

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	[MA167 trade name]*
Manufacturer of Prequalified Product	Ipca Laboratories Limited Plot no. 255/1, Village Athal Silvassa 396 230 Dadra and Nagar Haveli (U. T.) India Additional Testing and Release site Laboratórios Basi - Indústria Farmacêutica, S.A. Parque Industrial Manuel Lourenço Ferreira, lotes 8, 15 e 16 3450-232 Mortágua Portugal
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA167 trade name] is indicated for the treatment of uncomplicated malaria due to <i>Plasmodium falciparum</i> in adults, children and infants.

1. Introduction

[MA167 trade name] is indicated for the treatment of uncomplicated malaria caused by *Plasmodium falciparum* in adults, children and infants.

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration.

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 [MA167 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.

Both APIs are of BCS low solubility across the physiological pH range, hence particle size distribution (PSD) is considered a critical API parameter. PSD forms part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lots used in the FPP biobatch.

Other ingredients

Other ingredients used in the tablet formulation include anhydrous lactose, croscarmellose sodium, colloidal anhydrous silica, hypromellose, polysorbate 80, purified talc and magnesium stearate. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow-coloured, circular, uncoated, flat-faced, bevelled-edged, matt-finished tablets with a break line on one side and plain on the other side. The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are packed in either PVDC/PVC-Alu blister cards or PVC/PVDC-Alu blister cards.

This application is based entirely on data already submitted to WHO PQTm for prequalified [MA062 tradename], which was demonstrated to be bioequivalent to the WHO recommended comparator product Coartem[®] tablets, containing 20 mg artemether and 120 mg lumefantrine.

[MA167 trade name] is of the same formulation, manufactured at the same site and uses same sources of excipients, APIs and packaging as [MA062 trade name].

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, average weight, disintegration time, tablet dimensions, hardness, friability, identification of the APIs (HPLC and TLC), uniformity of dosage units (by content uniformity), assay (HPLC), dissolution (HPLC detection), related substances (TLC), moisture content (by KF) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product proved to be quite stable at both storage conditions. 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 2016 according to internationally accepted guidelines.

Study title: A randomized, balanced, open label, two-treatment, three-sequence, three-period, crossover partial replicate, single dose, bioequivalence study of Artemether 20 mg + Lumefantrine 120 mg tablets (4 tablets) manufactured by M/s Ipca Laboratories Ltd., India, with Coartem®

(artemether 20 mg + lumefantrine 120 mg tablets) (4 tablets) of M/s. Novartis Pharma Ltd in normal, healthy, adult, male and female human subjects under non-fasting conditions (study no. ARL/15/559).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 20/120mg FDC tablet manufactured for/by Ipca Laboratories Ltd. (test drug) with the reference formulation Coartem® 20/120 mg FDC tablet (Novartis Pharma Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion, of which treatment R twice:

Treatment T: Test – 4 tablets Artemether/Lumefantrine 20/120 mg tablet
(artemether 80 mg + lumefantrine 480 mg)
Batch no. : HWE0160029

Treatment R: References – 4 tablets Coartem® 20/120 mg
(artemether 80 mg + lumefantrine 480 mg)
Batch no. K0041

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 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 and lumefantrine were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/ml for artemether and about 100 ng/mL for lumefantrine.

The study was performed with 60 participants; data generated from a total of 56 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 (ANOVA log)
t_{max} (h)	2.60 ± 0.96	2.45 ± 0.83	–	–
C_{max} (ng/mL)	158 ± 92	164 ± 90	95.9	88.1–104.5
AUC _{0-t} (ng·h/mL)	478 ± 273 (409)	472 ± 226 (418)	97.9	91.0–105.3
AUC _{0-inf} (ng·h/mL)	495 ± 283	488 ± 234	-	-

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 (ANOVA log)
t _{max} (h)	5.71 ± 0.58	5.79 ± 0.62	–	–
C _{max} (µ/mL)	5768 ± 2173 (5379)	6110 ± 2225 (5712)	94.2	88.2–100.6
AUC _{0-t} (µ·h/mL)	98728 ± 40657 (91287)	105049 ± 43769 (96034)	95.1	89.1–101.4

The results of the study show that present acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding artemether and lumefantrine. Accordingly, the test Artemether/Lumefantrine 20/120 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem[®] 20/120 mg tablet (Novartis Pharma Ltd).

4. Summary of product safety and efficacy

[MA167 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, [MA167 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem[®] 20/120 mg tablet (Novartis Pharma Ltd) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA167 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 [MA167 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA167 trade name] has been shown to be bioequivalent with Coartem[®] (artemether 20 mg + lumefantrine 120 mg tablets), (Novartis Pharma Ltd.).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA167 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 [MA167 trade name] was acceptable for the following indication: ‘treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults,

children and infants', and would allow inclusion of [MA167 trade name], manufactured at Ipca Laboratories Limited, Plot no. 255/1, Village Athal, Silvassa 396 230, Dadra and Nagar Haveli (U.T.), India, in the list of prequalified medicinal products.