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	[MA158 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Ltd
Active Pharmaceutical Ingredient(s) (API)	Pyrimethamine, sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarial, Pyrimethamine combinations (ATC code P01BD51)
Therapeutic indication	[MA158 trade name] is indicated for intermittent preventive treatment of malaria in women in their first or second pregnancy and in infants aged less than 12 months

1. Introduction

[MA158 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.

[MA158 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%).

[MA158 trade name] should ideally be administered as directly observed therapy (DOT).

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)

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 [MA158 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 dispersible tablet formulation include pregelatinized starch, croscarmellose sodium, colloidal silicon dioxide, microcrystalline cellulose, aspartame, orange flavour and sodium stearyl fumarate. None of the excipients used in the manufacture of the tablets are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, flat faced bevelled edge, uncoated tablet debossed with 'F' and '42' on either side of 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. The tablets are packaged in clear PVC/PVDC-Alu blister cards.

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 Fansidar® 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 develop a palatable, dispersible tablet formulation, bioequivalent to the comparator product, Fansidar® tablets. The selection of excipients was based physico-chemical characteristics of the API, API-excipient compatibility and the target product profile. Orange flavour and aspartame were used to improve the taste of the dispersible tablets. Due to the poor flow properties of the APIs, 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 the dispersible tablets include tests for description, identification of APIs (HPLC and TLC), friability, hardness, disintegration time, water content (KF), fineness of dispersion, uniformity of dosage units (content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), subdivision of tablets (weight variation and content uniformity) 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: Single-dose fasting in vivo bioequivalence study of fixed dose combination of Sulfadoxine and Pyrimethamine dispersible tablets 500 mg/ 25 mg (Macleods Pharmaceuticals Limited, India) to

Fansidar® (sulphadoxine/pyrimethamine) tablets 500 mg/25 mg (AkaciaTM HealthCare (Pty) Ltd., South Africa) in healthy adult, human subjects (study no. BEQ-2439-SuPy (F)-2018).

The objective of the study was to compare the bioavailability of the stated Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet manufactured for/by Macleods Pharmaceuticals Limited, India (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. : ESB3802A

Treatment R: References – 1 tablet Pyrimethamine/Sulfadoxine 25/500 mg (pyrimethamine 25 mg + sulfadoxine 500 mg) Batch no. Z1588

Serial blood samples (1 pre-dose sample and 25 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 1504 ng/ml for sulfadoxine.

The study was performed with 33 participants; data generated from a total of 32 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)	2.44 ± 1.29	3.06 ± 1.42	–	–
C_{max} (ng/mL)	192 ± 35 (189)	182 ± 29 (180)	105.3	94.9 – 116.7
AUC_{0-72} (ng·h/mL)	9323 ± 1676 (9174)	9099 ± 1119 (9033)	101.6	92.2 – 111.8

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)	4.34 ± 1.19	4.03 ± 0.96	–	–
C_{max} (µg/mL)	75.2 ± 7.7 (74.9)	67.9 ± 6.2 (67.7)	110.7	104.3 – 117.4
AUC_{0-72} (µg·h/mL)	4429 ± 547 (4396)	4013 ± 372 (3997)	110.0	102.9 – 117.6

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 (Macleods Pharmaceuticals Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Pyrimethamine/Sulfadoxine 12.5/250 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 to be the same.

4. Summary of product safety and efficacy

According to the submitted data on quality, [MA158 trade name] is a direct-scale down of Pyrimethamine/Sulfadoxine 25/500 mg FDC dispersible tablet (Macleods Pharmaceuticals Limited, India). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Fansidar® 25/500 mg tablet (Akacia™ HealthCare (Pty) Ltd.) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [MA158 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 [MA158 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA158 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, [MA158 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 [MA158 trade name] was acceptable for the following indication: '**intermittent preventive treatment of malaria in women in their first or second pregnancy and in infants aged less than 12 months**', and would allow inclusion of [MA158 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Phase II, Plot No 25 - 27, Survey No 366, Premier Industrial Estate, Kachigam, Daman 396210, India, in the list of prequalified medicinal products.