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	[MA137 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA137 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

[MA137 trade name] indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults, children and infants of 5 kg and above.

[MA137 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 Series No. 953, 2009, Annex 4). This procedure provides an assurance that these APIs, used in the manufacture of [MA137 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), silicon dioxide, crospovidone, hypromellose, microcrystalline cellulose, sucralose, cherry flavour and magnesium

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

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.

The aim of the product development was to obtain a stable and robust formulation of artemether/lumefantrine 20mg/120mg dispersible tablets, bioequivalent to the comparator product, Coartem® dispersible tablets (artemether/lumefantrine 20mg/120mg). The comparator product was characterized to define a quality target product profile. The excipients selected were based on the comparator product information, suitability to achieve the desired quality target product profile and API-excipient compatibility studies. To improve the flow properties a non-aqueous wet granulation manufacturing process was used for the manufacture of lumefantrine granules. Artemether was incorporated in the extra granular stage to avoid any undue exposure to heat during drying of the wet granules. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with 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, fineness of dispersion, uniformity of dosage units (by content uniformity), dissolution (HPLC for artemether and UV/VIS detection for lumefantrine), 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 2016/2017 according to internationally accepted guidelines:

Single-dose fed in vivo bioequivalence study of fixed dose combination of Artemether and Lumefantrine dispersible tablets 20 mg/120 mg (Macleods Pharmaceuticals Limited, India) to Coartem® (artemether/lumefantrine) dispersible tablets 20 mg/120 mg (Novartis Pharma Schweiz AG; Switzerland) in healthy adult, human subjects (study no. BEQ-2008-ArLu (F)-2016).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 20mg/120mg FDC dispersible tablet manufactured by/for Macleods Pharmaceuticals Limited, India (test drug) with the reference dispersible 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 dispersible tablet Artemether/Lumefantrine 20mg/120mg (artemether 20 mg + lumefantrine120 mg) Batch no.16TAL002.

Treatment R: Reference– 1dispersible tablet Coartem® (artemether 20 mg + lumefantrine120 mg) Batch no. K0065.

The tablets were dispersed in water before intake. A 32-day wash-out period was observed between the test and reference. Serial blood samples (1 pre-dose sample and 30 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 1.5 ng/mL for artemether and 25 ng/mL for lumefantrine.

The study was performed with 54 participants; data generated from a total of 48 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)	2.89 ± 0.79	2.97 ± 0.94	-	-
C_{max} (ng/mL)	158 ± 61 (145)	147 ± 61 (135)	107.6	98.8 – 117.1
AUC_{0-t} (ng·h/mL)	512 ± 192 (471)	504 ± 191 (462)	102.0	95.4 – 109.0
AUC_{0-inf} (ng·h/mL)	536 ± 198 (494)	526 ± 200 (481)	102.5	96.0 – 109.5

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)	7.03 ± 0.71	7.23 ± 1.04	-	-
C_{max} (ng/mL)	1109 ± 437 (1026)	1051 ± 404 (982)	104.5	97.1 – 112.4
AUC_{0-72}(ng·h/mL)	18743 ± 7826 (17106)	17793 ± 7381 (16450)	104.0	97.1 – 111.4

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 20mg/120mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference dispersible formulation Coartem®(Novartis).

4. Summary of product safety and efficacy

[MA137 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, [MA137 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product reference dispersible formulation Coartem® (Novartis) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA137 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 [MA137 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA137 trade name] has been shown to be bioequivalent with dispersible formulation Coartem® (Novartis).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA137 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 [MA137 trade name]was acceptable for the following indication: treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults, children and infants of 5 kg and above., and would allow inclusion of [MA137 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.