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	[MA208 trade name]*
Manufacturer of Prequalified Product	Ipca Laboratories Limited Plot no. 255/1, Village Athal, Silvassa 396 230 U.T. of Dadra and Nagar Haveli and Daman and Diu, India
Active Pharmaceutical Ingredient(s) (API)	Primaquine phosphate
Pharmaco-therapeutic group (ATC Code)	Aminoquinoline anti-protozoal agent. ATC code: P01BA03
Therapeutic indication	[MA208 trade name] is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria, in adults and children. It is also used to reduce the transmissibility *of Plasmodium falciparum* infections in low-transmission areas. Except in primary prophylaxis, primaquine is used in conjunction with an effective blood schizonticide: either artemisinin-based combination therapy (ACT) or chloroquine for *vivax* or *ovale* malaria.

1. Introduction

[MA208 trade name] is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria.

Primaquine is used in conjunction with an effective blood schizonticide: either artemisinin-based combination therapy (ACT) or chloroquine for *P. vivax* or *P. ovale* malaria.

Testing for glucose-6-phosphate-dehydrogenase (G6PD) deficiency is needed beforehand to guide appropriate treatment.

[MA208 trade name] is also used in combination with an ACT to reduce the transmissibility of *Plasmodium falciparum* infections in low-transmission areas.

Treatment regimens should take into account the most recent official treatment guidelines (e.g. those of the WHO) and local information on the prevalence of resistance to antimalarial drugs.

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

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)

A certificate of suitability issued by the EDQM was submitted for primaquine diphosphate ensuring good manufacturing control and applicability of the respective Ph.Eur monograph to control the quality of the API. Additional user requirements for primaquine diphosphate include test for particle size distribution, the limits of which were set on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the dispersible tablet formulation include lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, purified talc, sucralose, trusil tonovin SPL and magnesium stearate, all except trusil tonovin SPL being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The flavourant is controlled by acceptable specifications. Lactose and magnesium stearate are of bovine and vegetable origins respectively. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a mottled orange to light orange, round, dispersible tablet. It is biconvex (rounded on top and bottom) with bevelled edge. The tablet has a break line on one side and is 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 data. The tablets are packaged in aluminium foil on aluminium foil blister cards.

Three strengths of Primaquine (as phosphate) dispersible tablets proportionally similar in composition were developed: 7.5mg, 5mg and 2.5mg. The highest strength was used in the BE study against the WHO recommended comparator product, Primaquine phosphate 15mg tablets (manufactured by Sanofi Aventis US LLC).

The development of the final composition of the multisource product has been described. The objective was to develop a stable, robust, dispersible tablet, bioequivalent to the WHO recommended comparator product. The comparator product was characterized and on that basis a quality target product profile was defined, and critical quality attributes were identified. The selection of excipients was based on the excipients used in the comparator product and API-excipient compatibility data. The composition included a sweetener and a flavouring agent to improve the palatability of the formulation. Based on the manufacturer's experience with a related prequalified product and the hygroscopic nature of the API, direct compression manufacturing method was finalised for the multisource product. Based on the satisfactory data of optimization trials, the formulation was finalised resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain N-nitrosamine impurities and hence no risk was identified, though the manufacturer undertook to conduct confirmatory testing for potential N-nitroso primaquine on selected batches post prequalification.

Specifications

The finished product specifications include tests for description, identification (UV and HPLC), average weight of tablet, hardness, friability, disintegration time, fineness of dispersion, assay (HPLC), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), organic impurities (HPLC), loss on drying 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 condition and for six months at 40°C/75%RH as accelerated storage conditions in the packaging intended for marketing of the product. The data provided indicate that all the tested parameters remained within acceptable limits at both storage conditions, with no obvious trend or variability. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2024 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study of Primaquine dispersible tablets 2 x 7.5 mg (dose 15 mg) of Ipca Laboratories Ltd., India comparing with Primaquine phosphate tablets, USP 26.3 mg (=15 mg base) of Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807 in normal, healthy, adult, human subjects under fasting conditions (study no. 23-102).

The objective of the study was to compare the bioavailability of the stated Primaquine 7.5 mg dispersible tablet manufactured by/for Ipca Laboratories Ltd., India (test drug) with the reference formulation Primaquine Phosphate 15 mg tablet, USP (Sanofi-Aventis U.S. LLC) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 2 tablets Primaquine diphosphate 7.5 mg (primaquine 15 mg) Batch no. KED0130039.
Treatment R:	Reference – 1 tablet Primaquine Phosphate 15 mg USP (primaquine 15 mg) Batch no. 8125520.

The Test tablets were dispersed in 15 ml water (+ 15 ml of rinsing water) and administered. The Reference tablet was administered with 240 ml water. A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 36h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for primaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.5 ng/ml for primaquine.

The study was performed with 60 participants; data generated from a total of 56 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for primaquine as well as statistical results are summarised in the following table:

Primaquine

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)	1.71 ± 0.64	1.85 ± 0.52	-	-
C_{max} (ng/mL)	90 ± 36 (83)	87 ± 28 (82)	101.0	94.6 – 107.9
AUC_{0-t} (ng·h/mL)	750 ± 323 (687)	772 ± 271 (724)	94.8	90.0 – 100.0
AUC_{0-inf} (ng·h/mL)	768 ± 332 --	790 ± 284 --	-	-

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding primaquine. Accordingly, the test Primaquine Phosphate 7.5 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Primaquine 15 mg tablet USP (Sanofi-Aventis U.S. LLC).

4. Summary of product safety and efficacy

[MA208 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, [MA208 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Primaquine 15 mg tablet USP (Sanofi-Aventis U.S. LLC) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA208 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 [MA208 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA208 trade name] has been shown to be bioequivalent with Primaquine 15 mg tablet USP (Sanofi-Aventis U.S. LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA208 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 [MA208 trade name] was acceptable for the following indication: 'Treatment of radical cure (prevention of relapse) of *Plasmodium vivax* and *Plasmodium ovale* malaria, in adults and children. It is also used to reduce the transmissibility of *Plasmodium falciparum* infections in low-transmission areas. Except in primary prophylaxis, primaquine is used in conjunction with an effective blood schizonticide: either artemisinin-based combination therapy (ACT) or chloroquine for *vivax* or *ovale* malaria.' and would allow inclusion of [MA208 trade name], manufactured at Ipca Laboratories Limited, Village Athal, Silvassa, U.T. of Dadra and Nagar Haveli and Daman and Diu, India, in the list of prequalified medicinal products.