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	[MA125 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited, Phase II and Phase III, Unit II, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 396 210, India
Active Pharmaceutical Ingredient(s) (API)	Amodiaquine (as hydrochloride) /Artesunate
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations (P01BF03)
Therapeutic indication	MA125 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and to artesunate.

1. Introduction

[MA125 trade name] is indicated for the treatment of uncomplicated malaria due to Plasmodium falciparum.

[MA125 trade.name] should be initiated by a health care provider experienced in the management of malaria infection.

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)

Amodiaquine hydrochloride and artesunate 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 these APIs, used in the manufacture of [MA125 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 assessment 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 tablet formulation include calcium carbonate, maize starch, povidone, croscarmellose sodium, silicon dioxide, magnesium stearate and microcrystalline cellulose. BSE/TSE compliance declarations were provided for all excipients. None of them are of human or animal origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a bilayer round flat, bevelled edged, uncoated tablet having plain surface on both sides, one layer is yellow coloured, the other one is white to off white coloured. The tablets are presented in Alu-Alu blisters.

Three strengths of Amodiaquine (as hydrochloride)/artesunate tablets proportionally similar in composition and manufactured from a common blend were developed: 270 mg/100 mg, 135 mg/50 mg and 67.5 mg/25 mg. The development focused on the highest strength, which was used in the BE study against the comparator product, Artesunate Amodiaquine Winthrop tablets of the same strength. Once the formula for the 270 mg/100 mg strength was finalized, the 135 mg/50 mg and 67.5 mg/25 mg strengths were planned using dose-proportionality approach.

The aim of the product development was to obtain a stable and robust formulation of amodiaquine hydrochloride/artesunate tablets, bioequivalent to the comparator product. Similar to the comparator product a bilayer tablet containing amodiaquine hydrochloride and artesunate in two distinct layers was developed. The excipients selected are well known and commonly used in solid oral formulations. From physicochemical characterization of amodiaquine hydrochloride and artesunate it was observed that both APIs exhibited very poor flow characteristics. Compatibility studies which were conducted showed that the APIs were compatible with the selected excipients. The bilayer tablet was manufactured by dry granulation process consisting of compaction of amodiaquine hydrochloride and direct compression of the artesunate layer.

Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC, TLC and colour reaction), average weight, hardness, friability, loss on drying, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75% RH (zone IVb) as long-term storage conditions and for six months at accelerated condition in the packaging proposed for marketing of the product. Some degradation was noted for artesunate, though within the agreed specification limits at both long term and accelerated storage conditions in the proposed packaging configuration. Based on the available stability data the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The tablets must be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2015 according to internationally accepted guidelines.

Study title: Bioequivalence study of two tablets as single dose of fixed dose combination of artesunate and amodiaquine tablets 100 mg/270 mg manufactured by Macleods Pharmaceuticals Limited, India, comparing with two tablets of Winthrop® (artesunate and amodiaquine) tablets 100 mg/270 mg manufactured by Sanofi-Aventis, Morocco in healthy, adult, human subjects under fasting condition (study no. BEQ-1254-AA (F)-2013).

The objective of the study was to compare the bioavailability of the stated Artesunate/amodiaquine 100/270 mg FDC tablet manufactured for/by Macleods Pharmaceuticals Limited, India (test drug) with the reference formulation Artesunate/amodiaquine 100/270 mg (Winthrop®) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, four-period, fully replicated crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive twice each of the following treatments in a randomized fashion:

Treatment T: Test – 2 tablets Artesunate/amodiaquine 100/270 mg (artesunate 200 mg + amodiaquine 540 mg) Batch no. EAC8402A

Treatment R: Reference – 2 tablets Artesunate/amodiaquine Winthrop® 100/270 mg (artesunate 200 mg + amodiaquine 540 mg) Batch no. 6101

A 49 day wash-out period was observed between administration of tests and references. Serial blood samples (1 pre-dose sample and 29 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 artesunate and amodiaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5.3 ng/mL for artesunate and about 0.4 ng/mL for amodiaquine.

The study was performed with 60 participants; data generated from a total of 49 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate and amodiaquine as well as statistical results are summarised in the following tables:

Artesunate

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) #	0.39 ± 0.28	0.41 ± 0.41	–	–
C_{max} (ng/mL)	407 ± 334 (331)	411 ± 255 (349)	94.9	85.2 – 105.8
AUC_{0-t} (ng·h/mL)	242 ± 159 (205)	243 ± 112 (219)	93.8	88.2 – 99.8
AUC_{0-inf} (ng·h/mL)	253 ± 158 --	262 ± 108 --	--	--

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) #	0.85 ± 0.70	1.00 ± 1.01	-	-
C_{max} (ng/mL)	10.5 ± 4.6 (10.3)	11.0 ± 6.0 (10.3)	100.4	93.5 – 107.9
AUC_{0-t} (ng·h/mL)	88 ± 44 (83)	91 ± 40 (86)	97.2	90.9 – 104.0
AUC_{0-inf} (ng·h/mL)	102 ± 49 --	107 ± 45 --	--	--

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding artesunate and amodiaquine. Accordingly, the test Artesunate/Amodiaquine 100/270 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Artesunate/Amodiaquine Winthrop 100/270 mg tablet (Winthrop®).

A biowaiver was granted for the additional 25/67.5 mg and 50/135 mg FDC tablet strengths (Macleods Pharmaceuticals Ltd., India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Artesunate/Amodiaquine 25/67.5 mg and 50/135 mg FDC tablets were determined to be qualitatively essentially the same, the ratio of active ingredient and excipients between the strengths was considered essentially 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 [MA125 trade.name] is a direct scale-down of [MA127 trade.name]. The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Artesunate + Amodiaquine Winthrop® 100 mg /270 mg tablet (Sanofi-Aventis) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [MA125 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA125 trade name] has fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA125 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 [MA125 trade name] was acceptable for the following indication: 'treatment of malaria due to Plasmodium falciparum', and would allow inclusion of [MA125 trade name], manufactured at Macleods Pharmaceuticals Limited, Phase II and Phase III, Unit II, Plot No 25-27, Survey No 366, Premier Industrial Estate, Kachigam, Daman, 396 210, India in the list of prequalified medicinal products.