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	[MA115 trade name]*
Manufacturer of Prequalified Product	Cipla Limited Unit IV, Plot no. 9 & 10 Pharma zone, Phase II Indore special economic zone Pithampur (MP)-454775 India
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA115 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.

Introduction

[MA115 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.

[MA115 trade name] should be initiated by a health care provider experienced in the management of malaria.

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

Artemether is manufactured from artemisinin via dihydroartemisinin (artenimol) – both the starting material and the intermediate are described in the Ph.Int. The production includes a purification step for artemether and leads consistently to one polymorphic form. The API is of BCS low solubility, hence particle size distribution (PSD) is considered a critical parameter. The PSD acceptance criteria in the specifications were set on the information of the API lot used in the FPP biobatch.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, melting range, specific optical rotation, sulfated ash, loss on drying, related substances (HPLC), assay (HPLC), PSD and residual solvents.

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

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Lumefantrine

Lumefantrine has 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 lumefantrine, used in the manufacture of [MA115 trade name], is 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.

Lumefantrine is of BCS low solubility across the physiological pH range, hence PSD and polymorphism are considered critical API parameters. PSD and polymorphism form part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lot used in the FPP biobatch.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, crospovidone, hydroxypropyl methylcellulose, polysorbate 80, colloidal anhydrous silica, saccharin sodium, cherry flavour 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 shaped, flat bevelled, uncoated tablet, debossed with 'CL' on one side and plain on the other side. The tablets are presented in PVC/Aclar/PVC-Alu blister packs. The aim of the development was to formulate a stable dispersible tablet that is pharmaceutically equivalent and bioequivalent to the comparator product Coartem® Dispersible 20 mg/120 mg. The quality target product profile was defined based on the properties of the APIs and characterization of the comparator product. The excipients selected are, with the exception of the cherry flavour, qualitatively the same as in the comparator product. Supportive API-API and API-excipient compatibility studies were conducted.

Wet granulation was selected as a method of manufacture based on past experience and the physicochemical properties of the APIs, in particular their poor flow properties and poor solubility. Various studies were performed to optimize the concentration of excipients and process parameters to obtain a product of desired 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 artemether (HPLC, TLC) and lumefantrine (HPLC, UV), average weight, weight variation, tablet dimensions, friability, hardness, disintegration (≤ 3 min), fineness of dispersion, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection; 2-point for artemether), related substances (artemether by TLC and lumefantrine by HPLC), assay (HPLC) and microbiological examination of non-sterile products. 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, showing no apparent negative trends. 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.

Assessment of bioequivalence

The following bioequivalence study has been performed in 2014 according to internationally accepted guidelines.

Study title: A randomized, open label, two treatment, two period, two sequence, single dose, truncated, crossover, bioequivalence study of Artemether 20 mg and Lumefantrine 120 mg dispersible tablets of Cipla Ltd., India with Coartem® dispersible artemether/lumefantrine 20mg/120 mg of Novartis Pharma AG, Basel, Switzerland in normal, healthy, adult human subjects under non-fasting condition (study no. ARL/09/323).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 20mg/120 mg FDC dispersible tablet manufactured for/by Cipla Ltd., India (test drug) with the reference formulation Coartem® (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 tablets [MA115 trade name] (artemether 80 mg + lumefantrine 480 mg)
Batch no. FD4430

Treatment R: Reference – 4 tablets Coartem® (artemether 80 mg + lumefantrine 480 mg)
Batch no. F0770

A 30 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 35 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 analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2ng/ml for artemether and about 100ng/ml for lumefantrine.

The study was performed with 60 participants; data generated from a total of 51 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 lumefantrineas 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)	2.68 ± 0.87	2.68 ± 0.73	–	–
C_{max} (ng/mL)	98 ± 73 (81)	95 ± 60 (80)	101.9	92.1 – 112.7
AUC_{0-t} (ng·h/mL)	254 ± 181 (207)	242 ± 147 (205)	100.9	92.5 – 110.0
AUC_{0-inf} (ng·h/mL)	261 ± 184 (NA)	250 ± 150 (NA)	–	–

NA: not analysed

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)	6.09 ± 0.97	6.15 ± 1.08	–	–
C_{max} (ng/mL)	3225 ± 1302 (2963)	3540 ± 2054 (3107)	95.4	86.0 – 105.7
AUC_{0-t} (ng·h/mL)	53859 ± 28757 (46495)	58029 ± 40579 (48270)	96.3	86.1 – 107.8

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 and lumefantrine. Accordingly, the test [MA115 trade name] dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis Pharma AG.).

Summary of product safety and efficacy

[MA115 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, [MA115 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem® (Novartis Pharma AG.) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA115 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.

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 [MA115 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA115 trade name] has been shown to be bioequivalent with Coartem® (Novartis Pharma AG.).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA115 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 [MA115 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 [MA115 trade name], manufactured at Cipla Limited, Unit IV, Plot no, 9 & 10, Pharma Zone, Indore special economic zone, Pithampur (MP)-454775, India, in the list of prequalified medicinal products.