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	[MA136 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)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA136 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.

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

1. Introduction

[MA136 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.

[MA136 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 [MA136 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 microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, hypromellose, polysorbate 80, saccharin sodium, crospovidone, flavour cherry permaseal and magnesium stearate. None of the excipients are derived from animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource dispersible tablets are yellow coloured, circular, flat-faced, bevelled edge and uncoated, with "i" debossed on one side and plain on the other side. The tablets are packed in Alu-Alu and PVC/PCTFE/PVC-Alu blister cards.

The aim of the development was to formulate a stable dispersible tablet that is pharmaceutically equivalent and bioequivalent to the comparator product Coartem® Dispersible, containing 20 mg artemether and 120 mg lumefantrine. The choice of excipients was based on the qualitative composition of the comparator product, supported by drug excipient compatibility studies. Optimisation of excipients was performed in order to obtain the desired quality attributes – like dispersion, disintegration and dissolution – matching the comparator product.

Both artemether and lumefantrine possess poor flowability and compressibility hence a wet granulation approach was selected for manufacture of the tablets. The process is typical for tablets and includes sifting, dry mixing, granulation, drying, milling, blending and compression stages.

During the development of the dispersible tablets, the polymorphic forms of artemether and lumefantrine were studied by XRPD to evaluate any change due to processing or ageing. The polymorphic form remained unchanged for both APIs during manufacture and shelf life.

Specifications
The finished product specifications include tests for description, identification of artemether (HPLC, TLC) and lumefantrine (HPLC, UV), average tablet weight, disintegration time (≤ 3 minutes), tablet dimensions, friability, hardness, fineness of dispersion, uniformity of dosage units (by content uniformity), assay (HPLC), dissolution (HPLC detection; 2-point for artemether), related substances (artemether by TLC and lumefantrine by HPLC), moisture content (IR/halogen moisture balance) 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 in both pack types, showing a slight increase in degradation products though well 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 2016 according to internationally accepted guidelines.

Study title:
A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of [MA136 trade name] (4 tablets) manufactured by M/s Ipca Laboratories Ltd., India, with Coartem® dispersible (artemether 20 mg + lumefantrine 120 mg dispersible tablets) (4 tablets) of M/s. Novartis Pharma AG, Basle, Switzerland, in normal, healthy, adult, male and female human subjects under non-fasting conditions (study no. ARL/15/709).

The objective of the study was to compare the bioavailability of the stated [MA136 trade name] manufactured for/by Ipca Laboratories Ltd., India (test drug) with the reference formulation Coartem®Dispersible (Novartis Pharma AG) 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 treatments in a randomized fashion:

Treatment T:	Test – 4 dispersible tablets Artemether/Lumefantrine 20 mg/120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. FWR40029
Treatment R:	Reference– 4 dispersible tablets Coartem®20 mg / 120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. K0042

A 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 70 participants; data generated from a total of 66 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)	3.22 ± 0.87	3.09 ± 1.00	–	–
C_{max} (ng/mL)	145 ± 74 (127)	136 ± 60 (124)	102.7	95.5 – 110.5
AUC_{0-t} (ng·h/mL)	452 ± 229 (395)	443 ± 194 (402)	98.3	91.8 – 105.3
AUC_{0-inf} (ng·h/mL)	466 ± 235 (--)	457 ± 201 (--)		

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)	5.83 ± 0.60	5.84 ± 0.57	–	–
C_{max} (ng/mL)	6678 ± 1998 (6397)	7652 ± 2541 (7260)	88.1	83.1 – 93.5
AUC_{0-72h} (ng·h/mL)	118215 ± 37725 (112477)	137388 ± 45148 (130428)	86.2	81.8 – 90.9

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 [MA136 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to Coartem® Dispersible (Novartis Pharma AG).

4. Summary of product safety and efficacy

[MA136 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, [MA136 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem® dispersible (Novartis Pharma AG) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA136 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 [MA136 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA136 trade name] has been shown to be bioequivalent with Coartem® (artemether 20 mg + lumefantrine 120 mg dispersible tablets), Novartis Pharma AG, Switzerland.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA136 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 [MA136 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 [MA136 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.