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	[MA130 trade name]*
Manufacturer of Prequalified Product	Ajanta Pharma Limited B-4-5-6, MIDC Industrial Area Paithan, Aurangabad, 431148 Maharashtra, India.
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA130 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35kg and above

1. Introduction

[MA130 trade name] is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults and children of 35kg 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 [MA130 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 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 two APIs, used in the manufacture of [MA130 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.

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

The APIs are of BCS low solubility, hence particle size distribution (PSD) and polymorphism are considered critical parameters. 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 biowaiver batch.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, crospovidone, sodium lauryl sulfate, colloidal silicon dioxide, purified talc and magnesium stearate. BSE/TSE compliance declarations were provided for all excipients. Magnesium stearate and sodium lauryl sulfate are from vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, capsule shaped, biconvex uncoated tablet with break line on one side. The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are presented in clear PVC/PVdC-Alu blisters.

Four strengths of Artemether/Lumefantrine Tablets, proportionally similar in composition and manufactured from a common blend, were developed: 20 mg/120 mg, 40 mg/240 mg, 60 mg/360 mg and 80 mg/480 mg. The development focused on the lowest strength.

The objective of the development studies was to obtain a stable formulation of artemether and lumefantrine tablets pharmaceutically and therapeutically similar to the WHO recommended comparator product, Coartem® 20/120 manufactured by Novartis. The comparator product was evaluated to define the quality target profile, including dissolution profiles. Critical quality attributes of the APIs that may have potential impact on the product's manufacture and performance were studied and discussed. These include solubility, PSD, flow properties and bulk/tapped density.

Direct compression was chosen due to its ease of processability and reduced process time compared to a process that involves wet granulation. Due to the poor flow properties of lumefantrine the excipients were carefully selected and in order to be suitable for the direct compression process. Process parameters were optimised to get tablets of the desired characteristics. Appropriate in-process controls were set to ensure batch-to-batch quality.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), average weight, uniformity of weight and content, resistance to crushing, water content, related substances (artemether by TLC and lumefantrine by HPLC), dissolution (artemether by HPLC detection and lumefantrine by UV/VIS detection), assay (HPLC) and microbiological purity. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted in the proposed packaging at 30°C/75%RH as long-term storage condition and for six months at 40°C/75%RH as accelerated conditions. 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 2013 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of [MA130 trade name] of Ajanta Pharma Ltd., India with Coartem® 20/120 (artemether 20 mg + lumefantrine 120 mg tablets) of Novartis Pharmaceuticals in normal, healthy, adult, male and female human subjects under non fasting condition (study no. ARL/12/394).

The objective of the study was to compare the bioavailability of the stated [MA130 trade name] FDC tablet manufactured by Ajanta Pharma Ltd., India (test drug) with the reference formulation Coartem® (Novartis) 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 two treatments in a randomized fashion:

Treatment T:	Test – 4 tablets [MA130 trade name] (artemether 80 mg + lumefantrine 480 mg)Batch no. P0352I.
Treatment R:	Reference – 4 tablets Coartem® (artemether 80 mg + lumefantrine 480 mg)Batch no. F2782.

A 21 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for artemether, its metabolite dihydroartemisinin and lumefantrine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 2 ng/mL for artemether, 6 ng/mL for dihydroartemisinin and 100 ng/mL for lumefantrine.

The study was performed with 72 participants; data generated from a total of 70 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether, its metabolite dihydroartemisinin 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)	2.83 ± 0.94	2.51 ± 0.75	-	-
C_{max} (ng/mL)	81 ± 41 (71)	90 ± 47 (78)	91.2	84.5 – 98.5
AUC_{0-t} (ng·h/mL)	238 ± 125 (202)	247 ± 125 (214)	94.5	88.7 – 100.6
AUC_{0-inf} (ng·h/mL)	250 ± 127 (213)	255 ± 128 (222)	96.0	90.4 – 102.0

Dihydroartemisinin

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)	3.04 ± 0.78	2.71 ± 0.76	-	-
C_{max} (ng/mL)	135 ± 46	142 ± 45	-	-
AUC_{0-t} (ng·h/mL)	392 ± 124	401 ± 118	-	-
AUC_{0-inf} (ng·h/mL)	415 ± 146	422 ± 130	-	-

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)	5.93 ± 0.73	5.84 ± 0.83	-	-
C_{max} (ng/mL)	6136 ± 2880 (5493)	6350 ± 2919 (5708)	96.2	89.8 – 103.1
AUC_{0-72h} (ng·h/mL)	99070 ± 48130 (85699)	100394 ± 51333 (87536)	97.9	90.8 – 105.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding artemether and lumefantrine. Accordingly, the test FDC tablet [MA130 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis).

A biowaiver was granted for the additional 80/480 mg tablet strength (Ajanta Pharma Ltd., India) in accordance to WHO guideline. In comparison with the 20/120 mg strength of the test product used in the bioequivalence study, the [MA130 trade name] were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the API was determined to be the same.

4. Summary of product safety and efficacy

[MA130 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, [MA130 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 [MA130 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 [MA130 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA130 trade name] has been shown to be bioequivalent with Coartem® (artemether 20 mg + lumefantrine 120 mg tablets), Novartis Pharmaceuticals Corporation, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA130 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 [MA130 trade name] was acceptable for the following indication: ' **treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35kg and above**', and would allow inclusion of [MA130 trade name], manufactured at Ajanta Pharma Limited, B-4-5-6, MIDC Industrial Area, Paithan, Aurangabad, Maharashtra, India, in the list of prequalified medicinal products.