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	[MA111 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	[MA111 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

1. Introduction

[MA111 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.

[MA111 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

Artemether is described in the Ph.Int. It is manufactured from artemisinin via dihydroartemisinin (artenimol). The specifications for the starting material and the intermediate ensure adequate control thereof.

The API specifications, which are Ph.Int. based, include tests for description, solubility, identification, melting range, specific optical rotation, sulfated ash, loss on drying, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC) and particle size distribution.

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 packing material.

Lumefantrine

Lumefantrine is described in the Ph.Int. Lumefantrine is of BCS low solubility over the full physiological pH range.

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

Lumefantrine (reference numbers WHOAPI-137 and WHOAPI-121) 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 Artemether/Lumefantrine 20mg/120mg Tablets, 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.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, crospovidone, sodium lauryl sulfate, colloidal silicon dioxide, purified talc and magnesium stearate. 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 circular flat uncoated tablet. The tablets are packed in clear PVC/PVdC-aluminium blisters.

The objective of the development studies was to obtain a stable formulation of artemether and lumefantrine tablets pharmaceutically and therapeutically similar to the comparator product, Coartem® 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, particle size distribution, 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. Validation data presented on three consecutive production scale batches demonstrated the consistency of the process and the quality of the product.

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, related substances (for artemether by TLC and for lumefantrine by HPLC), dissolution (artemether by HPLC detection and lumefantrine by UV/VIS), assay (HPLC) and microbiological purity.

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 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 Artefan 20/120 (artemether 20 mg + lumefantrine 120 mg tablets) 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 Artefan 20/120 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 Artefan 20/120
(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 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, 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**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_{0-72} (ng·h/mL)	99070 ± 48130 (85699)	100394 ± 51333 (87536)	97.9	90.8 – 105.6

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 FDC tablet Artefan 20/120 meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis).

4. Summary of product safety and efficacy

[MA111 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [MA111 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator 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 [MA111 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA111 trade name] has shown to be bioequivalent with the Coartem® (artemether 20 mg + lumefantrine 120 mg tablets), Novartis Pharmaceuticals Corporation, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA111 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 [MA111 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 [MA111 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.