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:	[MA124 trade name][*]
Manufacturer of Prequalified Product:	Cipla Limited Plot no. D-7 (Unit 1) MIDC Industrial Atrea Kurkumbh Dist: Pune 413 802 India
Active Pharmaceutical Ingredient (API):	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarial: artemisinin derivative, ATC Code P01BE03
Therapeutic indication:	[MA124 trade name] is indicated for pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment.

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

1. Introduction

[MA124 trade name] is indicated for pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment.

The patient should be immediately referred to a facility where accurate diagnosis and complete treatment with effective antimalarials can be instituted.

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)

Artesunate API is described in the Ph.Int. It is manufactured in a two-step process from artemisinin via dihydroartemisinin (artenimol), followed by a purification step. The specifications for the starting material and the intermediate ensure adequate control thereof. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The Ph.Int. based artesunate specifications include tests for description, solubility, identification, specific optical rotation, heavy metals, sulfated ash, water content, pH, related substances (HPLC), assay (HPLC), residual organic solvents (GC) and particle size distribution.

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

The capsule fill blend contains hard fat and medium chain triglyceride. The capsule shell contains gelatin, glycerol and titanium dioxide. Medium chain triglyceride is also used as an external lubricant and is removed by further processing (degreasing). None of the excipients, except gelatin, is derived from animal origin. The supplier of gelatin provided an EDQM CEP demonstrating TSE/BSE-compliance of this excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The suppositories are white to off white coloured, elongated, soft gelatin capsules containing white to off white paste. The soft gelatin capsules are presented in Alu-Alu blisters, protecting the capsules from moisture.

The development of the product is described. The objective was to obtain a stable formulation of suppositories that would be bioequivalent to the then WHO recommended comparator product, Artesunate suppositories 100 mg (manufactured by Catalent (Eberbach, Germany) and packed and distributed by Scanpharm (Birkerod, Denmark) on behalf of WHO-TDR (Geneva, Switzerland).

The selection of excipients was based on the qualitative composition of the comparator product, API-excipient compatibility studies and stability information. Since the API is present in the solid state in the product, particle size distribution was regarded a CQA.

The manufacturing process involves two basic steps, namely API blend preparation and gelatin shell preparation. The API blend is prepared by mixing artesunate with a dispersion consisting of hard fat and medium chain triglyceride. The API blend is then deaerated and strained through a 60 mesh screen. Gelatin mass for encapsulation is prepared from gelatin, glycerol (as plasticizer) and titanium dioxide (as opacifier). The drug blend is encapsulated into the gelatin mass shell to form soft gelatin capsules. The capsules are then dried and degreased.

Mixing processes are required to ensure even distribution of the API particles. Homogeneity achieved by the mixing procedure was verified by blend uniformity results and confirmed by the blend assessment studies conducted on the primary batches. Uniformity of dosage units is also controlled in the FPP specification.

Forced degradation studies conducted at elevated temperature and relative humidity had a significant impact on the assay as well as related substances of the suppositories. It showed that the product is not stable with respect to temperature and humidity. Hence, temperature and humidity are controlled at suitable levels during manufacture.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (HPLC and IR) and colorant, average weight, net fill content per suppository, loss on drying (shell), disintegration time, rupture time, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), microbial limits, qualitative physical attributes testing (QPAT) and water content (KF). QPAT entails observations of defined events at specified time points during disintegration of the suppositories using a product specific designed apparatus. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. Significant changes were seen at the accelerated condition and relatively rapid changes at the zone IVb condition compared to zone II. This was mainly due to degradation of the API. The regulatory stability data complements the observations during the development studies, namely that the product is sensitive to heat and humidity.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Procurers and distributers should take care to avoid excursions above 30°C during storage and transport of the product. However, it is understood that this storage requirement may not always be adhered to when the product is handled by community health workers (CHWs) located in areas where the ambient temperature is above 30°C. Therefore, procurers and distributors need to ensure that the product is distributed to CHWs located in such areas only as a short term stock, generally not exceeding 4-6 months depending on the remaining shelf life of a given batch and severity of the ambient conditions where the batch is to be distributed.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2015 according to internationally accepted guidelines.

Study title: A randomised, single dose, open label, four-period, replicate cross-over bioequivalence study comparing the test product, Artesunate suppositories 100 mg (Cipla Ltd., India) with the reference product, Artesunate suppositories 100 mg (Manufactured by Catalent [Eberbach, Germany] and packed and distributed by Scanpharm, [Birkerod, Denmark] on behalf of WHO-TDR [Geneva, Switzerland]), in healthy adult male human subjects under fasting conditions (study no. 14-11-107).

The objective of the study was to compare the bioavailability of the stated Artesunate suppositories 100 mg manufactured by Cipla Ltd., India (test formulation) with the reference formulation Artesunate suppositories 100 mg, manufactured by Catalent (Eberbach, Germany), and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, four-period, single dose, replicate, cross-over study in healthy subjects under fasting conditions. Each subject received a single

rectal dose of one artesunate suppository 100mg under fasting conditions in each period in a randomized fashion:

Treatment T: Test - Artesunate suppositories 100 mg (Cipla)
(artesunate 100 mg)
Batch no. KB50270

Treatment R: Reference – Artesunate suppositories 100 mg (Catalent)
(artesunate 100 mg)
Batch no. 142103B

A wash-out period of at least 7 days was observed between the administrations of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 10 h post-dose) were taken during each study period to obtain bioavailability characteristics AUC0-t, C_{max}, and t_{max}, and to evaluate bioequivalence. Drug concentrations for artesunate were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/mL for artesunate.

The study was performed with 80 subjects; data from 78 subjects were utilized for analysis to establish pharmacokinetic parameters and to assess bioequivalence.

Arithmetic and geometric mean values of the pharmacokinetic variables for artesunate as well as statistical results are summarised in the following table:

Artesunate

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)	0.44 (0.25-3.50)#	0.44 (0.25-4.00)#	-	-
C_{max} (ng/mL)	121.12 ± 78.37 (97.74)	117.96 ± 98.66 (93.18)	103.02	94.17 – 112.72
AUC_{0-t} (ng·h/mL)	107.45 ± 64.81 (89.81)	108.12 ± 64.11 (90.27)	98.43	91.74 – 105.62
AUC_{0-inf} (ng·h/mL)	140.39 ± 252.12	113.26 ± 63.73	103.57	96.07 – 111.65

Median (range)

Conclusion

The results of the study show that the preset acceptance limits of 80 -125 % are met by the 90% confidence intervals for both AUC0-t and C_{max} of artesunate. Accordingly, the test Artesunate 100 mg suppository meets the criteria for bioequivalence with regard to rate and extent of absorption, and is therefore bioequivalent to the reference Artesunate suppository 100 mg (Catalent; Eberbach, Germany).

4. Summary of Product Safety and Efficacy

Severe *Plasmodium falciparum* malaria in children is a medical emergency that requires prompt, effective treatment. Children bear the greatest burden of this disease, and the risk of death from severe malaria is greatest in the first 24 hours. Because isolated rural communities often do not have timely access to health care facilities and effective treatment, these populations are at highest risk of dying from severe malaria.

In situations where complete treatment of severe malaria is not possible, current WHO Malaria Treatment Guidelines recommend pre-referral treatment options as follows: for children under 6 years, in descending order of preference, intramuscular artesunate, rectal artesunate, intramuscular artemether, and intramuscular quinine.

A rectally administered pediatric formulation of artesunate is intended as emergency treatment while the ill child is transferred to a facility which can provide complete curative therapy.

Evidence for reduction of malaria-related death and disability in children by rectal artesunate is derived primarily from a large placebo-controlled study conducted at 3 sites in Africa and one in Asia, Study 13, which utilized a rectal suppository formulation developed in collaboration with the WHO (the "TDR formulation").

The "TDR" is the WHO Special Programme for Research and Training in Tropical Diseases.

Safety and efficacy data were derived from several sources, including: 1) the Study 13 Final Report, as well as other material submitted by the WHO TDR as part of the US FDA New Drug Application, 2) the published Study 13 from The Lancet in 2009, Gomes M et al, and 3) proceedings of an FDA Anti-infective Drugs Advisory Committee, which was convened to consider the TDR NDA.

The 100 mg strength (or matching placebo) was used in children ≤6 years of age, and a 400 mg strength (or matching placebo) in children ≥7 years of age and adults. A separate analysis was pre-specified for children ≤ 6 years old, who received the 100 mg artesunate suppositories.

Assessment of efficacy of the 100 mg suppository was assessed based on the results from 8050 children 6 years of age and younger (4063 artesunate and 3987 placebo).

Treatment with artesunate 100 mg rectal suppositories was associated with substantial reductions in mortality and rates of persistent neurological disability which were consistent across a variety of analyses.

For the primary efficacy analysis, a statistically significant decrease was seen in deaths recorded at 7-30 days, with 123 (3.0%) deaths in the artesunate group compared to 163 (4.1%) deaths in the placebo group (RR=0.74; p=0.01, 95% CI 0.59-0.93). Similar results were seen for the co-primary efficacy analysis, a combined endpoint of deaths and persistent serious neurological disability, with 125 cases (3.1%) observed in the artesunate group, versus 176 cases (4.4%) in the placebo group (RR 0.69, p=0.001).

Prospectively collected safety data in Study 13 was limited chiefly to neurological adverse events, and data concerning other adverse events were not collected systematically. No clear safety signal was evident in Study 13 in children aged 6 years of age and younger. Assessment of safety was bolstered by examination of the non-modified Intent-to-Treat population with negative malaria smears, including 1839 patients who received artesunate suppositories, and 1889 patients who received placebo.

In the segment of the study conducted in Asia where both children and adults were studied and the 400 mg formulation was used for age 7 and above, a favourable outcome was observed in young children ≤ age 6 given rectal artesunate (7 deaths vs 19), but an adverse outcome was seen in older patients ≥ age 7 (22 deaths vs 9). Thus, in children above 6 years and adults, the current evidence suggests more deaths with treatment. Rectal artesunate suppositories should not be given over age 6.

5. Benefit risk assessment and overall conclusion

Quality

[MA124 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 [MA124 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product [MA124 trade name] for which benefits have been proven in terms of clinical efficacy.

Bioequivalence

[MA124 trade name] has shown to be bioequivalent with Artesunate suppositories 100 mg (Catalent, Eberbach, Germany).

Efficacy and Safety

Study 13 supports the efficacy of the TDR formulation 100 mg artesunate rectal suppository as a pre-referral treatment for severe malaria in children 6 years of age and younger, if complete treatment is

not possible and the patient will be referred immediately to an appropriate facility for definitive treatment. In this age group, treatment resulted in a 26% decrease in mortality and a 30% reduction in combined mortality and permanent disability due to severe malaria. Numerical decreases in mortality were seen across all study sites in all ages, up to 6 years.

The Prequalification Team considers that the consistency of the Study 13 data for the 100 mg suppository from Africa and Asia in children 6 years of age and younger supports a positive benefit-risk assessment for the TDR 100 mg artesunate suppository for pre-referral treatment of severe malaria. While replication of Study 13 would be ideal, especially to clarify the issues in persons age 7 and above, it is highly unlikely that this will ever occur, due to ethical considerations.

In 2017 the WHO produced a document based on pharmacokinetic considerations, recommending a dose of 100 mg of rectal artesunate for children age 2 months to 3 years, and a higher dose (200 mg) for children age 3 to 6 years. (Rectal artesunate for pre-referral treatment of severe malaria, World Health Organization Global Malaria Programme, October 2017, file:///C:/Users/rayco/AppData/Local/Temp/WHO-HTM-GMP-2017.19-eng.pdf)

This dosing recommendation has been followed in the SmPC and PIL for the Cipla rectal artesunate product.
The Prequalification Team believes that the overall benefit-risk balance is favourable for use of the 100 mg suppository in children 6 years of age and younger, when used within the restrictions of the Summary of Product Characteristics. Text in the SmPC and PIL clearly warns against rectal artesunate use in children over age 6.

The accepted indication is: “As pre-referral treatment for suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment. The patient should be immediately referred to a facility where accurate diagnosis and complete treatment with effective antimalarials can be instituted.”

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 [MA124 trade name] was acceptable for the following indication: **“pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment.”** and has advised that the quality, efficacy and safety of [MA124 trade name] are acceptable to allow inclusion of [MA124 trade name], manufactured at Cipla Limited, Plot no. D-7 (Unit 1), MIDC Industrial Area, Kurkumbh, Dist: Pune 413802, India in the list of prequalified medicinal products.