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:	[MA138 trade name][*]
Manufacturer of Prequalified Product:	Strides Pharma Science Limited KRS Gardens Tablet Block 36/7, Suragajakkanahalli Indlavadi cross Anekal Taluk Bangalore 562106 India
Active Pharmaceutical Ingredient (API):	Artemether and Lumefantrine
Pharmaco-therapeutic group (ATC Code):	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication:	[MA138 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children weighing 35 kg and above.

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

1 Introduction

[MA138 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children weighing 35 kg and above.

[MA138 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 Ingredients (APIs)

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 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 biobatch.

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 packaging.

Lumefantrine

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 lumefantrine, used in the manufacture of Artemether/Lumefantrine 80mg/480mg 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. 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 biobatch.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, povidone, polysorbate 80, sodium lauryl sulfate and magnesium stearate. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow-coloured, capsule-shaped, biconvex tablet with a break-line on one side and plain on the other 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, transparent PVC/PE/PVDC-Alu blister packs of 6 tablets. One such blister is packed in a carton.

The aim of the formulation development was to develop a stable, robust and reproducible tablet dosage form of Artemether/Lumefantrine 80mg/480mg Tablets which is bioequivalent to the WHO recommended comparator product Coartem® 20mg/120mg Tablets. The excipients selected are commonly used in pharmaceutical preparations. The manufacturing process involving wet granulation was developed and optimized during the development of the formulation. Critical process steps and process parameters were identified and their impact on the process and product was investigated. The results of in-process controls have demonstrated that the manufacturing method is appropriate for the production of the finished pharmaceutical product with reproducible high quality.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC, TLC), water content (KF), uniformity of weight, dissolution (HPLC detection; 2-point for artemether), related substances (artemether by TLC and lumefantrine by HPLC), uniformity of dosage units (by content uniformity), uniformity of dosage units (by weight variation), assay (HPLC) and microbial limits. 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. 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 Bio-Equivalence

The following bioequivalence study has been performed in 2016/2017 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, two-treatment, three-period, three-sequence, single dose, crossover, partial-replicate, reference scaled, oral bioequivalence study of Artemether and Lumefantrine tablets 80/480 mg of Strides Shasun Limited, India comparing with that of Coartem® (artemether and lumefantrine) tablets 20/120 mg of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936 in healthy, adult, human subjects under fed conditions (study no. 776/15).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 80 mg/480 mg FDC tablet manufactured for/by Strides Pharma Science Limited, India (test drug) with the reference formulation Coartem® 20 mg/120 mg (Novartis Pharmaceuticals Corporation) 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, of which treatment R twice:

Treatment T:	Test – 1 tablet Artemether/Lumefantrine 80 mg/480 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. 7226792
Treatment R:	Reference – 4 tablets Coartem® 20 mg/120 mg (artemether 80 mg + lumefantrine 480 mg) Batch no. F0171

A 21-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 22 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 2.5 ng/mL for artemether and about 50 ng/mL for lumefantrine.

The study was performed with 60 participants; data generated from a total of 54 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.47 ± 0.80	2.16 ± 0.74	-	-
C_{max} (ng/mL)	186 ± 89 (164)	173 ± 86 (151)	109.0	100.4 – 118.3
AUC_{0-t} (ng.h/mL)	493 ± 214 (444)	462 ± 226 (407)	109.1	102.2 – 116.5
AUC_{0-inf} (ng.h/mL)	513 ± 222 (463)	480 ± 231 (424)	109.3	102.5 – 116.5

* geometric mean

Lumefantrine

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)	6.02 ± 0.89	5.99 ± 0.82	-	-
C_{max} (µg/mL)	6.23 ± 2.20 (5.93)	6.50 ± 2.67 (5.94)	99.8	93.3 – 106.8
AUC_{0-72h} (µg.h/mL)	100.4 ± 40.4 (93.9)	109.9 ± 53.8 (97.7)	96.2	89.5 – 103.3

* geometric mean

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 mg/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 Pharmaceuticals Corporation).

4. Summary of Product Safety and Efficacy

[MA138 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, [MA138 trade name] 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 [MA138 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA138 trade name] has shown to be bioequivalent with the Coartem® (artemether 20 mg + lumefantrine 120 mg tablets), Novartis Pharmaceuticals, USA.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA138 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 [MA138 trade name] was acceptable for the following indication**: "treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children weighing 35 kg and above"** and would allow inclusion of [MA138 trade name], manufactured at Strides Pharma Science Limited, KRS Gardens, Tablet Block, 36/7, Suragajakkanahalli, Indlavadi Cross, Anekal Taluk, Bangalore, 562106, India, in the list of prequalified medicinal products.