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	[MA080 trade name][*]
Manufacturer of Prequalified Product	Ipca Laboratories Ltd Plot No. 255/1 Village Athal 396 230 Silvassa U.T. of Dadra and Nagar Haveli and Daman and Diu, India
Active Pharmaceutical Ingredients (APIs)	amodiaquine (as hydrochloride), artesunate
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF03)
Therapeutic indication	[MA080 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine as well as to artesunate.

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

1. Introduction

[MA080 trade name] is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum.*

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 Artesunate/ Amodiaquine (as hydrochloride) 25 mg/ 67.5 mg.

2. Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredients (APIs)

Amodiaquine hydrochloride

Amodiaquine hydrochloride API is described in the Ph.Int. and the USP and is considered well-established in the WHO Prequalification Programme. The API, which is manufactured by IPCA Laboratories, is adequately controlled by the quality specifications which are pharmacopoeial based, with additional specifications including residual solvents.

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.

Artesunate

Artesunate (reference number WHOAPI-081) has 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 artesunate, used in the manufacture of Amodiaquine & Artesunate Tablets (67.5 mg/25 mg), 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.

Other ingredients

Other ingredients used in the tablet formulation include colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, maize starch, mannitol and pregelatinised starch. Magnesium stearate is from vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 88.2 mg amodiaquine hydrochloride equivalent to 67.5 mg amodiaquine and 25 mg artesunate. The tablet is round, bilayered; one layer is yellow coloured and the other one is white to slightly yellow, plain on both sides. The tablets are packaged in Alu-Alu blister strips.

The development of the final composition of the tablets has been described. The objective was to develop a robust, stable, immediate release fixed-dose combination product, essential similar in formulation and bioequivalent to the WHO comparator product, Coarsucam® of the same strength. Characterization of the comparator product identified a quality target product profile that included rapid dissolution and other aspects of product quality.

Similar to the comparator product, a bilayered tablet, allowing minimal contact between artesunate and amodiaquine, was developed. Both tablet layers are obtained through wet granulation, using non-aqueous granulation for the artesunate layer, the latter API being susceptible to hydrolysis. Compatibility of the selected excipients with the APIs has been demonstrated. A number of small scale trial batches were produced using different approaches in which the excipients and their levels were varied to establish a formulation which gave satisfactory dissolution profiles, assay and also

demonstrated acceptable physical properties.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data demonstrated the consistency of the process. The tablets are packaged in aluminium-aluminium blisters, similar to the comparator product, to protect against moisture and light.

Three strengths, proportionally similar in composition, were developed: 100 mg/270 mg, 50 mg/135 mg and 25 mg/67.5 mg.

Product specifications

The FPP specifications include tests for description, identification (HPLC and TLC), average weight, tablet dimensions, hardness, friability, disintegration time, dissolution, assay (HPLC), related substances (HPLC), uniformity of dosage units (by content uniformity), loss on drying, residual solvent and microbial limits.

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. A slight increase of the degradation products was noted at all storage conditions, though well within the accepted specification limits. The data support the proposed shelf-life and storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2009 according to internationally accepted guidelines.

A randomized, open label, two-treatment, two-period, two-sequence, crossover, single dose, bioequivalence study of fixed dose combination of Artesunate + Amodiaquine (100 mg/270 mg) tablets of Ipca Laboratories Limited, India with COARSUCAM® (100 mg/270 mg) tablets of Maphar Casablanca, Morocco for Sanofi-aventis in normal, healthy, adult, male human subjects under fasting condition (study no. ARL/09/035).

The objective of the study was to compare the bioavailability of the Artesunate/Amodiaquine 100 mg/270 mg fixed dose combination tablet manufactured by Ipca Laboratories Limited, India (test drug) with the same dose of the reference fixed dose combination formulation (CoArsucam, Sanofi-Aventis) and to assess bioequivalence. The comparison was performed as a single centre, randomized, crossover single dose study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – Artesunate/Amodiaquine 100 mg/270 mg fixed dose combination tablet (artesunate 100 mg + amodiaquine 270 mg) Batch no. CYZ8004F.
Treatment R:	Reference – CoArsucam® 100/270 mg fixed dose combination tablet (artesunate 100 mg + amodiaquine 270 mg) Batch no. 5014.

A 16 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 96 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 artesunate and its metabolite dihydroartemisinin and amodiaquine and its metabolite desethyl-amodiaquine were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 2 and 5 ng/mL for artesunate and dihydroartemisinin, respectively, and about 0.5 and 4 ng/mL for amodiaquine and desethyl-amodiaquine, respectively.

The study was performed with 86 participants; data generated from a total of 78 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate, dihydroartemisinin, amodiaquine and desethyl-amodiaquine as well as statistical results (were applicable) are summarised in the following tables:

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)
tmax (h)	0.48 ± 0.35	0.41 ± 0.41	-	-
Cmax (ng/mL)	144 ± 115 (113)	129 ± 82 (106)	106.6	93.4 – 121.6
AUC0-t (ng.h/mL)	91.4 ± 38.4 (83.8)	86.8 ± 36.9 (79.7)	105.2	99.5 – 111.2
AUC0-inf (ng.h/mL)	95.5 ± 38.1 (88.2)	91.7 ± 35.8 (84.5)	104.5	98.8 – 110.6

Dihydro-artemisinin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.06 ± 0.81	1.02 ± 0.72	-	-
C_{max} (ng/mL)	383 ± 204	363 ± 176	-	-
AUC_{0-t} (ng.h/mL)	659 ± 306	631 ± 250	-	-
AUC_{0-inf} (ng.h/mL)	713 ± 475	654 ± 275	-	-

Amodiaquine

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)	0.89 ± 0.44	0.80 ± 0.38	-	-
C_{max} (ng/ml)	37.2 ± 13.7 (34.5)	37.8 ± 17.4 (34.5)	100.0	93.4 – 107.1
AUC_{0-t} (ng.h/ml)	330 ± 128 (308)	331 ± 129 (309)	99.8	95.2 – 104.5
AUC_{0-inf} (ng.h/ml)	363 ± 141 (340)	365 ± 131 (344)	99.0	94.7 – 103.5

Desethyl-amodiaquine

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD (geometric mean)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	4.2 ± 2.6	5.2 ± 5.7	-	-
C_{max} (ng/ml)	205 ± 72	202 ± 78	-	-
AUC_{0-t} (ng.h/ml)	7972 ± 2825	7873 ± 3250	-	-
AUC_{0-inf} (ng.h/ml)	14995 ± 6980	16325 ± 9952	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding artesunate and amodiaquine. Accordingly, the test fixed dose combination tablet

Artesunate/Amodiaquine 100 mg/270 mg meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference CoArsucam® (Sanofi-Aventis).

Conclusions

The results of the bioequivalence study were used to support the application for the fixed dose combination test tablets [MA080 trade name] and [MA081 trade name]. A biowaiver was granted for these tablet strengths in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the fixed dose combination test tablets [MA080 trade name] and [MA081 trade name] were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths is considered essentially the same, and the dissolution profiles between the formulations for the APIs were determined to be similar.

4. Summary of Product Safety and Efficacy

[MA080 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality [MA080 trade name] is a direct scale-down of [MA082 trade name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product CoArsucam® 100/270 mg fixed dose combination tablets (artesunate 100 mg + amodiaquine 270 mg) 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 [MA080 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA080 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA080 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [MA080 trade name] was acceptable for the following indication: **"treatment of malaria due to *Plasmodium falciparum*"** and has advised to include [MA080 trade name], manufactured at Ipca Laboratories Ltd, Plot No. 255/1, Village Athal, 396 230 Silvassa, U.T. of Dadra and Nagar Haveli and Daman and Diu, India in the list of prequalified medicinal products.