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	[MA146 trade name][*]
Manufacturer of Prequalified Product	S Kant Healthcare Ltd. Plot No. 1802-1805 G.I.D.C. Phase III Vapi 396 195 Gujarat India
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine + pyrimethamine/sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarials: Aminoquinolines (P01BA06) + Antimalarials, Diaminopyrimidines: Pyrimethamine combinations (P01BD51)
Therapeutic indication	[MA146 trade name] is indicated for malaria prevention during the malaria season in children aged 3 to less than 12 months.

1. Introduction

[MA146 trade name] is indicated for malaria prevention, as detailed in the summary of product characteristics (SmPC).

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 [MA146 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 magnesium hydroxide, silica colloidal anhydrous, mannitol, sodium bicarbonate, sucralose, crospovidone, polysorbate, purified talc, citric acid monohydrate, orange flavour and sodium stearyl fumarate. 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 dispersible tablet formulation include crospovidone, isomalt, methacrylic acid-methyl methacrylate copolymer, povidone, polyethylene glycol, sodium bicarbonate, citric acid monohydrate, sucralose, orange flavour, silica colloidal anhydrous and sodium stearyl fumarate. 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.

Finished pharmaceutical product (FPP)

The finished pharmaceutical product is a co-blistered product, consisting of three and one dosage units of amodiaquine (as hydrochloride) 75mg dispersible tablets and pyrimethamine/sulfadoxine 12.5 mg/250 mg dispersible tablets, respectively, per clear PVC/PVDC-Alu blister card.

Pharmaceutical development and manufacture

Amodiaquine (as hydrochloride) 75 mg dispersible tablets

The multisource product is a pale yellow to yellow, mottled circular, biconvex, uncoated tablet with break line on one side and plain 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: 75mg and 150mg.The development focused on the 150mg strength, which was used in the BE study against the amodiaquine 150 mg tablets of the WHO recommended comparator product SPAQ-CO™ tablets (pyrimethamine/sulfadoxine 25 mg/500 mg tablets + amodiaquine 150 mg tablets). Once the formulation for the 150 mg strength was finalized, the 75 mg strength was pursued using dose-proportionality approach.

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the amodiaquine 150 mg tablets of the WHO recommended comparator product SPAQ-CO™ tablets. The selection of excipients was based on the physico-chemical characteristics of the API, API-excipient compatibility and the target product profile. Amodiaquine hydrochloride API is bitter in taste, considering that the tablets are dispersible, taste-masking was done using magnesium hydroxide based on literature. Additionally, a sweetener and a flavouring agent were included in the formulation of the dispersible tablets. Due to the poor flow of amodiaquine hydrochloride API, 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 tablet dispersion time, disintegration time, taste and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Pyrimethamine/Sulfadoxine 12.5 mg/250 mg dispersible tablets

The multisource product is a white to off-white, circular, biconvex, uncoated tablet with break line on one side and plain 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 pyrimethamine/sulfadoxine 25 mg/500 mg tablets of the WHO recommended comparator product SPAQ-CO™ tablets. Once the formulation for

the 25 mg/500 mg strength was finalized, the 12.5 mg/250 mg strength was pursued using dose-proportionality approach.

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the comparator product, SPAQ-CO™ tablets. The selection of excipients was based physico-chemical characteristics of the API, API-excipient compatibility and the target product profile. Due to the poor flow of sulfadoxine API, 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 tablet dispersion time, disintegration time, taste and dissolution profile similarity with the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications for amodiaquine (as hydrochloride) 75 mg dispersible tablets include tests for description, identification of API (IR and HPLC), average weight, uniformity of weight, tablet dimensions (diameter and thickness), hardness, disintegration time, dispersion time, fineness of dispersion, water content, assay (HPLC), dissolution (UV detection), related substances (HPLC), breakability into tablet halves (weight variation) and microbial limits. The test procedures have been adequately validated.

The finished product specifications for pyrimethamine/sulfadoxine 12.5 mg/250 mg dispersible tablets include tests for description, identification of APIs (TLC and HPLC), average weight, uniformity of weight, tablet dimensions (diameter and thickness), hardness, disintegration time, dispersion time, fineness of dispersion, water content, dissolution (HPLC detection), related substances (HPLC), assay (HPLC), uniformity of content (HPLC), breakability into tablet halves (weight variation and uniformity of content) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25°C/60%RH, 30°C/65%RH and 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 2017 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two-treatment, single oral dose, parallel, truncated, bioequivalence study of Sulfadoxine 500 mg and Pyrimethamine 25 mg dispersible tablet of S Kant Healthcare Ltd with Pyrimethamine/Sulfadoxine 25 mg/500 mg tablets from SPAQ-CO* (amodiaquine (as hydrochloride) 150 mg tablets + pyrimethamine/sulfadoxine 25 mg/500mg tablets) of Guilin Pharmaceutical Co. Ltd. China, in normal, healthy, adult, human subject under fasting condition (study no. ARL/15/776).

The objective of the study was to compare the bioavailability of the stated pyrimethamine/sulfadoxine 25 mg/500 mg FDC dispersible tablet manufactured for/by S Kant Healthcare Ltd, India (test drug) with the reference formulation pyrimethamine/sulfadoxine 25 mg/500 mg tablet (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 dispersible tablet Pyrimethamine/Sulfadoxine 25 mg/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg)
Batch no.: WSQ7001

Treatment R: Reference – 1 tablet Pyrimethamine/Sulfadoxine 25mg/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg)
Batch no. LP160318

Serial blood samples (1 pre-dose sample and 22 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 and sulfadoxine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/mL for pyrimethamine and about 1203 ng/mL for sulfadoxine.

The study was performed with 24 participants. Data generated from a total of 23 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	4.55 ± 2.40	3.75 ± 1.83	–	–
C_{max} (ng/mL)	154 ± 21 (153)	157 ± 20 (156)	98.0	88.8 – 108.2
AUC_{0-72} (ng·h/mL)	7714 ± 824 (7668)	7810 ± 1297 (7716)	99.4	89.8 – 110.0

Sulfadoxine

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)	4.64 ± 6.53	3.83 ± 1.29	–	–
C_{max} (µg /mL)	65.8 ± 6.0 (65.6)	66.4 ± 6.8 (66.1)	99.2	92.5 – 106.4
AUC_{0-72} (µg ·h/mL)	3760 ± 300 (3749)	3882 ± 380 (3864)	97.0	90.9 – 103.6

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding pyrimethamine and sulfadoxine. Accordingly, the test pyrimethamine/ sulfadoxine 25 mg/500 mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references pyrimethamine/sulfadoxine 25 mg/500 mg tablet (Guilin Pharmaceutical Co. Ltd.).

A biowaiver was granted for the additional 12.5/250 mg FDC tablet strength (S Kant Healthcare Ltd, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the pyrimethamine/sulfadoxine 12.5 mg/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 2018 according to internationally accepted guidelines.

Study title: A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Amodiaquine dispersible tablets 150 mg of S Kant Healthcare Ltd., India with Amodiaquine (as hydrochloride) 150 mg tablets from SPAQ-CO* (Amodiaquine [as hydrochloride] 150 mg tablets + Pyrimethamine/Sulfadoxine 25 mg/500 mg tablets) of Guilin Pharmaceutical Co. Ltd., China, in normal, healthy, adult, human subjects under fasting condition (study no. ARL/15/739).

The objective of the study was to compare the bioavailability of the stated amodiaquine 150 mg dispersible tablet manufactured for/by S Kant Healthcare Ltd, India (test drug) with the reference formulation amodiaquine 150 mg 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 150 mg)
Batch no.: WAM8001

Treatment R: Reference – 1 tablet Amodiaquine 150 mg (amodiaquine 150 mg)
Batch no.: LP160318

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 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 amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 pg/mL for amodiaquine.

The study was performed with 44 participants. Data generated from a total of 42 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.33 ± 0.91	1.24 ± 0.56	–	–
C_{max} (ng/mL)	3.91 ± 1.73 (3.61)	4.28 ± 1.36 (4.06)	88.8	81.2 – 97.1
AUC_{0-t} (ng·h/mL)	40.1 ± 10.5 (39.0)	39.1 ± 10.3 (37.7)	103.2	99.3 – 107.3

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding amodiaquine. Accordingly, the test Amodiaquine 150 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Amodiaquine 150 mg tablet (Guilin Pharmaceutical Co. Ltd.).

A biowaiver was granted for the additional 75 mg tablet strength (S Kant Healthcare Ltd, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the amodiaquine 75 mg 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

According to the submitted data on quality, [MA146 trade name] is a direct scale-down of [MA147 trade name] (amodiaquine 150 mg + pyrimethamine/sulfadoxine 25 mg/500 mg dispersible tablets). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product, 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 [MA146 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA146 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, [MA146 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 [MA146 trade name] was acceptable for the following indication: '**malaria prevention during the malaria season in children aged 3 to less than 12 months** ', and would allow inclusion of [MA146 trade name], manufactured at S Kant Healthcare Ltd, Plot No. 1802-1805, G.I.D.C. Phase III, Vapi 396 195, Gujarat, India, in the list of prequalified medicinal products.