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	[MA189 trade name][*]
Manufacturer of Prequalified Product	Ipca Laboratories Limited Plot no. 255/1, Village Athal, Silvassa 396 230 U.T. of Dadra and Nagar Haveli and Daman and Diu, India
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine hydrochloride, pyrimethamine, sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarial: P01BA06
Therapeutic indication	Seasonal malaria chemoprevention (SMC) in patients aged 1 year to 10 years.

1. Introduction

[MA189 trade name] is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in patients aged 1 year to 10 years.

[MA189 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)

Amodiaquine hydrochloride, pyrimethamine and sulfadoxine 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 the APIs, used in the manufacture of [MA189 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 inspection 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 amodiaquine (as hydrochloride) dispersible tablet formulation include croscarmellose sodium, microcrystalline cellulose, povidone, sucralose, sodium bicarbonate and magnesium stearate. None of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificate from the supplier has been provided for magnesium stearate.

Other ingredients used in the pyrimethamine/sulfadoxine dispersible tablet formulation include microcrystalline cellulose, pregelatinized starch, crospovidone, colloidal silicon dioxide, povidone, sucralose and magnesium stearate. None of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificate from the supplier has been provided for magnesium stearate.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-blistered product, consisting of three and one dosage units of amodiaquine (as hydrochloride) 76.5 mg dispersible tablets and pyrimethamine/sulfadoxine 12.5mg/250mg dispersible tablets, respectively, per clear colourless plastic (PVC) on aluminium foil blister card

Pharmaceutical development and manufacture

Amodiaquine (as hydrochloride) 76.5mg dispersible tablets

The multisource product is a yellow to light yellow, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has a score line on one side and plain on the other side. The score line is not intended for breaking the tablet.

Two strengths of amodiaquine (as hydrochloride) dispersible tablets proportionally similar in composition were developed: 76.5mg and 153mg.The development focused on the 153mg strength, which was used in the BE study against the amodiaquine 153mg tablets of the WHO recommended comparator product SPAQ-CO™ dispersible tablets (pyrimethamine/sulfadoxine 25mg/500mg tablets + amodiaquine 153mg tablets). Once the formulation for the 153mg strength was finalized, the 76.5mg strength was pursued using dose-proportionality approach.

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the amodiaquine 153mg tablets of the WHO recommended comparator product SPAQ-CO™ tablets. The selection of excipients was based on the comparator product. Amodiaquine hydrochloride API is bitter in taste, considering that the tablets are dispersible, some taste-masking was achieved by inclusion of sodium bicarbonate to provide a micro alkaline environment which reduces the bitterness of the API. Additionally, a sweetening agent was included in the formulation of the dispersible tablets. Due to the high concentration of amodiaquine hydrochloride API in the tablet, a wet granulation process was chosen for manufacturing of the dispersible tablets. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including fineness of dispersion, disintegration time and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitrosamines on selected batches post prequalification.

Pyrimethamine/Sulfadoxine 12.5mg/250mg dispersible tablets

The multisource product is a white to off-white, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has a score line on one side and plain on the other side. The score line is not intended for breaking the tablet.

Two strengths of pyrimethamine/sulfadoxine dispersible tablets proportionally similar in composition were developed: 12.5mg/250mg and 25mg/500mg.The development focused on the 25mg/500mg strength, which was used in the BE study against the pyrimethamine/sulfadoxine 25mg/500mg tablets of the WHO recommended comparator product SPAQ-CO™ dispersible tablets (pyrimethamine/sulfadoxine 25mg/500mg tablets + amodiaquine 153mg tablets). Once the formulation for the 25mg/500mg strength was finalized, the 12.5mg/250mg strength was pursued using dose-proportionality approach.

The aim of the product development was to formulate a robust, immediate release oral dosage form, which is stable, dispersible, pharmaceutically equivalent and bioequivalent to the WHO recommended comparator product. The selection of excipients was based on the physico-chemical characteristics of the APIs, API-excipient compatibility and the quality target product profile. Sulfadoxine API is slightly bitter in taste, and considering that the tablets are dispersible, a sweetening agent was included in the formulation. Wet granulation process was chosen for manufacturing of the dispersible tablets as it gave satisfactory dissolution profiles, matching those of the comparator product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications for amodiaquine (as hydrochloride) 153mg dispersible tablets include tests for description, identification (IR and HPLC), average weight, hardness, disintegration time, fineness of dispersion, friability, uniformity of dosage units (by mass variation), assay (HPLC), dissolution (UV detection), related substances (HPLC), loss on drying (IR balance), moisture content (by KF) and microbial limits. The test procedures have been adequately validated.

The finished product specifications for pyrimethamine/sulfadoxine 25mg/500mg dispersible tablets include tests for description, identification of APIs (TLC and HPLC), average weight, friability, hardness, disintegration time, fineness of dispersion, dissolution (HPLC detection), assay (HPLC), related substances (HPLC), uniformity of dosage units (content uniformity), loss on drying and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage conditions in the packaging intended for marketing of the product. The product proved to be quite stable at these storage conditions. The data support the proposed shelf life at the 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 2022 according to internationally accepted guidelines.

Single dose oral bioequivalence study of Sulfadoxine/ Pyrimethamine 500 mg/25 mg dispersible tablets and Sulfadoxine/Pyrimethamine 500 mg/25 mg dispersible tablets of SPAQ-CO™ Co-blister in healthy adult Human subjects under fasting conditions (study no. C1B01297).

The objective of the study was to compare the bioavailability of the stated Sulfadoxine/Pyrimethamine 500//25 mg FDC tablet manufactured for/by Ipca Laboratories Ltd., India (test drug) with the reference formulation SPAQ-CO™ (pyrimethamine/sulfadoxine + amodiaquine) tablets 25/500 mg (Guilin Pharmaceutical Co., Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, parallel study in healthy subjects under fasting conditions. Each subject was assigned to receive one of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet Sulfadoxine/Pyrimethamine 500//25 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: IBI0310029

Treatment R: References – 1 tablet SPAQ-CO™ (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: LF190321

The tablets were administered (dispersed) with 20 ml water. There was no wash-out period as this was a parallel designed study. Serial blood samples (1 pre-dose sample and 12 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 pyrimethamine and sulfadoxine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 4 ng/ml for pyrimethamine and about 1.5 µg/ml for sulfadoxine.

The study was performed with 52 participants; data generated from a total of 50 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for pyrimethamine and sulfadoxine as well as statistical results are summarised in the following tables:

Pyrimethamine

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)	3.04 ± 1.29	3.53 ± 1.49	-	-
C_{max} (ng/ml)	203 ± 19 (202)	208 ± 32 (205)	98.2	92.4 – 104.2
AUC_{0-72h} (ng.h/ml)	9605 ± 1269 (9522)	10170 ± 1727 (10029)	94.9	88.2 – 102.2

* geometric mean

Sulfadoxine

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)	3.60 ± 2.02	3.31 ± 1.78	-	-
C_{max} (µg/ml)	85.5 ± 7.6 (85.1)	83.0 ± 8.7 (82.5)	103.2	98.4 – 108.1
AUC_{0-72h} (µg.h/ml)	4794 ± 419 (4776)	4581 ± 451 (4559)	104.8	100.2 – 109.5

* 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 pyrimethamine and sulfadoxine. Accordingly, the test Sulfadoxine/Pyrimethamine 500//25 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference G- SPAQ-CO™ 25/500 mg tablet (Guilin Pharmaceutical Co., Ltd.).

A biowaiver was granted for the additional 12.5/250 mg FDC tablet strength (Ipca Laboratories Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Sulfadoxine/Pyrimethamine 12.5/250 mg FDC tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

The following bioequivalence study has been performed in 2020 according to internationally accepted guidelines.

Study title: An open label, randomized, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, truncated oral bioequivalence study of Amodiaquine Hydrochloride dispersible tablets 153 mg base manufactured by Ipca Laboratories Ltd., India and Amodiaquine dispersible tablet 153 mg of SPAQ-CO™ dispersible tablets manufactured by Guilin Pharmaceutical Co., Ltd. China, in healthy, adult, human subjects under fasting conditions (study no. NCS-718-19-CS).

The objective of the study was to compare the bioavailability of the stated Amodiaquine 153 mg dispersible tablet manufactured for/by Ipca Laboratories Ltd., India (test drug) with the reference formulation SPAQ-CO™ 153 mg dispersible tablet (Guilin Pharmaceutical Co. Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T:	Test – 1 dispersible tablet Amodiaquine 150 mg (amodiaquine 153 mg) Batch no.: JAZ0200019
Treatment R:	Reference – 1 dispersible tablet SPAQ-CO™ 153 mg (amodiaquine 153 mg) Batch no. LF190321

The tablets were administered (dispersed) with 20 ml water. A 14-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 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 amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10.6 pg/ml for amodiaquine.

The study was performed with 50 participants; data generated from a total of 46 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Amodiaquine

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)	1.00 ± 0.79	0.92 ± 0.35	-	-
C_{max} (pg/ml)	5767 ± 2032 (5341)	5556 ± 1823 (5264)	101.5	95.2 – 108.1
AUC_{0-t} (pg.h/ml)	49754 ± 9703 (48397)	48171 ± 10541 (47367)	102.2	99.1 – 105.3

* 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 amodiaquine. Accordingly, the test Amodiaquine 153 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference SPAQ-CO™ 153 mg dispersible tablet (Guilin Pharmaceutical Co. Ltd.).

A biowaiver was granted for the additional 76.5 mg dispersible tablet strength (Ipca Laboratories Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Amodiaquine 76.5 mg dispersible tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of product safety and efficacy

[MA189 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, [MA189 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product SPAQ-CO™ dispersible tablets manufactured by Guilin Pharmaceutical Co., Ltd. China for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA189 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 [MA189 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA189 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, [MA189 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 [MA189 trade name] was acceptable for the following indication: malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in patients aged 1 year to 10 years., and would allow inclusion of [MA189 trade name], manufactured at Ipca Laboratories Limited, Village Athal, Silvassa 396 230, India in the list of prequalified medicinal products.