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	[MA108 trade name]
Manufacturer of Prequalified Product	Novartis Pharma AG Postfach CH-4002 Basel Switzerland
Active Pharmaceutical Ingredient(s) (API)	Artemether, lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	MA108 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above

1. Introduction

[MA108 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35 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 80mg/480mg Tablets. Official guidance will normally include WHO and local health authorities' guidelines.

[MA108 trade name] should be initiated by a health care provider experienced in the management of malaria infection.

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 include tests for description, clarity and absorbance of solution, particles size distribution, identification (IR), residual solvents, sulfated ash, specific optical rotation, heavy metals, crystal modification (XRPD), organic impurities (HPLC), microbial enumeration and assay (HPLC).

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 synthesis from 9H-fluorene. The manufacturing process leads consistently to one polymorphic form.

The quality of the API is adequately controlled by its specifications, which include tests for description, particle size distribution, clarity of solution, identification (IR), residual solvents, loss on drying, sulphated ash, heavy metals, organic impurities (HPLC), microbial enumeration and assay (HPLC).

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 microcrystalline cellulose, croscarmellose sodium, hypromellose, colloidal anhydrous silica, polysorbate 80 and magnesium stearate. None of the excipients are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Artemether/Lumefantrine 80 mg/480 mg Tablets ([MA108 trade name]) are yellow, ovaloid with compound cup tablets, debossed with “C4” on one side and “NVR” on the other side.

Riamet 80/480 mg is a new dosage strength of Riamet 20/120 mg. Instead of taking 4 tablets of 20/120 mg per dose, 1 tablet of 80/480 mg should be taken per dose. The size, weight and shape of the tablet were increased proportionately using the commercial Riamet 20 mg/120 mg final blend to get the required dose. The tablets are produced according to standard manufacturing processes: mixing, wet granulation, screening, blending, and compression.

The data gathered during process validation show that the manufacturing process is robust and consistently yields a product which meets the predetermined quality characteristics. The chosen in-process tests have been shown to be suitable for monitoring the manufacturing process.

Specifications

The FPP specifications include tests for description, mean mass, identification (TLC, HPLC), degradation products of lumefantrine (HPLC) and artemether (TLC), assay (HPLC), dissolution (lumefantrine by UV/VIS detection and artemether by HPLC detection), uniformity of dosage units (by content uniformity) and microbial enumeration. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 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. The data showed slight degradation for artemether, though all parameters were well within the agreed limits at both storage conditions. Lumefantrine proved to be quite stable with no apparent trend. 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 2012 according to internationally accepted guidelines.

A randomized, open-label, single dose, two-period, within formulation crossover study of Coartem to evaluate the bioequivalence between the novel single 4-in-1 tablet and a dose of four individual tablets and between a novel single 3-in-1 tablet and a dose of three individual tablets in healthy volunteers (study no. COA566A2102).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 80mg/480mg FDC tablet manufactured by Novartis Pharmaceuticals Corporation (test drug) with the reference formulation Riamet®/Coartem® (artemether 20 mg + lumefantrine 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 two treatments in a randomized fashion:

Treatment T:	Test – 1 tablet [MA108 trade name] (artemether 80 mg + lumefantrine 480 mg) Batch no. F0004.
Treatment R:	Reference – 4 tablets Coartem® /Riamet® (artemether 20 mg + lumefantrine 120 mg) Batch no. F2230

A 5 week wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 264h 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 3 ng/ml for artemether and dihydro-artemisinin and about 50 ng/ml for lumefantrine.

The study was performed with 60 participants; data generated from a total of 58 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)	3.0 (1.0 – 8.0)[#]	3.0 (0.75 – 12.0)[#]	-	-
C_{max} (ng/mL)	113 ± 70 (97)	113 ± 59 (100)	97	89 – 106
AUC_{0-t} (ng·h/mL)	389 ± 207 (345)	408 ± 198 (364)	95	89 – 101
AUC_{0-inf} (ng·h/mL)	408 ± 209 (383)	443 ± 202 (402)	95	89 – 102

[#] median (range)

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)	3.0 (1.0 – 8.0)[#]	3.0 (1.5 – 12.0)[#]	-	-
C_{max} (ng/mL)	107 ± 54 (97)	110 ± 51 (101)	95	88 – 105
AUC_{0-t} (ng·h/mL)	376 ± 126 (361)	386 ± 130 (368)	98	93 – 104
AUC_{0-inf} (ng·h/mL)	397 ± 122 (383)	397 ± 130 (384)	100	96 – 105

[#] median (range)

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)	6.0 (4.0 – 10.0)[#]	6.0 (5.0 – 12.0)[#]	-	-
C_{max} (µg/mL)	8.9 ± 3.2 (8.4)	9.5 ± 4.4 (8.7)	97	89 – 105
AUC_{0-t} (µg·h/mL)	236 ± 93 (219)	243 ± 122 (218)	100	93 – 108
AUC_{0-inf} (µg·h/mL)	261 ± 106 (242)	277 ± 146 (242)	100	92 – 109

[#] median (range)

The results of the study show that preset acceptance limits of 80 -125% are met by both AUC and C_{max} values regarding artemether, dihydro-artemisinin (supportive data) and lumefantrine. Accordingly, the test FDC tablet Artemether/Lumefantrine 80 mg/480 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Riamet® (Novartis Pharmaceuticals Corporation).

4. Summary of product safety and efficacy

The clinical safety of [MA108 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 [MA108 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA108 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, [MA108 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 [MA108 trade name] was acceptable for the following indication: 'treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above', and would allow inclusion of [MA108 trade name], manufactured at Novartis Pharma AG, in the list of prequalified medicinal products.