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	[MA088 trade name]*
Manufacturer of Prequalified Product	Strides Arcolab Limited KRS Gardens, Tablet Block 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk Bangalore – 562 106 India Tel : +91-80-67840600 Fax : +91-80-67840606
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA088 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

[MA088 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 Artemether/Lumefantrine 20mg/120mg Tablets. 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

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

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 production includes a purification step for artemether and leads consistently to one polymorphic form.

The API specifications include tests for description, solubility, identification (IR, melting range and TLC), sulphated ash, heavy metals, loss on drying, specific optical rotation, related substances (HPLC), assay (HPLC), residual solvents, particle size distribution, foreign matter and microbial limits.

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. The production of the API entails a multi-step chemical conversion process from fluorene. The manufacturing process leads consistently one polymorphic form (Form 1).

The quality of the API is adequately controlled by its specifications, which include tests for description, solubility, identification (IR), melting range, los on drying, sulphated ash, heavy metals, related substances (HPLCP), assay (titrimetric), residual solvents, bulk density, particle size distribution and foreign matter.

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 colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose and polysorbate 80. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Artemether/Lumefantrine 20mg/120mg Tablets are yellow coloured, circular, flat bevel edged uncoated tablets with break-line on one surface and plain on other side. The break-line is to facilitate breaking of the tablets for ease of swallowing. The tablets are packaged in clear transparent PVC/PE/PVDC-Alu blisters.

The development of the final composition of the tablets has been described. The objective was to develop a stable, immediate release, fixed-dose combination tablet, which is bioequivalent to the WHO comparator product, Coartem®. The excipients selected are qualitatively the same as those used in the comparator product. Initially both direct compression and wet granulation approaches were investigated for manufacture. Since direct compression was not feasible due to poor flow properties of the blend, wet granulation using an aqueous organic medium was chosen and with this approach an optimized formula and process were derived.

The multisource product showed dissolution profiles similar to that of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data demonstrated the consistency of the process and the quality of the product.

Specifications

The FPP specifications include tests for description, identification of the APIs (HPLC and TLC), uniformity of weight, uniformity of dosage units (by content uniformity), loss on drying, disintegration time, dissolution, related substances (HPLC and TLC), assay (HPLC), microbial limits and residual solvents.

Stability testing

Stability studies have been conducted at 25°C/60%RH and 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Significant changes were observed at accelerated storage conditions (with respect to e.g. dissolution and artemether assay), which are regarded negative for excursions above the recommended storage temperature. The data collected at the long term storage conditions support the proposed shelf-life and storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines:

A randomized, open label, balanced, single center, two treatment, three period, three sequence, single dose, partial replicate, reference scaled, three way crossover bioequivalence study of four tablets of fixed dose combination containing COMBIART (Artemether and Lumefantrine tablets [20/120mg]) manufactured by Strides Arcolab Limited, Bangalore, India and four tablets of Coartem® (Artemether/Lumefantrine) tablets 20/120 mg manufactured by Novartis Pharmaceuticals Corp. Suffern, New York 10901 in healthy human adult male subjects, under fed conditions (study no. S-11-175).

The objective of the study was to compare the bioavailability of the stated fixed dose Artemether/Lumefantrine 20/120 mg tablet manufactured by Strides Arcolab Ltd., India (test drug) with the same dose of the reference formulation (Coartem®, Novartis Pharmaceuticals Corporation) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, partial replicate, crossover study in healthy male 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 Artemether/Lumefantrine 20/120 mg (Artemether 80 mg + lumefantrine 480 mg) Batch no. 7214441.

Treatment R: Reference – 4 tablets Coartem® (Artemether 80 mg + lumefantrine 480 mg) Batch no. F2130.

A 21 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 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 5 ng/mL for artemether, 3 ng/mL for dihydro-artemisinin and about 205 ng/mL for lumefantrine.

The study was performed with 63 participants; data generated from a total of 39 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)	2.42 ± 0.86	2.47 ± 0.99	-	-
C_{max} (ng/mL)	162 ± 72	165 ± 66	98.9	88.9 – 110.0

	(146)	(148)		
AUC_{0-t} (ng·h/mL)	509 ± 213 (463)	473 ± 203 (424)	109.1	99.1 – 120.0
AUC_{0-inf} (ng·h/mL)	528 ± 220 (481)	490 ± 206 (443)	108.7	99.2 – 119.1

Dihydro-artemisinin

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)	2.96 ± 0.90	2.85 ± 0.94	-	-
C_{max} (ng/ml)	114 ± 43 (134)	115 ± 42 (128)	98.9	91.5 – 107.1
AUC_{0-t} (ng·h/mL)	392 ± 121 (373)	361 ± 118 (358)	108.4	102.4 – 114.6
AUC_{0-inf} (ng·h/mL)	405 ± 122 (402)	373 ± 120 (387)	108.2	102.3 – 114.4

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)	7.44 ± 1.94	6.81 ± 1.06	-	-
C_{max} (µg/ml)	3.37 ± 1.94 (2.72)	2.93 ± 1.64 (2.66)	102.1	85.7 – 121.6
AUC_{0-72h} (µg·h/ml)	61.7 ± 51 (43.6)	50.2 ± 33 (43.1)	101.2	82.7 – 123.9

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 Artemether/Lumefantrine 20/120 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis Pharmaceuticals Corporation).

4. Summary of product safety and efficacy

[MA088 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, [MA088 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Coartem® (Novartis Pharmaceuticals Corporation) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA088 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 [MA088 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA088 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, [MA088 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 [MA088 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 [MA088 trade name], manufactured at Strides Arcolab Limited, KRS Gardens, Tablet Block, 36/7, Suragajakkanahalli, Indlavadi cross, Anekal Taluk, Bangalore – 562 106, India in the list of prequalified medicinal products.