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	[MA092 trade name]*
Manufacturer of Prequalified Product	Ajanta Pharma Limited B-4-5-6, MIDC Industrial Area Paithan, Aurangabad, 431148 Dist: Aurangabad Maharashtra, India. Tel.: +91-2431-664000 Fax: +91-2431-664100
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA092 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

[MA092 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.

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 [MA092 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 described in the Ph.Int.

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

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

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

Data provided show that lumefantrine is of BCS low solubility over the full physiological pH range. The production thereof entails several chemical steps, plus a purification step which consistently yields one polymorphic form, Form 1, characterised by XRPD.

The quality is adequately controlled by the API specifications, which include tests for description, solubility, identity, melting point, loss on drying, residue on ignition, heavy metals, related substances (HPLC), residual solvents, polymorphic form (XRPD), assay (HPLC) 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.

Other ingredients

Other ingredients used in the tablet formulation include aspartame, capsaroma flavour orange DC 116 PH, capsaroma flavour peppermint DC 117 PH, colloidal anhydrous silica, crospovidone, low-substituted hydroxypropyl cellulose, magnesium stearate, mannitol and microcrystalline cellulose. TSE/BSE-free certifications have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The product is a yellow coloured, circular, flat bevelled edge, dispersible tablet. The tablets are packed in clear PVC/PVdC-aluminium blister packs.

The development of the final composition of product has been described. The objective was to develop a stable formulation of artemether and lumefantrine dispersible tablets pharmaceutically and therapeutically similar to the comparator product, Coartem® 20 mg/120 mg dispersible tablets manufactured by Novartis. 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 processibility. Excipients were selected accordingly in order to be suitable for the direct compression process. The composition includes aspartame as sweetener and a combination of orange and peppermint for flavouring. 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 and uniformity of weight, tablet diameter, resistance to crushing, disintegration time (≤ 3 minutes), fineness of dispersion, dissolution (HPLC detection), uniformity of content, related substances (TLC and HPLC), assay (HPLC) and microbiological purity.

Stability testing

Stability studies have been conducted in the proposed blister packs 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 a slight increase in disintegration time, though staying within the

pharmacopoeial requirement of 3 minutes. 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 2011 according to internationally accepted guidelines.

A randomized, balanced, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of test product [MA092 trade name] (artemether 20 mg + lumefantrine 120 mg dispersible tablets) of Ajanta Pharma Limited India., with reference product Coartem® dispersible (artemether 20 mg + lumefantrine 120 mg dispersible tablets) of Novartis Pharma AG, Switzerland., in normal, healthy, adult, male and female human subjects under fed conditions. (study no. ARL/11/366)

The objective of the study was to compare the bioavailability of the stated [MA092 trade name] manufactured by Ajanta Pharma Limited India (test drug) with the same dose of 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 two treatments in a randomized fashion:

Treatment T: Test – 4 tablets [MA092 trade name]
(artemether 80 mg + lumefantrine 480 mg)
Batch no. P0241E.

Treatment R: Reference – 4 tablets Coartem®
(artemether 80 mg + lumefantrine 480 mg)
Batch no. F0323.

A 21day 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, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for artemether, dihydro-artemisinin and lumefantrine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 4 ng/mL for artemether, 6 ng/mL for dihydro-artemisinin and 100 ng/mL for lumefantrine.

The study was performed with 60 participants; data generated from a total of 49 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether, dihydro-artemisinin 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)	3.85 ± 0.94	3.99 ± 0.87	-	-
C_{max} (ng/mL)	178 ± 73 (164)	175 ± 80 (159)	103.4	95.4 – 112.0
AUC_{0-t} (ng·h/mL)	491 ± 165 (458)	496 ± 192 (458)	100.0	93.7 – 106.7
AUC_{0-inf} (ng·h/mL)	509 ± 171	513 ± 197	100.0	94.0 – 106.5

	(475)	(475)		

Dihydro-artemisinin

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)	4.04 ± 0.71	4.14 ± 0.64	-	-
C_{max} (ng/mL)	168 ± 56	164 ± 47	-	-
AUC_{0-t} (ng·h/mL)	482 ± 140	494 ± 134	-	-
AUC_{0-inf} (ngh/mL)	502 ± 144	513 ± 140	-	-

- not calculated

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)	6.71 ± 1.32	6.84 ± 1.68	-	-
C_{max} (µg/mL)	8.02 ± 3.33 (7.35)	8.60 ± 3.73 (7.79)	94.3	86.2 – 103.2
AUC_{0-72h} (µg·h/mL)	142 ± 73 (126)	151 ± 78 (131)	95.9	88.2 – 104.4

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 fixed dose combination tablet [MA092 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis Pharma AG).

4. Summary of product safety and efficacy

[MA092 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, [MA092 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 [MA092 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 [MA092 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA092 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, [MA092 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 [MA092 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 [MA092trade name], manufactured at Ajanta Pharma Limited, B-4-5-6, MIDC Industrial Area, Paithan, Aurangabad, 431148, Dist: Aurangabad, Maharashtra, India, in the list of prequalified medicinal products.