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	[MA120 trade name]*
Manufacturer of Prequalified Product	Cipla Limited - Unit I Village Upper Malpur P.O. Bhud, Tehsil Nalagarh District Solan Himachal Pradesh 173205 India
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA120 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 kg and above.

1. Introduction

[MA120 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 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 [MA120 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

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 biowaiver biobatch.

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

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.

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 [MA120 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 biowaiver biobatch.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, hypromellose, polysorbate 80, colloidal anhydrous silica and magnesium stearate. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, capsule shaped, biconvex uncoated tablet, debossed with '40' on one side and central breakline on the other side. The breakline is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in PVC/Aclar/PVC-Alu blister packs.

Three strengths of artemether/lumefantrine tablets, proportionally similar in composition and manufactured from a common blend, were developed: 40 mg/240 mg, 60 mg/360 mg and 80 mg/480 mg. The development focussed on the highest strength, which was used in the BE study against the comparator Coartem® 80/480 manufactured by Novartis.

The objective of the development studies was to obtain a stable formulation with acceptable tablet characteristics and dissolution profiles similar to those of the comparator product. The excipients selected are qualitatively the same as in the comparator product.

The manufacture involves an aqueous wet granulation processes for lumefantrine, thereby overcoming its poor flow properties. Due to good flow properties of artemether, it was decided to add it extra-granularly at the blending stage. 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 and with the lower strengths. 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, disintegration, hardness, friability, 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.

3. Assessment of bioequivalence

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

Study title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Artemether and Lumefantrine tablet 80/480 mg of Cipla Ltd., India with Coartem® (artemether 20 mg and lumefantrine 120 mg) tablets [4 x (20 mg / 120 mg) tablets] of Novartis Pharma AG, Basel, Switzerland in normal, healthy, adult, male and female human subjects under fed condition (study no. ARL/13/268).

The objective of the study was to compare the bioavailability of the stated artemether and lumefantrine 80 mg/480 mg FDC 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 – 1 tablet Artemether/Lumefantrine 80 mg/480 mg
	(artemether 80 mg + lumefantrine 480 mg)
	Batch no. D41582
Treatment R:	Reference – Reference – 4 tablets Coartem®
	(artemether 80 mg + lumefantrine480 mg)
	Batch no. F3212

A 30 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 34 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 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 72 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)	2.36 ± 0.79	2.39 ± 0.84	–	–
C_{max} (ng/mL)	75 ± 45 (64)	77 ± 45 (65)	97.6	90.8 – 104.9
AUC_{0-t} (ng·h/mL)	221 ± 131 (185)	221 ± 115 (190)	97.1	90.7 – 103.9
AUC_{0-inf} (ng·h/mL)	229 ± 134 (NA)	230 ± 117 (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)	6.67 ± 0.85	6.51 ± 0.91	–	–
C_{max} (ng/mL)	3349 ± 1760 (2968)	3391 ± 1962 (2897)	102.4	93.4 – 112.4
AUC_{0-t} (ng·h/mL)	55578 ± 33311 (48112)	55914 ± 34021 (46820)	102.8	93.3 – 113.2

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 Artemether/Lumefantrine 80/480 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® (Novartis Pharma AG.).

A biowaiver was granted for the additional 40/240 mg and 60/360 mg tablet strengths (Cipla Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Artemether/Lumefantrine 40/240 mg and 60/360 mg FDC tablets were determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths is considered essential the same and the dissolution profiles between the formulations for the API were determined the same.

4. Summary of product safety and efficacy

According to the submitted data on quality, [MA120 trade name] is a direct-scale down of Artemether/Lumefantrine 80 mg/480 mg FDC tablet. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator 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 [MA120 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA120 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence [MA120 trade name] and Coartem® (artemether 20 mg + lumefantrine 120 mg tablets), Novartis Pharma AG, can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA120 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 [MA120 trade name] was acceptable for the following indication: ' **treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in patients weighing 15 kg to less than 25 kg or 35 kg and above**', and has advised that the quality, efficacy and safety of [MA120 trade name] allow inclusion of [MA120 trade name], manufactured at Cipla Limited, Unit I, Village Upper Malpur, P.O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh – 173205, India, in the list of prequalified medicinal products.