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	[MA198 trade name][*]
Manufacturer of Prequalified Product	Ajanta Pharma Limited B-4/5/6, MIDC Industrial Area Paithan Chhatrapati Sambhajinagar – 431148 Maharashtra, India
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine (as hydrochloride), Pyrimethamine, Sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarials: aminoquinolines (P01BA06) Antimalarials: diaminopyrimidines, pyrimethamine combinations (P01BD51)
Therapeutic indication	[MA198 trade name] is indicated for malaria prevention in children during the malaria season (seasonal malaria chemoprevention, SMC).

1. Introduction

[MA198 trade name] is indicated for malaria prevention in children during the malaria season (seasonal malaria chemoprevention, SMC).

Prophylaxis regimens should take into account the most recent official prophylaxis guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

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)

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 [MA198 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

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

standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the amodiaquine (as hydrochloride) tablet formulation include microcrystalline cellulose, croscarmellose sodium, povidone, sucralose, sodium bicarbonate and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. None of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Other ingredients used in the pyrimethamine/sulfadoxine tablet formulation include low substituted hydroxypropyl cellulose, hypromellose, sucralose and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. one of the excipients used in the manufacture of the tablets are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-blistered product, consisting of three and one dosage units of amodiaquine (as hydrochloride) 153mg dispersible tablets and pyrimethamine/sulfadoxine 25mg/500mg dispersible tablets, respectively, per clear plastic (PVC) on aluminium foil blister card.

Pharmaceutical development and manufacture

Amodiaquine (as hydrochloride) 153 mg dispersible tablets

The multisource product is a yellow, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablets have ‘A1’ debossed (stamped into) one side and a break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies.

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

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the amodiaquine 153 mg tablets of the WHO recommended comparator product SPAQ-CO Disp® tablets. The selection of excipients was based on the physico-chemical characteristics of the API, API-excipient compatibility and the quality target product profile. To mask the bitter taste of amodiaquine hydrochloride, sucralose was included in the formulation of the dispersible tablets. Due to the poor flow of amodiaquine hydrochloride, a non-aqueous granulation process was chosen for manufacturing of the dispersible tablets. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Pyrimethamine/Sulfadoxine 25 mg/500 mg dispersible tablets

The multisource product is a white to off-white, round, uncoated tablets. They are flat on the top and bottom with a bevelled edge. The tablets have ‘SD1’ debossed (stamped into) one side and a break line on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies.

Two strengths of pyrimethamine/sulfadoxine dispersible tablets proportionally similar in composition were developed: 12.5 mg/250 mg and 25 mg/500 mg. The development focused on the 25 mg/500 mg

strength, which was used in the BE study against the WHO recommended comparator product SPAQ-CO Disp® tablets. Once the formulation for the 25 mg/500 mg strength was finalized, the 12.5 mg/250 mg strength was pursued using a dose-proportionality approach.

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the comparator product, SPAQ-CO Disp® tablets. The selection of excipients was based on the physico-chemical characteristics of the API, API-excipient compatibility and the quality target product profile. Sucralose was included as a sweetening agent in the formulation of the dispersible tablets. Due to the poor flow of pyrimethamine and sulfadoxine, a non-aqueous granulation process was chosen for manufacturing of the dispersible tablets. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. 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 nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications for amodiaquine (as hydrochloride) 153 mg dispersible tablets include tests for description, identification of API (IR and HPLC), average weight, disintegration time, water content (KF), fineness of dispersion, dissolution (UV detection), uniformity of dosage units (by weight variation), organic impurities (HPLC), residual solvents (GC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

The finished product specifications for pyrimethamine/sulfadoxine 25 mg/500 mg dispersible tablets include tests for description, identification of APIs (IR and HPLC), average weight, disintegration time, water content (KF), fineness of dispersion, dissolution (HPLC detection), uniformity of dosage units [pyrimethamine; by content uniformity and sulfadoxine; by weight variation], organic impurities (HPLC), residual solvents (GC), assay (HPLC) 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 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 2023 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, truncated, crossover design, bioequivalence study of test products: amodiaquine (as hydrochloride) 153 mg dispersible tablets + pyrimethamine/sulfadoxine 25 mg/500 mg dispersible tablets of Ajanta Pharma Limited, with reference product: SPAQ-CO® Disp (amodiaquine [as hydrochloride] 153 mg dispersible tablets + pyrimethamine/sulfadoxine 25 mg/500 mg dispersible tablets) of Guilin Pharmaceuticals Co., Ltd. in normal, healthy, adult, human, subjects under fasting condition (study no. ARL/21/303).

The objective of the study was to compare the bioavailability of the stated pyrimethamine/sulfadoxine 25/500 mg FDC dispersible tablet + amodiaquine (as hydrochloride) 153 mg dispersible tablet,

manufactured for/by Ajanta Pharma Limited., India (test drug) with the reference formulation SPAQ-CO® Disp (pyrimethamine/sulfadoxine 25/500 mg FDC dispersible tablet + amodiaquine 153 mg dispersible tablet, Guilin Pharmaceutical Co., Ltd.) and to assess bioequivalence.
There were 2 comparisons performed: for pyrimethamine/sulfadoxine, the study was conducted as a single centre, open label, single dose, randomized, parallel study in healthy subjects under fasting conditions and for amodiaquine, the study was conducted as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive one (parallel study) or each (crossover study) of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet pyrimethamine/sulfadoxine 25/500 mg + 1 tablet amodiaquine 153 mg
(pyrimethamine 25 mg + sulfadoxine 500 mg + amodiaquine 153 mg)
Batch no.: PA05913

Treatment R: References – 1 tablet SPAQ-CO® Disp
(pyrimethamine 25 mg + sulfadoxine 500 mg + amodiaquine 153 mg)
Batch no.: LF200368

Each test and reference dispersible tablet was dispersed in 10 mL water (+ 10 mL of rinsing water) and administered. There was no wash-out period in the parallel designed study and the washout period in the crossover study was 18 days. For pyrimethamine and sulfadoxine, serial blood samples (1 pre-dose sample and 21 samples within 72 hours post dose) and for amodiaquine, serial blood samples (1 pre-dose sample and 24 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 pyrimethamine, sulfadoxine and amodiaquine, were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 10 ng/mL for pyrimethamine, about 1200 ng/mL for sulfadoxine and about 0.051 ng/mL for amodiaquine.

For pyrimethamine and sulfadoxine, the study was performed with 56 participants; data generated from a total of 56 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence. For amodiaquine, the study was performed with 48 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 pyrimethamine, sulfadoxine and amodiaquine, 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)	3.09 ± 2.50	4.12 ± 2.74	-	-
C_{max} (ng/mL)	241 ± 36 (238)	249 ± 33 (247)	96.5	90.4 – 103.0
$AUC_{0\text{-}72h}$ (ng.h/mL)	11537 ± 2070 (11359)	12271 ± 1638 (12168)	93.4	87.0 – 100.2

* 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)	3.51 ± 1.39	3.58 ± 0.91	-	-
C_{max} (µg/mL)	74.9 ± 8.2 (74.5)	78.5 ± 6.5 (78.2)	95.2	90.9 – 99.7
AUC_{0-72h} (µg.h/mL)	4197 ± 471 (4171)	4432 ± 369 (4417)	94.4	90.3 – 98.7

* geometric mean

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)	0.77 ± 0.50	0.79 ± 0.33	-	-
C_{max} (ng/mL)	7.57 ± 2.36 (7.21)	7.35 ± 2.80 (6.91)	104.4	96.3 – 113.2
AUC_{0-72h} (ng.h/mL)	55 ± 11 (54)	53 ± 14 (52)	103.7	99.0 – 108.6

* 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, sulfadoxine and amodiaquine. Accordingly, the test pyrimethamine/sulfadoxine 25/500 mg dispersible FDC tablet + 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® Disp tablets (Guilin Pharmaceutical Co., Ltd.).

A biowaiver was granted for the additional 12.5/250 mg FDC tablet + 76.5 mg tablet strengths (Ajanta Pharma Limited., India) in accordance to WHO guidelines. In comparison with the strength of the test products used in the bioequivalence studies, the pyrimethamine/sulfadoxine 12.5 mg/250 mg dispersible FDC tablet + amodiaquine 76.5 mg dispersible tablet was determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

[MA198 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products, for which benefits have been proven in terms of clinical efficacy.

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 [MA198 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA198 trade name] has shown to be bioequivalent with SPAQ-CO Disp® tablets (Guilin Pharmaceutical Co., Ltd.)

Efficacy and Safety

Regarding clinical efficacy and safety, [MA198 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 [MA198 trade name] was acceptable for the following indication: malaria prevention in children during the malaria season (seasonal malaria chemoprevention, SMC), and would allow inclusion of [MA198 trade name], manufactured at Ajanta Pharma Limited, B-4/5/6, MIDC Industrial Area, Paithan, Chhatrapati Sambhajinagar – 431148, Maharashtra, India, in the list of prequalified medicinal products.