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	[MA205 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Phase II/Phase III, Unit II Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India Oxalis Labs Village Theda, P.O. Lodhimajra, Baddi, Distt. Solan, Himachal Pradesh, 174101, India Tel: +91-1795 661400 Fax: +91-1795 661452
Active Pharmaceutical Ingredient(s) (API)	Artemether/Lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA205 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

[MA205 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.

[MA205 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*.

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

Active pharmaceutical Ingredient (API)

Artemether and lumefantrine have 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 these APIs, used in the manufacture of [MA205 trade name], are 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 assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include corn starch, colloidal silicon dioxide, sodium starch glycolate, hypromellose, microcrystalline cellulose, low substituted hydroxypropyl cellulose and magnesium stearate, all being pharmacopoeial controlled. None of the excipients are derived from human or animal origin. TSE/BSE free certificates have been provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablets are plain on both sides. The tablets are packaged in clear plastic (PVC/Aclar) or clear plastic (PVC/PE/PVDC) on aluminium foil blister cards.

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 finished product specifications include tests for description, identification of the APIs (HPLC and TLC), average weight, hardness, friability, disintegration time, loss on drying, dissolution (detection: HPLC for artemether and UV for lumefantrine), uniformity of dosage units (by content uniformity), residual solvents, related substances (TLC for artemether and HPLC for lumefantrine), assay (HPLC), N-Nitrosodibutylamine (NDBA) content (LCMS≤ 0.03ppm) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage 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 Artemether/Lumefantrine 20/120 mg FDC tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference FDC 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, Cmax and tmax 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 10 ng/mL for artemether, about 10 ng/mL for dihydroartemisinin 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 of artemether, dihydroartemisinin and lumefantrine.

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

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)**	2.00 (0.75 – 4.50)	2.00 (0.75 – 5.00)	-	-
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

** median (range)

Dihydroartemisinin

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) **	2.25 (1.25 – 5.00)	2.25 (1.00 – 5.00)	-	-
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	-

** median (range)

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) **	6.00 (4.50 – 10.00)	6.50 (4.00 – 10.00)	-	-
C_{max} (µg/mL)	7.65 ± 3.68 (6.75)	7.07 ± 3.71 (6.19)	109.0	101.3 – 117.2
AUC_{0-72h} (µg.h/mL)	145 ± 81 (122)	131 ± 74 (114)	107.1	98.6 – 116.3

** median (range)

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

4. Summary of product safety and efficacy

[MA205 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [MA205 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem® (Novartis Pharmaceuticals Corporation) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA205 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer 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 [MA205 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA205 trade name] has been shown to be bioequivalent with Coartem® (Novartis Pharmaceuticals Corporation)

Efficacy and Safety

Regarding clinical efficacy and safety, [MA205 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 [MA205 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 [MA205 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II/Phase III, Unit II, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India and Oxalis Labs Village Theda, P.O. Lodhimajra, Baddi, Distt. Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.