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	[MA143 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited At, Oxalis Labs Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh-174101, India Tel: +91-1795 661400 Fax: +91-1795 661452
Active Pharmaceutical Ingredient(s) (API)	Artemether and Lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA143 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to artemether and lumefantrine in patients weighing 15 kg to less than 25 kg or 35 kg and above.

1. Introduction

[MA143 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum*strains which are susceptible to artemether and lumefantrine in patients weighing 15 kg to less than 25 kg or 35 kg and above.

[MA143 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 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 SeriesNo. 953, 2009, Annex 4). This procedure

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

provides an assurance that these APIs, used in the manufacture of [MA143 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 (maize starch), colloidal silicon dioxide, sodium starch glycolate, hypromellose, microcrystalline cellulose, low substituted hydroxypropyl cellulose and magnesium stearate. Magnesium stearate is of vegetable origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow-coloured, circular, flat, bevelled-edged, uncoated tablet with plain surface on both sides. The tablets are presented in PVC/PE/PVDC-Alu blisters.

Two strengths of artemether/lumefantrine tablets proportionally similar in composition were developed: 80mg/480mg and 40mg/240mg.The development focused on the 80mg/480mg strength, which was used in the BE study against the WHO comparator product Coartem®, (artemether/lumefantrine 20mg/120mg tablets). Once the formulation for the 80mg/480mg strength was finalized, the 40mg/240mg strength was pursued using dose-proportionality approach.

The aim of the product development was to obtain a stable and robust formulation of artemether/lumefantrine tablets, bioequivalent to the comparator product, Coartem® tablets (artemether/lumefantrine 20mg/120mg). The comparator product was characterized to define a 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 (HPLC detection for artemether and UV/VIS detection for lumefantrine), uniformity of dosage units (by content uniformity), residual solvents (GC), related substances (HPLC for lumefantrine and TLC for artemether), assay (HPLC) 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 accelerated condition in the packaging proposed for marketing of the product. Some degradation was noted for artemether at the long-term storage condition in the proposed packaging configuration. Based on the available stability data the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The tablets must be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines:

Single-dose fed in vivo bioequivalence study of fixed dose combination of Azunate-L 480 (artemether and lumefantrine 80 mg/480 mg) tablets (one tablet) (Oxalis Labs, India) with 4 tablets of Coartem® (artemether/lumefantrine) tablets 20 mg/120 mg (Novartis Pharmaceuticals Corporation, USA) in healthy adult, human subjects (study no. BEQ-2060-ArLu (F)-2016).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 80mg/480mg FDC tablet manufactured by/for Macleods Pharmaceuticals Limited, India (test drug) with the reference formulation Coartem® (Novartis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Artemether/Lumefantrine 80mg/480mg
(artemether 80 mg + lumefantrine 480 mg)
Batch no. 15TAM003A.
Treatment R: Reference – 4 tablets Coartem®
(artemether 80 mg + lumefantrine 480 mg)
Batch no. F0171W1.

A 30 day wash-out period was observed between the test and reference. Serial blood samples (1 pre-dose sample and 32 samples within 72h 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 and lumefantrine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 5 ng/mL for artemether and 99 ng/mL for lumefantrine.

The study was performed with 48 participants; data generated from a total of 44 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether 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)	2.53 ± 1.01	2.43 ± 1.06	–	–
C_{max} (ng/mL)	162 ± 68 (147)	146 ± 54 (134)	109.8	100.7 – 119.6
AUC_{0-t} (ng·h/mL)	466 ± 195 (419)	415 ± 147 (381)	110.1	103.6 – 117.0
AUC_{0-inf} (ng·h/mL)	487 ± 202 --	438 ± 158 --	-	-

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)	6.72 ± 0.60	6.65 ± 0.53	–	–
C_{max} (ng/mL)	6272 ± 2456 (5780)	6910 ± 2796 (6365)	90.8	82.6 – 99.9
AUC_{0-72} (ng·h/mL)	100656 ± 41092 (92824)	113226 ± 50356 (103374)	89.8	82.1 – 98.2

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 Artemether/Lumefantrine 80mg/480mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulation Coartem® (Novartis).

A biowaiver was granted for the additional 40mg/240 mg FDC tablet strength (Macleods Pharmaceuticals Limited, India) in accordance to the WHO guideline. In comparison with the 80mg/480mg FDC strength of the test product used in the bioequivalence study, the [MA143 trade name] was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be the same.

4. Summary of product safety and efficacy

[MA143 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [MA143 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. The clinical safety of [MA143 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 [MA143 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA143 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA143 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 [MA143 trade name] was acceptable for the following indication: **''for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 kg and above.indication''**, and would allow inclusion of [MA143 trade name], manufactured at Macleods Pharmaceuticals Limited, At, Oxalis Labs, Village Theda, P.O. Lodhimajra ,Tehsil Baddi, Dist. Solan, Himachal Pradesh-174101, India, in the list of prequalified medicinal products.