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	[MA172 trade name][*]
Manufacturer of Prequalified Product	Universal Corporation Limited Club Road, Plot No. 13777 P.O.Box 1748-00902 Kikuyu, Kenya. Tel: +254 20 2693835 / 20 2693836 Email: info@ucl.co.ke
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine (as hydrochloride) , Pyrimethamine, Sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarial: P01BA06
Therapeutic indication	[MA172 trade name] is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in children aged 3 months to less than 1 year.

1. Introduction

[MA172 trade name] is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in children aged 3 months to less than 1 year.

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.*

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

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 [MA172 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.

Other ingredients

Other ingredients used in the amodiaquine (as hydrochloride) dispersible tablet formulation include sodium bicarbonate, sodium chloride, maize starch, microcrystalline cellulose, croscarmellose sodium, silica colloidal anhydrous, crospovidone, sucralose, vanilla flavour, purified talc and magnesium stearate. 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 lactose monohydrate, maize starch, erythrosine soluble colour, povidone, microcrystalline cellulose, silica colloidal anhydrous, sodium bicarbonate, croscarmellose sodium, sucralose, orange flavour, purified talc and magnesium stearate. 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 regard to lactose monohydrate and 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) 75 mg dispersible tablets and pyrimethamine/sulfadoxine 12.5 mg/250 mg dispersible tablets, respectively, per white opaque PVC/PVDC-Alu blister card.

Pharmaceutical development and manufacture

Amodiaquine (as hydrochloride) 75mg dispersible tablets

The multisource product is a yellow, round-shaped, flat, bevelled edge tablet, with a score line on one side and plain on the other. The score line is not intended for breaking the tablet.

Two strengths of amodiaquine (as hydrochloride) dispersible tablets proportionally similar in composition were developed: 75 mg and 150 mg.The development focused on the 150 mg 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 75mg 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 quality target product profile. 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 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 fineness of dispersion, disintegration time, taste 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 appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Pyrimethamine/Sulfadoxine 12.5 mg/250 mg dispersible tablets

The multisource product is a pink, round-shaped, flat bevelled edge tablet, with a score line on one side and plain on the other. The score line is not intended for breaking the tablet.

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 25mg/500mg strength, which was used in the BE study against the WHO recommended comparator product Fansidar® (pyrimethamine/sulphadoxine 25/500 mg) tablets. Once the formulation for the 25 mg/500 mg strength was finalized, the 12.5mg/250 mg 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 API, API-excipient compatibility and the target product profile. Sulfadoxine API is slightly bitter in taste, and considering that the tablets are dispersible, a sweetener and a flavouring agent were included in the formulation. Due to the high dose of sulfadoxine API, poor flow properties and insolubility of both APIs, the 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. 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) 75 mg dispersible tablets include tests for description, identification (HPLC and UV), disintegration time, friability, fineness of dispersion, loss on drying, water content (by KF), uniformity of dosage units (by content uniformity), assay (HPLC), dissolution (UV detection), related substances (HPLC) 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 (HPLC and UV), disintegration time, friability, uniformity of dosage units (weight variation and content uniformity), content uniformity, assay (HPLC), dissolution (HPLC detection), related substances (HPLC), loss on drying, breakability into tablet halves (weight variation), fineness of dispersion 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 2019 according to internationally accepted guidelines.

Study title:

An open-label, balanced, randomized, single-dose, two-treatment, single-period, parallel, oral bioequivalence study of Sulfadoxine/Pyrimethamine 500 mg/25 mg dispersible tablets with Fansidar® (sulfadoxine/pyrimethamine) 500 mg/25 mg tablets of Akacia Healthcare (Pty) Ltd., 4 Brewery Street, Isando, Gauteng, 1609, South Africa in healthy, male and non-pregnant female adult, human subjects under fasting conditions (study no. BE/18/012).

The objective of the study was to compare the bioavailability of the stated Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet manufactured for/by Universal Corporation Ltd., Kenya, (test drug) with the reference formulation Fansidar® (pyrimethamine/sulphadoxine/) tablets 25/500 mg (Akacia™ HealthCare (Pty) 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 Pyrimethamine/Sulfadoxine 25/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: 5805612
Treatment R:	References – 1 tablet Fansidar® 25/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no.: Z1764

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 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 2.5 µg/mL for sulfadoxine.

The study was performed with 92 participants; data generated from a total of 92 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)	3.54 ± 1.85	4.06 ± 2.04	-	-
C_{max} (ng/mL)	207 ± 30 (205)	203 ± 38 (200)	102.9	97.0 – 109.0
$AUC_{0\text{-}72h}$ (ng·h/mL)	10890 ± 1508 (10787)	10559 ± 1628 (10435)	103.4	98.2 – 108.8

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)	4.18 ± 1.62	4.76 ± 1.90	-	-
C_{max} (µg/mL)	78.9 ± 12.8 (78.0)	77.7 ± 17.5 (76.2)	102.3	96.6 – 108.5
AUC_{0-72h} (µg·h/mL)	4438 ± 509 (4411)	4384 ± 585 (4345)	101.5	97.2 – 106.0

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 Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Fansidar® 25/500 mg tablet (Akacia™ HealthCare (Pty) Ltd.).

A biowaiver was granted for the additional 12.5/250 mg FDC tablet strength (Universal Corporation Ltd., Kenya) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Pyrimethamine/Sulfadoxine 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 2019/2020 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, four-period, fully replicate, cross over oral bioequivalence study of Amodiaquine 150 mg dispersible tablet from the strip of Amodiaquine 150 mg + Sulfadoxine 500 mg + Pyrimethamine 25 mg dispersible tablet manufactured by Universal Corporation Limited, Kenya with Amodiaquine dispersible tablets 153 mg from SPAQ-CO® DT (amodiaquine + sulfadoxine + pyrimethamine dispersible tablet 153 mg + 500 mg + 25 mg) of Guilin Pharmaceutical Co. Ltd., China in normal healthy, adult, human subjects under fasting condition. (study no. 909-19).

The objective of the study was to compare the bioavailability of the stated Amodiaquine 150 mg dispersible tablet manufactured by Universal Corporation Limited, Kenya (test drug) with the reference formulation Amdodiaquine 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, fully replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments twice in a randomized fashion:

Treatment T: Test – 1 dispersible tablet Amodiaquine 150 mg (amodiaquine 150 mg)
Batch no.: 6807164
Treatment R: Reference – 1 dispersible tablet Amodiaquine 153 mg (amodiaquine 153 mg)
Batch no. LF180604

The tablets were administered with 20 mL water. A 15 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within

96 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 14.3 pg/mL for amodiaquine.

The study was performed with 40 participants; data generated from a total of 39 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)	1.27 ± 1.23	1.15 ± 0.89	-	-
C_{max} (pg/mL)	8634 ± 3758 (8201)	9298 ± 3764 (8650)	94.8	87.3 – 102.9
AUC_{0-t} (pg·h/mL)	86151 ± 40416 (81933)	81097 ± 33405 (76472)	107.1	100.3 – 114.4

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 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 153 mg dispersible tablet (Guilin Pharmaceutical Co. Ltd.).

A biowaiver was granted for the additional 75 mg dispersible tablet strength (Universal Corporation Limited, Kenya) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Amodiaquine 75 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

According to the submitted data on quality, [MA172 trade name] is a direct scale-down of [MA169 trade name] (amodiaquine 150 mg + pyrimethamine/sulfadoxine 25mg/500mg 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 [MA172 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA172 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, [MA172 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 [MA172 trade name] was acceptable for the following indication: malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in children aged 3 months to less than 1 year, and would allow inclusion of [MA172 trade name], manufactured at Universal Corporation Limited, Club Road, Plot No. 13777, P.O.Box 1748-00902, Kikuyu, Kenya in the list of prequalified medicinal products.