laboratoire.

#### Efficacy and Safety

Regarding clinical efficacy and safety, Amodiaquine Hydrochloride Tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are considered.

#### 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 Amodiaquine Hydrochloride Tablets was acceptable for the following indication: treatment of uncomplicated malaria and has advised that the product characteristics are acceptable to allow inclusion of Amodiaquine Hydrochloride Tablets, manufactured at Guilin Pharmaceutical Co., Ltd., Guangxi, China, in the list of prequalified medicinal products.

### References:

General:
Guidelines for the Treatment of Malaria, World Health Organization, 2010
(http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf)