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	[MA100 trade name]*
Manufacturer of Prequalified Product	Mylan Laboratories Limited F-4, F-12, Malegaon M.I.D.C. Sinnar, Nashik – 422113 Maharashtra state, India
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA100 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 15 kg and above

1. Introduction

[MA100 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 15 kg and above.

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 [MA100 trade name]. Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and local health authorities' guidelines.

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 (prequalified APIs)

Artemether (reference number WHOAPI-153) and lumefantrine (reference number WHOAPI-155) 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 two APIs, used in the manufacture of [MA100 trade name], are of good quality and manufactured in accordance

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

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 colloidal silicon dioxide, croscarmellose sodium, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate 80 and talc. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round, flat-faced, bevelled edge tablet debossed with 'M' on one side of the tablet and 'AL' above the score and '2' below the score on the other side. The tablets are packaged in Alu-Alu (desiccant embedded) blisters, Alu-Alu blisters or PVC/Aclar-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 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 past experience and demonstrated acceptable compatibility with the APIs.

Both APIs show poor flow properties, thus direct compression was not considered. Artemether is introduced via a dry granulation process and lumefantrine via an aqueous wet granulation process. 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, UV and TLC), dissolution (HPLC and UV detection), uniformity of dosage units (by content uniformity), assay (artemether by HPLC and lumefantrine by UV), water content, hardness, friability, disintegration time, uniformity of mass (for subdivided tablets), related substances (TLC and 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 different pack types proposed for marketing of the product.A slight increase in degradation products was observed, 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 2012 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, oral bioequivalence study of artemether/lumefantrine 20mg/120mg tablets of Mylan Laboratories Limited, India and Coartem® (artemether/lumefantrine) tablets 20mg/120 mg of Novartis

Pharmaceuticals Corp. Suffern, New York 10901 in healthy human adult subjects, under fed conditions (study no. CPL-12-427).

The objective of the study was to compare the bioavailability of the stated artemether/lumefantrine 20/120 mg FDC tablet manufactured by Mylan Laboratories Ltd., India (test drug) with the same dose of the reference FDC formulation (Coartem®, 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 20mg/120mg (artemether 80 mg + lumefantrine 480 mg) Batch no. 1103746.

Treatment R: Reference – 4 tablets Coartem® (artemether 80 mg + lumefantrine 480 mg) Batch no. F2094

A 27-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 samples within 72 hours 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 a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/mL for artemether, to be about 3 ng/mL for dihydroartemisinin and to be about 204 ng/mL for lumefantrine.

The study was performed with 64 participants; data generated from a total of 32 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence of artemether and dihydroartemisinin and data generated from a total of 52 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence of 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)	2.17 (1.33 – 5.00)	2.33 (1.33 – 5.50)	-	-
C_{max} (ng/mL)	156 ± 85 (137)	160 ± 81 (144)	95.5	84.1 – 108.4
AUC0-t (ng.h/mL)	449 ± 228 (406)	419 ± 153 (395)	102.8	91.0 – 116.0
$AUC_{0\text{-inf}}$ (ng.h/mL)	468 ± 233 (425)	438 ± 156 (414)	102.6	91.3 – 115.5

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)	2.67 (1.67 – 5.50)	2.50 (1.33 – 5.00)	-	-
C_{max} (ng/mL)	135 ± 45 (128)	135 ± 48 (126)	101.7	93.0 – 111.2
AUC_{0-t} (ng.h/mL)	432 ± 112 (421)	412 ± 99 (398)	105.7	99.6 – 112.1
AUC_{0-inf} (ng.h/mL)	445 ± 113 (435)	425 ± 100 (411)	105.7	99.8 – 111.9

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)	6.50 (6.00 – 8.00)	6.50 (6.00 – 10.00)	-	-
C_{max} (ng/mL)	3.27 ± 2.21 (2.63)	2.77 ± 1.50 (2.49)	105.5	94.4 – 117.8
AUC_{0-72h} (µg.h/mL)	52.1 ± 36.4 (40.2)	47.2 ± 36.1 (39.1)	102.7	89.7 – 117.7

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, dihydroartemisinin and lumefantrine. Accordingly, the test FDC tablet artemether/lumefantrine 20mg/120mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis).

A biowaiver was granted for the additional strength FDC tablet [MA100 trade name] (Mylan Laboratories Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the FDC tablet [MA100 trade name] was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be similar.

4. Summary of product safety and efficacy

According to the submitted data on quality [MA100 trade name] is a direct scale-up of Artemether/lumefantrine 20mg/120mg tablets. The latter 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 [MA100 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA100 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, [MA100 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 [MA100 trade name] was acceptable for the following indication: **'treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 15 kg and above'**, and would allow inclusion of [MA100 trade name], manufactured at Mylan Laboratories Limited, F-4, F-12, Malegaon M.I.D.C., Sinnar, Nashik – 422113, Maharashtra state, India in the list of prequalified medicinal products.