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	[MA160 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
Active Pharmaceutical Ingredient(s) (API)	Artemether and Lumefantrine
Pharmaco-therapeutic group (ATC Code)	Antimalarials, blood schizontocide (P01BF01)
Therapeutic indication	[MA160 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above.

1. Introduction

[MA160 trade name] is indicated in the treatment of malaria, as detailed in the summary of product characteristics.

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 Ingredients (APIs)

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 [MA160 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.

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

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 is derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
The multisource product is a yellow coloured, biconvex, capsule shaped, uncoated tablet with break line on one side and "i" debossed on the other side. The tablets are packed in Alu-Alu blister cards.
The development of [MA160 trade name] was based on dose- proportionality approach with [MA062 trade name] which is bioequivalent to the WHO recommended comparator product Coartem® tablets, containing 20 mg artemether and 120 mg lumefantrine and prequalified by WHO PQ.
Both artemether and lumefantrine possess poor flowability and compressibility hence a wet granulation approach was selected for manufacture of the tablets. 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 [MA160 trade name] biobatch. Satisfactory in-process controls have been established.
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), dissolution (HPLC detection), assay (HPLC), related substances (TLC), uniformity of dosage units (by content uniformity for artemether and by weight variation for lumefantrine), 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.

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 20mg/120 mg fixed dose combination tablet manufactured by/for Ipca Laboratories Ltd., India (test drug) with the same dose of the reference formulation (Coartem® 20/120 mg tablet, Novartis) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover, partial replicate study in healthy male and female subjects under fed conditions. Each subject

was assigned to receive each of the following two treatments in a randomized fashion, of which reference treatment R twice:

Treatment T:	Test – 4 tablets artemether/lumefantrine 20 mg / 120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. HWE0160029.
Treatment R:	Reference – 4 tablets Coartem® 20 mg / 120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. K0041.

An up to 30-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, 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 2 ng/mL for artemether and 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.60 ± 0.96	2.45 ± 0.83	-	-
C_{max} (ng/mL)	158 ± 92 (134)	164 ± 90 (140)	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 --	-	-

* geometric mean

Lumefantrine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	5.71 ± 0.58	5.79 ± 0.62	-	-
C_{max} (ng/mL)	5768 ± 2173 (5379)	6110 ± 2225 (5712)	94.2	88.2 – 100.6
AUC_{0-72h} (ng.h/mL)	98728 ± 40657 (91287)	105049 ± 43769 (96034)	95.1	89.1 – 101.4

* geometric mean

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 fixed dose combination tablet artemether/lumefantrine 20 mg /120 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis).

A biowaiver was granted for the additional 80mg/480 mg tablet strength (Ipca Laboratories Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the artemether/lumefantrine 80mg/480 mg tablet was determined to be essentially the same qualitatively; 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 the same.

4. Summary of product safety and efficacy

[MA160 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, [MA160 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem® (Novartis) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA160 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 [MA160 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA160 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. Hence, [MA160 trade name] and Coartem® (Novartis) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA160 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 [MA160 trade name] was acceptable for the following indication: **treatment of uncomplicated malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above**, and would allow inclusion of [MA160 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.