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	[MA211 trade name]*
Manufacturer of Prequalified Product	Quality Chemical Industries Limited Plot 1-7, 1st Ring Road, Luzira Industrial Park, P.O. Box 34871, Kampala-Uganda. Email: contactus@qcil.com
Active Pharmaceutical Ingredient(s) (API)	Artemether/Lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA211 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum.*

1. Introduction

[MA211 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum*. [MA211 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 and 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 these APIs, used in the manufacture of [MA211 trade name], are 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.

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

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, croscarmellose sodium, polysorbate 80, maize starch, purified talc and magnesium stearate, all being pharmacopoeial controlled. Magnesium stearate is of vegetable origin. TSE/BSE free certificates have been provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablets have a break line on one side and are plain on the other side. The break-line can be used to break the tablet for ease of swallowing but not to divide it into equal doses. The tablets are packaged in clear plastic (PVC/Aclar) on aluminium foil blister cards.

The product is a full technology transfer version of MA064 which has been prequalified for Cipla Limited. The product was transferred from Cipla Limited to Quality Chemical Industries Limited as per the WHO guidelines on technology transfer in pharmaceutical manufacturing. The technology transfer report established that the formulation and manufacturing process, which were identical to those of Cipla limited, have been adequately transferred. Additionally, the controls of the FPP are aligned with those of Cipla Limited.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC {for artemether}; HPLC and UV {for lumefantrine}), average weight, disintegration time, hardness, friability, loss on drying, uniformity of dosage units (by content uniformity), dissolution (by HPLC detection), related substances (TLC for artemether and HPLC for lumefantrine), assay (HPLC), elemental impurities, N-nitrosodibutylamine (NDBA) content (LCMS≤ 0.028 ppm) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage conditions in the packaging proposed for marketing of the product. Some degradation was noted for artemether, though these stayed within acceptable limits, at the long-term storage conditions in the proposed packaging configuration. 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 2007 according to internationally accepted guidelines.

A randomized, open label, two treatment, two period, two sequence, single dose, truncated, crossover, bioequivalence study of Artemether 20 mg and Lumefantrine 120 mg tablets of Cipla Ltd., India with Riamet® tablets (containing artemether 20 mg and lumefantrine 120 mg) of Novartis Pharma GmbH, Germany in normal, healthy, adult human subjects under non-fasting condition (study no. ARL/09/314).

The objective of the study was to compare the bioavailability of the stated Artemether/Lumefantrine 20/120 mg FDC tablet manufactured by Cipla Ltd, India (test drug) with the same dose of the reference FDC formulation Riamet® (Novartis Pharma GmbH) 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 Artemether/Lumefantrine 20/120 mg

(artemether 80 mg + lumefantrine 480 mg)
Batch no. KXX9080.

Treatment R: Reference – 4 tablets Riamet®

(artemether 80 mg + lumefantrine 480 mg)

Batch no. X0100

A 22-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 32 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, 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, about 6 ng/ml for dihydroartemisinin and about 100 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 of artemether, dihydroartemisinin and lumefantrine.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artemether, dihydroartemisinin 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)	2.5 ± 0.9	2.6 ± 1.0	-	-
C_{max} (ng/ml)	119 ± 54 (105)	125 ± 62 (111)	94.7	86.7 – 103.5
AUC_{0-t} (ng.h/ml)	349 ± 164 (303)	352 ± 187 (309)	98.1	90.1 – 106.9

* geometric mean

Dihydroartemisinin

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)	2.7 ± 0.8	2.7 ± 1.0	-	-
C_{max} (ng/ml)	146 ± 51	150 ± 52	-	-
AUC_{0-t} (ng.h/ml)	420 ± 151	409 ± 124	-	-

* 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)	6.0 ± 0.8	6.1 ± 1.1	-	-
C_{max} (µg/ml)	4.91 ± 2.53 (4.39)	5.10 ± 2.89 (4.47)	98.3	89.3 – 108.2
AUC_{0-72h} (µg.h/ml)	73.9 ± 44.5 (64.1)	79.3 ± 54.1 (65.5)	97.9	88.7 – 108.1

* 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 FDC tablet Artemether/Lumefantrine 20/120 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Riamet® tablet (Novartis Pharma GmbH).

4. Summary of product safety and efficacy

[MA211 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, [MA211 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Riamet® tablet (Novartis Pharma GmbH).

for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA211 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 [MA211 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA211 trade name] has been shown to be bioequivalent with Riamet® tablet (Novartis Pharma GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA211 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 [MA211 trade name] was acceptable for the following indication: 'treatment of uncomplicated cases of malaria due to *Plasmodium falciparum*, and would allow inclusion of [MA211 trade name], manufactured at Quality Chemical Industries Limited, Plot 1-7, 1st Ring Road, Luzira Industrial Park,P.O. Box 34871,Kampala-Uganda in the list of prequalified medicinal products.