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	[MA064 trade name][*]
Manufacturer of Prequalified Product	Cipla Ltd. Manufacturing division Plot No. A-33/1/2 & A-42 Patalganga Industrial area Dist: Raigad 410 220 Patalganga Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	artemether/lumefantrine
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF01)
Therapeutic indication	[MA064 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to artemether as well as to lumefantrine.

1. Introduction

[MA064 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to artemether and lumefantrine, as detailed in the summary of product characteristics.

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 and lumefantrine have been classified as class 4/3 APIs according to the Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms)*.

Artemether

Artemether is described in the Ph.Int.

Artemether is manufactured from artemisinin via dihydroartemisin (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. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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

The specifications of artemether are Ph.Int. based. Individual limits have been set for artemisinin, dihydroartemisinin and α-artemether, while the unspecified and total impurities are limited to acceptable levels. Particle size as well as tapped and untapped bulk density are additional user requirements.

Based on the results of stability testing conducted according to the requirements of WHO, a re-test period of 18 months was approved for artemether, when stored not above 25°C and protected from light.

Lumefantrine

The monograph for lumefantrine has been adopted by WHO's Expert Committee on Specifications for Pharmaceutical Preparations for addition to the Fourth edition of the Ph.Int., Second Supplement.

The production of lumefantrine entails a multi-step chemical conversion process from fluorene, plus a purification step. Adequate specifications are provided for the starting material and isolated intermediate. The manufacturing process leads consistently to one polymorphic form (Form 1). The quality of the API is adequately controlled by its specifications, which include requirements for related substances by HPLC and residual solvents. Particle size distribution and tapped and untapped bulk density are additional user requirements.

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 36 months was approved for lumefantrine, when stored not above 30°C.

Other ingredients

Other ingredients used in the tablet formulation include croscarmellose sodium, magnesium stearate, polysorbate 80 and purified talc, maize starch, microcrystalline cellulose. A certificate was provided for magnesium stearate, confirming that the material is TSE/BSE risk free certificates.

Finished pharmaceutical product (FPP)

Presentation

[MA064 trade name] are yellow-coloured, circular, uncoated, flat-faced, bevelled edged, matt finished tablets, with a break-line on one side and plain on the other side. The score-line is non-functional, and matches the appearance of the innovator tablet, Coartem®. The tablets are packaged in clear transparent PVDC-coated PVC/aluminium blister cards (pack sizes: 6, 12, 18 or 24 tablets).

Pharmaceutical development and manufacture

The manufacturing process involves a conventional wet granulation step. Studies were conducted to optimize the final formulation and manufacturing process during development. API-API and API-excipient compatibility was demonstrated. Extensive studies were performed during development to set the dissolution conditions and acceptance criteria for batch release and to establish similarity of dissolution profiles between the generic formulation and the comparator product used in the bioequivalent studies, namely Coartem®. Critical steps of the manufacturing process were optimized and appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three primary batches demonstrated the consistency of the process and the quality of the product.

The proposed specifications, analytical methods with validation, and batch quality control results ensure consistent quality for this finished pharmaceutical product. The product dissolution requirements are discriminatory and considered to be bio-relevant.

Stability testing

Stability studies have been performed on three primary batches at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. At the time of prequalification, a shelf-life of 24 months has been allowed for the FPP when stored not above 30°C, protected from light.

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 bioequivalence study comparing the fixed dose combination (FDC) Artemether and Lumefantrine tablets x 4 (containing 20 mg artemether and 120 mg lumefantrine) of Cipla Ltd., India with the fixed dose combination (FDC) Coartem® tablets x 4 (containing 20 mg artemether and 120 mg lumefantrine) manufactured by Beijing Novartis Pharma Ltd., China for Novartis Pharma AG, Basel, Switzerland in 60 healthy adult human male subjects (study no. BBRC/EX/07/044).

The objective of the study was to compare the bioavailability of the stated Artemether/lumefantrine 20mg/120mg fixed dose combination tablet manufactured by Cipla Ltd., India (test drug) with the same dose of the reference formulation (Coartem®, Novartis) and to assess bioequivalence.

The comparison was performed as a single centre, open label, randomized, crossover study in healthy male subjects under fed conditions.

The results of the study showed that the preset acceptance limits of 80 -125 % were met by both AUC and C_{max} values regarding artemether and lumefantrine. Accordingly, the test fixed dose combination tablet Artemether/lumefantrine 20/120 mg met the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Coartem® (Novartis).

However, after a WHO inspection of the study facility had revealed several critical and major deviations from the GLP and GCP standards, WHO issued a Notice of Concern on July 21, 2009. In consequence, the supplier provided a new bioequivalence study performed in 2009, conducted at a different facility, which is detailed below.

Title: 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 (ARL/09/134).

The objective of the study was to compare the bioavailability of the stated artemether/lumefantrine 20mg/120mg fixed dose combination tablet manufactured by Cipla Ld, India (test drug) with the same dose of the reference formulation (Riamet®, Novartis) and to assess bioequivalence.

The comparison was performed as a single centre, open label, randomized, 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 of artemether/lumefantrine 20mg/120mg
(artemether 80 mg + lumefantrine 480 mg)
Batch no. KXX9080.

Treatment R: Reference – 4 tablets of Riamet® 20mg/120mg
(artemether 80 mg + lumefantrine 480 mg)
Lot no. X0100

A 22-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 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, 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, 6 ng/mL for dihydroartemisinin and 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.

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)	118.5 ± 53.7 (105)	124.6 ± 61.8 (110.9)	94.7	86.66 – 103.5
AUC_{0-t} (ng.h/mL)	348.5 ± 163.7 (303.1)	352.4 ± 186.7 (308.8)	98.1	90.10 – 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 ± 0.95	-	-
C_{max} (ng/mL)	145.8 ± 50.5	150.3 ± 51.7	-	-
AUC_{0-t} (ng.h/mL)	419.5 ± 151.1	409.0 ± 123.8	-	-

* 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)	5.97 ± 0.80	6.1 ± 1.1	-	-
C_{max} (ng/mL)	4 909 ± 2 529 (4 395)	5 098 ± 2 889 (4 473)	98.3	89.3 – 108.2
AUC_{0-72h} (ng.h/mL)	73 865 ± 44 516 (64 32)	79 306 ± 54 163 (65 512)	97.9	88.7 – 108.1

* geometric mean

The results of the study show that the 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 artemether/lumefantrine 20mg/120 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore, bioequivalent to the reference Riamet® (Novartis).

4. Summary of product safety and efficacy

[MA064 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, [MA064 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Riamet® (Novartis) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA064 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 [MA064 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA064 trade name] has been shown to be bioequivalent with Riamet® (Novartis).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA064 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 [MA064 trade name] was acceptable for the following indication: '**the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to artemether and lumefantrine**', and would allow inclusion of [MA064 trade name], manufactured at Cipla Ltd, Manufacturing division Plot No. A-33/1/2 & A-42, Patalganga Industrial area, Dist: Raigad, 410 220 Patalganga, Maharashtra, India, in the list of prequalified medicinal products.