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	[MA091 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Unit II, Phase II/Phase III, Plot No. 25 – 27 Survey No. 366 Premier Industrial Estate Kachigam Daman – 396210, India
Active Pharmaceutical Ingredient(s) (API)	Artemether and lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA091 trade name] is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults, children and infants of 5 kg and above.

1. Introduction

[MA091 trade name]is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults, children and infants weighing5 kg and above.

[MA091 trade name] should be initiated by a health care provider experienced in the management of malaria.

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)

Artemether

Artemether is described in the Ph.Int. It is manufactured from artemisinin via dihydroartemisinin (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.

The API specifications include tests for description, solubility, identification (IR and TLC), melting range, specific optical rotation, loss on drying, sulphated ash, related substances (HPLC), assay (HPLC), residual solvents and particle size distribution.

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

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.

Lumefantrine

Lumefantrine is described in the Ph.Int. The manufacturing process leads consistently to one polymorphic form.

The quality of the API is adequately controlled by its specifications, which include tests for description, solubility, identification (IR), los on drying, sulphated ash, heavy metals, related substances (HPLC and GC), assay, residual 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 corn starch, colloidal silicon dioxide, hypromellose, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate. TSE/BSE certificates confirmed that none of the excipients are derived from animal sources or come into contact with any animal product.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, circular, flat, bevelled edged, uncoated tablet having "MPL" debossed on one side and plain surface on the other side. The tablets are packaged in clear PVC/Aclar-Alu and PVC/PE/PVdC-Alu blisters.

The development of the final composition of the tablets has been described. The objective was to develop a stable, immediate release, fixed-dose combination tablet, which is bioequivalent to the WHO comparator product, Coartem®. The comparator product was characterised to define the quality target product profile, including dissolution and other product attributes. Batches of the APIs were evaluated for their key physico-chemical characteristics – such as solubility, particle size and flow properties – which may influence the manufacture and performance of the finished product. The selection of excipients for development was based on the desired process and product attributes, as well as demonstrated acceptable compatibility with the APIs.

Due to its demonstrated poor flow characteristics, a non-aqueous granulation process was selected for the lumefantrine part. Artemether, with acceptable flow characteristics, was incorporated in an extra granular stage. The composition and process parameters were optimised to obtain tablets of desired characteristics. The multisource product showed dissolution profiles similar to those of the comparator product. Satisfactory in-process controls have been established.

Specifications

The FPP specifications include tests for description, identification of the APIs (HPLC and TLC), average weight, hardness, friability, disintegration time, loss on drying, uniformity of dosage units (by content uniformity), dissolution (HPLC and UV), residual solvents, related compounds (HPLC and TLC), assay (HPLC) and microbial limits.

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 pack types proposed for marketing of the product. The product proved to be quite stable at both storage conditions in both proposed pack types, showing a slight increase in degradation products, though staying within agreed limits. 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 2011 according to internationally accepted guidelines:

Bioequivalence study of four tablets as single dose of fixed dose combination of Artemether 20 mg and Lumefantrine 120 mg tablets manufactured by Macleods Pharmaceuticals Ltd., India in comparison with four tablets of Coartem® (artemether/ lumefantrine) tablets 20 mg/120 mg manufactured and distributed by Novartis Pharmaceuticals Corporation, USA in healthy, adult, human subjects under fed condition. (study no. BEQ-641-AL(F)-2010).

The objective of the study was to compare the bioavailability of the stated fixed dose Artemether/Lumefantrine 20/120 mg tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference formulation (Coartem®, Novartis Pharmaceuticals Corporation) 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 80 mg + lumefantrine 480 mg) Batch no. EAB5102A.
Treatment R:	Reference – 4 tablets Coartem® (artemether 80 mg + lumefantrine 480 mg) Batch no. F1444L1.

A 30 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 32 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for artemether, dihydro-artemisinin and lumefantrine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/ml for artemether and dihydro-artemisinin and about 100 ng/ml for lumefantrine.

The study was performed with 60 participants; data generated from a total of 55 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether, dihydro-artemisinin (only supportive pharmacokinetic data) and lumefantrine as well as statistical results are summarised in the following tables:

Artemether

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)	2.19 ± 0.99	2.30 ± 1.03	–	–
C_{max} (ng/mL)	217 ± 98 (196)	203 ± 91 (182)	108.0	97.7 – 119.3
AUC_{0-t} (ng·h/mL)	559 ± 252 (497)	523 ± 250 (466)	106.6	99.7 – 114.0
AUC_{0-inf} (ng·h/mL)	594 ± 261 (531)	563 ± 255 (512)	103.6	96.0 – 111.9

Dihydro-artemisinin

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)	2.37 ± 0.93	2.40 ± 0.93	–	–
C_{max} (ng/mL)	147 ± 65 (134)	142 ± 72 (128)	105.3	
AUC_{0-t} (ng·h/mL)	393 ± 119 (373)	382 ± 135 (358)	104.3	
AUC_{0-inf} (ng·h/mL)	422 ± 121 (402)	410 ± 136 (387)	103.9	

Lumefantrine

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)	6.32 ± 1.24	6.47 ± 1.21	-	-
C_{max} (µg/mL)	7.65 ± 3.68 (6.75)	7.07 ± 3.71 (6.19)	109.0	101.3 – 117.2
AUC_{0-72} (µg·h/mL)	145 ± 81 (122)	131 ± 74 (114)	107.1	98.6 – 116.3

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding artemether and lumefantrine. Accordingly, the test fixed dose Artemether/Lumefantrine 20/120 mg Tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis Pharmaceuticals Corporation).

4. Summary of product safety and efficacy

[MA091 trade name] 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 [MA091 trade name] 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 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 [MA091 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA091 trade name] has shown to be bioequivalent with Coartem® (artemether 20 mg + lumefantrine 120 mg tablets), Novartis Pharmaceuticals Corporation, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA091 trade name] 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 [MA091 trade name] was acceptable for the following indication: ‘treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults, children and infants weighing 5 kg and above’ and would allow inclusion of [MA091 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Phase II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman 396210, India, in the list of prequalified medicinal products.