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	[MA196 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 (as phosphate)
Pharmaco-therapeutic group (ATC Code)	Aminoquinoline anti-protozoal agent. ATC code: P01BA03
Therapeutic indication	[MA196 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

[MA196 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.

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*.

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

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 core tablet formulation include lactose, microcrystalline cellulose, pregelatinised starch, purified talc and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, ethyl cellulose, triacetin, titanium dioxide and iron oxide red. Lactose is of bovine origin. TSE/BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown to light brown, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat 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 blister.

The goal of the formulation development strategy was to obtain a robust, stable multisource product bioequivalent to the WHO recommended comparator product, Primaquine (as phosphate) 15mg tablets (manufactured by Sanofi Aventis US LLC). The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility data. Direct compression approach was selected as the manufacturing process for the finished pharmaceutical product. Various experiments were performed to select and optimize the concentration of excipients and process parameters to obtain tablets of desired characteristics. Satisfactory in-process controls have been established.

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, disintegration time, assay (HPLC), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), organic impurities (HPLC), primaquine lactose adduct impurity (HPLC), residual solvents (GC), 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 (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. 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 2022 according to internationally accepted guidelines.

Single dose oral bioequivalence study of Primaquine phosphate tablets USP 15 mg (Test) and Primaquine 15 mg tablet (Reference) in healthy adult human subjects under fasting conditions (study no. C1B00842).

The objective of the study was to compare the bioavailability of the stated Primaquine Phosphate 15 mg tablet manufactured by/for IPCA, 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 – 1 tablet Primaquine Phosphate 15 mg
(primaquine 15 mg)
Batch no. HTZ0220019.

Treatment R: Reference – 1 tablet Primaquine Phosphate 15 mg USP
(primaquine 15 mg)
Batch no. 8125520.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72h 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 50 participants; data generated from a total of 47 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)	2.80 ± 0.79	2.89 ± 0.89	-	-
C_{max} (ng/mL)	66 ± 26 (62)	64 ± 22 (60)	104.2	96.9 – 112.0
AUC_{0-t} (ng·h/mL)	635 ± 243 (597)	603 ± 215 (564)	105.8	99.8 – 112.1
AUC_{0-inf} (ng·h/mL)	645 ± 243 --	613 ± 216 --	-	-

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 15 mg 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

[MA196 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, [MA196 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 [MA196 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 [MA196 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA196 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, [MA196 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 [MA196 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 [MA196 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.