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	[MA170 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited, Unit II, Phase II, Plot No 25 - 27, Survey No 366, Premier Industrial Estate, Kachigam, Daman 396210, India
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine (as hydrochloride), Pyrimethamine, and Sulfadoxine
Pharmaco-therapeutic group (ATC Code)	Antimalarials (ATC code P01B)
Therapeutic indication	[MA170 trade name] is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in patients aged 3 months to less than 1 year

1. Introduction

[MA171] is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in patients 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*.

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 [MA171 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) dispersible tablet formulation include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, basic butylated methacrylate copolymer, aspartame, orange flavour, sodium bicarbonate 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 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. 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 PVC/PVDC-Alu blister card.

Pharmaceutical development and manufacture

Amodiaquine (as hydrochloride) 153mg dispersible tablets

The multisource product is a yellow, round, flat, bevelled edge, uncoated tablet debossed with ‘J’ and ‘l2’ on either side of score line on one side and plain on other side.

Two strengths of amodiaquine (as hydrochloride) dispersible tablets proportionally similar in composition were developed: 76.5mg and 153mg.The development focused on the 150mg strength, which was used in the BE study against the amodiaquine 153mg tablets of the WHO recommended comparator product SPAQ-CO™ tablets (pyrimethamine/sulfadoxine 25mg/500mg tablets + amodiaquine 153mg tablets). Once the formulation for the 150mg strength was finalized, the 76.5mg strength was pursued using dose-proportionality approach.

The aim of the product development was to develop a dispersible tablet formulation, bioequivalent to the amodiaquine 153mg 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, some taste-masking was achieved by selecting basic butylated methacrylate copolymer as binder and 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 micronized nature and 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.

Pyrimethamine/Sulfadoxine 25mg/500mg dispersible tablets

Pharmaceutical development and manufacture

The multisource product is a white to off-white, capsule shaped, biconvex, uncoated tablet debossed with ‘F’ and ‘41’ on either side of score line on one side and plain on other side. 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 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 amodiaquine (as hydrochloride) 153mg dispersible tablets include tests for description, identification (HPLC, UV and test for chlorides), average weight, hardness, friability, disintegration time, fineness of dispersion, uniformity of dosage units (weight variation), dissolution (UV detection), related substances (HPLC), assay (HPLC), residual solvent (GC), subdivision of tablets and microbial limits. The test procedures have been adequately validated.

The finished product specifications for pyrimethamine/sulfadoxine 25mg/500mg 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 Fansidar® 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 (*)	Reference (R) arithmetic mean ± SD (*)	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_{0-72h} (ng.h/ml)	9323 ± 1676 (9174)	9099 ± 1119 (9033)	101.6	92.2 – 111.8

* 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)	4.34 ± 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_{0-72h} (µg.h/ml)	4429 ± 547 (4396)	4013 ± 372 (3997)	110.0	102.9 – 117.6

* 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 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 12.5/250 mg FDC tablet (Macleods Pharmaceuticals Ltd, India) was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths was considered essentially the same and the dissolution profiles between the formulations for the APIs were determined to be the same.

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

Study title: Single dose fasting in vivo bioequivalence study of Amodiaquine dispersible tablets 153 mg (Macleods Pharmaceuticals Ltd., India) to SPAQ-COTM (sulfadoxine/pyrimethamine + amodiaquine) dispersible tablets 500/25+153 mg (Guilin Pharmaceuticals co. Ltd., China) in healthy, adult, human subjects (study no. BEQ-2329-AMOD-2017).

The objective of the study was to compare the bioavailability of the stated Amodiaquine 153 mg dispersible tablet manufactured for/by Macleods Pharmaceuticals Ltd., India (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, 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 153 mg (amodiaquine 153 mg) Batch no. : EAD6701A
Treatment R:	Reference – 1 dispersible tablet Amodiaquine 150 mg (amodiaquine 153 mg) Batch no. LF180604

The tablets were dispersed in 10 ml water before intake. 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 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 99 pg/ml for amodiaquine.

The study was performed with 60 participants; data generated from a total of 59 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	1.12 ± 0.56	0.82 ± 0.30	-	-
C_{max} (pg/ml)	7125 ± 3431 (6630)	7791 ± 2770 (7357)	90.1	84.5 – 96.1
AUC_{0-t} (pg.h/ml)	70284 ± 16449 (68421)	66379 ± 17242 (64273)	106.5	102.1 – 111.0

* 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 amodiaquine. Accordingly, the test 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 Amodiaquine 153 mg dispersible tablet (Guilin Pharmaceutical Co. Ltd.).

A biowaiver was granted for the additional 76.5 mg dispersible tablet strength (Macleods Pharmaceuticals Ltd.,) in accordance with the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Amodiaquine 76.5 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, Amodiaquine (as hydrochloride) 76.5 mg dispersible tablets in [MA170 trade name] is a direct scale-down of Amodiquine (as hydrochloride) 153 mg dispersible tablet (Macleods Pharmaceuticals Limited, India). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Amodiaquine 153 mg dispersible tablet (Guilin Pharmaceutical Co. Ltd.) for which benefits have been proven in terms of clinical efficacy.

Pyrimethamine/Sulfadoxine 12.5/250 mg tablets in [MA170 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 [MA170 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 [MA170 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA170 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, [MA170 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 [MA171 trade name] was acceptable for the following indication: **' malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in patients aged 3 months to less than 1 year'**, and would allow inclusion of [MA170 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.