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	[MA166 trade name][*]
Manufacturer of Prequalified Product	Universal Corporation Limited Club Road, Plot No. 13777 P.O. Box 1748-00902 Kikuyu Kenya
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine and Sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarials, diaminopyrimidines combinations (P01BD51)
Therapeutic indication	[MA166 trade name] is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in their first or second pregnancy, in areas of moderate to high malaria transmission in Africa. [MA166 trade name] is also indicated for intermittent preventive treatment of malaria in infants aged less than 12 months at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis and vaccination against measles, in areas of moderate-to-high malaria transmission of Africa (annual entomological inoculation rate ≥ 10), where the combination of sulfadoxine and pyrimethamine is still effective (prevalence of the Pfdhps 540 mutation of ≤ 50%).

1. Introduction

[MA166 trade name] is indicated in malaria prophylaxis, as detailed in the summary of product characteristics.

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)

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

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

provides an assurance that the APIs, used in the manufacture of [MA166 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 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)

Pharmaceutical development and manufacture

The multisource product is a pink, round-shaped, flat, bevel edge, tablet, scored on one side and plain on the reverse. The score line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in white, opaque rigid PVC/PVDC-Alu blisters.

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 WHO recommended comparator product Fansidar® (pyrimethamine/sulphadoxine 25/500 mg) 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 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 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 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 mg / 500 mg FDC dispersible tablet manufactured for/by Universal Corporation Ltd., Kenya, (test drug) with the reference formulation Fansidar® (pyrimethamine/sulphadoxine/) tablets 25 mg / 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 mg / 500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no. 5805612

Treatment R: Reference – 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 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 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 (*)**	**Reference (R) arithmetic mean ± SD (*)**	**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_{0-72h} (ng.h/mL)	10890 ± 1508 (10787)	10559 ± 1628 (10435)	103.4	98.2 – 108.8

* 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)	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
$AUC_{0\text{-}72h}$ (µg.h/mL)	4438 ± 509 (4411)	4384 ± 585 (4345)	101.5	97.2 – 106.0

*geometric mean

The results of the study show that the pre-set 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 reference Fansidar® 25/500 mg tablet (Akacia™ HealthCare [Pty] Ltd.).

A biowaiver was granted for the additional 12.5 mg / 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 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.

4. Summary of product safety and efficacy

[MA166 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, [MA166 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Fansidar® (Akacia™ HealthCare [Pty] Ltd.), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA166 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 [MA166 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA166 trade name] fulfilled all criteria for waiving an in vivo bioequivalence study as per relevant WHO guidance. Hence, [MA166 trade name] and Fansidar® (Akacia™ HealthCare [Pty] Ltd.) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA166 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, safety and efficacy the team of assessors considered that the benefit–risk profile of [MA166 trade name] was acceptable for the following indications:

- "intermittent preventive treatment of malaria as part of antenatal care for women in their first or second pregnancy, in areas of moderate to high malaria transmission in Africa and
- intermittent preventive treatment of malaria in infants aged less than 12 months at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis and vaccination against measles, in areas of moderate-to-high malaria transmission of Africa (annual entomological inoculation rate ≥ 10), where the combination of sulfadoxine and pyrimethamine is still effective (prevalence of the Pfdhps 540 mutation of ≤ 50%)",

and would allow inclusion of [MA166 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.