SCIENTIFIC DISCUSSION

| Name of the Finished Pharmaceutical Product: | Artemether 20 mg and Lumefantrine 120 mg Tablets* |
| Manufacturer of the Prequalified Product: | Ipca Laboratories, Ltd. - India |
| Active Pharmaceutical Ingredients (APIs): | Artemether/lumefantrine |
| Pharmaco-therapeutic group (ATC Code): | artemether, combinations (P01BE52) |
| Therapeutic indication: | The fixed dose combination of artemether/lumefantrine is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to artemether as well as to lumefantrine. |

* 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

Artemether 20 mg and Lumefantrine 120 mg Tablets is a fixed dose combination of artemether and lumefantrine. It is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum strains which are susceptible to artemether as well as to lumefantrine.

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 a combination of artemether and lumefantrine. Official guidance will normally include WHO (http://www.who.int/malaria/docs/TreatmentGuidelines2010.pdf) and public health authorities’ guidelines.

2. Assessment of Quality

Introduction

Artemether/Lumefantrine 20mg/120mg tablet is included in both the WHO Model List of Essential Medicines, 16th list, March 2009 and the WHO Model List of Essential Medicines for Children, 2nd list, March 2009.

Active pharmaceutical Ingredients (APIs)

Artemether and lumefantrine have been classified as class 4/3 APIs according to the Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms).

Artemether

Artemether is described in the Ph.Int. Artemether is manufactured from artemisinin via dihydroartemisin (artenimol). The specifications for the starting material and the intermediate ensure adequate control thereof. The production includes a purification step for artemether and leads consistently to one polymorphic form. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The specifications of artemether are Ph.Int. based. Individual limits have been set for artemisinin, dihydroartemisinin and α-artemether, while the unspecified and total impurities are limited to acceptable levels. Particle size and tapped and untapped bulk density are additional user requirements.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 18 months was approved for artemether, when stored not above 25°C, protected from light.

Lumefantrine

The monograph for lumefantrine has been adopted by WHO’s Expert Committee on Specifications for Pharmaceutical Preparations for addition to the Fourth edition of the Ph.Int., Second Supplement.

The production of lumefantrine entails a multi-step chemical conversion process from fluorene, plus a purification step. Adequate specifications are provided for the starting material and isolated intermediate. The manufacturing process leads consistently to one polymorphic form (Form 1). The quality of the API is adequately controlled by its specifications, which include requirements for related substances by HPLC and residual solvents. Particle size distribution and tapped and untapped bulk density are additional user requirements.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 36 months was approved for lumefantrine, when stored not above 30°C.
Other ingredients
Other ingredients used in the tablet formulation include colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose anhydrous, magnesium stearate, polysorbate 80 and purified talc. A certificate was provided for magnesium stearate, confirming that the material is TSE/BSE risk free certificates.

Finished pharmaceutical product (FPP)

Presentation
Artemether 20 mg and Lumeфанtrine 120 mg Tablets are yellow coloured, circular, uncoated, flat faced, bevelled edged, matt finished tablets with a break line on one side and plain on the other side. The score-line is non-functional, and matches the appearance of the innovator tablet, Coartem®. The tablets are packaged in clear transparent PVDC-coated PVC/aluminium blister cards (pack sizes: 6, 12, 18 or 24 tablets).

Pharmaceutical development and manufacture
The manufacturing process involves a conventional wet granulation step. Studies were conducted to optimize the final formulation and manufacturing process during development. API-API and API-excipient compatibility was demonstrated. Extensive studies were performed during development to set the dissolution conditions and acceptance criteria for batch release and to establish similarity of dissolution profiles between the generic formulation and the comparator product used in the bioequivalent studies, namely Coartem®. Critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three primary batches demonstrated the consistency of the process and the quality of the product.

The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product. The product dissolution requirements are discriminatory and considered to be bio-relevant.

Stability testing
Stability studies have been performed on three primary batches at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. At the time of prequalification a shelf-life of 24 months has been allowed for the FPP when stored not above 30°C, protected from light.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2007 according to internationally accepted guidelines.

A randomized, single dose, open label, bioequivalence study of a fixed dose combination of Artemether 20 mg and Lumeфанtrine 120 mg tablets in normal, healthy, adult, male subjects under non fasting condition (study no. WH/AHD/07/004).

The objective of the study was to compare the bioavailability of the stated artemether/lumefantrine 20/120 mg fixed dose combination tablet manufactured by Ipca Laboratories Ltd., India (test drug) with the same dose of the reference formulation (Coartem® 20/120 mg tablet, Novartis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:  Test – 4 tablets Artemether/lumefantrine 20/120 mg (artemether +lumefantrine 80 +480 mg)  
Batch no. BUQ7003F.

Treatment R:  Reference – 4 tablets Coartem® 20/120 mg (artemether +lumefantrine 80 +480 mg)  
Batch no. X1050.
A 47 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 26 samples within 240 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 artemether, dihydroartemisinin and lumefantrine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 2 ng/ml for artemether and dihydroartemisinin and 100 ng/ml for lumefantrine.

The study was performed with 72 participants; data generated from a total of 64 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether, dihydroartemisinin and lumefantrine as well as statistical results are summarised in the following tables:

### Artemether

<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>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVAlog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>2.51 ± 1.01</td>
<td>2.49 ± 0.88</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>107 ± 58 (95)</td>
<td>97 ± 48 (87)</td>
<td>109.6</td>
<td>101.0 – 118.9</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>317 ± 170 (280)</td>
<td>289 ± 145 (256)</td>
<td>109.2</td>
<td>102.4 – 116.6</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng.h/ml)</td>
<td>328 ± 174 (290)</td>
<td>298 ± 148 (265)</td>
<td>109.7</td>
<td>102.8 – 117.0</td>
<td></td>
</tr>
</tbody>
</table>

* geometric mean

### Dihydroartemisin

<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>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVAlog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>2.67 ± 0.95</td>
<td>2.75 ± 0.83</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>164 ± 61 (154)</td>
<td>153 ± 51 (144)</td>
<td>107.2</td>
<td>100.8 – 114.0</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-t}$ (ng.h/ml)</td>
<td>496 ± 165 (472)</td>
<td>468 ± 145 (444)</td>
<td>106.3</td>
<td>102.9 – 109.8</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng.h/ml)</td>
<td>505 ± 166 (482)</td>
<td>476 ± 146 (453)</td>
<td>106.3</td>
<td>102.9 – 109.8</td>
<td></td>
</tr>
</tbody>
</table>

* geometric mean
### Pharmacokinetic Parameter

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Test formulation (T)</th>
<th>Reference (R)</th>
<th>log-transformed parameters</th>
<th>Ratio T/R (%)</th>
<th>Conventional 90% CI (ANOVAlog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t\textsubscript{max} (h)</td>
<td>6.27 ± 1.65</td>
<td>5.98 ± 1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C\textsubscript{max} (ng/ml)</td>
<td>5891 ± 2256 (5469)</td>
<td>6193 ± 2157 (5858)</td>
<td>93.4</td>
<td>87.6 – 99.5</td>
<td></td>
</tr>
<tr>
<td>AUC\textsubscript{0-t} (µg.h/ml)</td>
<td>113.9 ± 54.9 (100.9)</td>
<td>119.5 ± 57.5 (106.4)</td>
<td>94.9</td>
<td>87.3 – 103.2</td>
<td></td>
</tr>
<tr>
<td>AUC\textsubscript{0-inf} (µg.h/ml)</td>
<td>126.0 ± 63.6 (111.4)</td>
<td>132.0 ± 65.9 (117.2)</td>
<td>95.0</td>
<td>87.6 – 103.0</td>
<td></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\textsubscript{max} values regarding artemether, dihydroartemisinin and lumefantrine. Accordingly, the test fixed dose combination tablet Artemether/lumefantrine 20/120 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Coartem* (Novartis).

### 4. Summary of Product Safety and Efficacy

The World Health Organization (WHO) recommends combinations of antimalarials for the treatment of uncomplicated *P. falciparum* malaria, to counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome. The WHO actively encourages malaria-endemic countries to switch to Artemisinin-based Combination Therapy (ACT), and most of them have included ACT in their malaria treatment protocols.

Artemether 20 mg and Lumefantrine 120 mg 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 Artemether 20 mg and Lumefantrine 120 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Coartem 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 Artemether 20 mg and Lumefantrine 120 mg Tablets is used in accordance with the conditions as stated in the SmPC.

#### Bioequivalence

Artemether 20 mg and Lumefantrine 120 mg Tablets has shown to be bioequivalent with the innovator, Coartem, by Novartis Pharma.
Efficacy and Safety

Regarding clinical efficacy and safety, Artemether 20 mg and Lumefantrine 120 mg 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 Artemether 20 mg and Lumefantrine 120 mg Tablets was acceptable for the following indication: treatment of uncomplicated malaria due to Plasmodium falciparum strains which are susceptible to artemether/lumefantrine and has advised that the product characteristics are acceptable to allow inclusion of Artemether 20 mg and Lumefantrine 120 mg Tablets, manufactured at Ipca Laboratories Ltd, Plot no. 255/1, Athal, Silvassa, Dadra & Nagar Haveli, India in the list of prequalified medicinal products.