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	[MA176 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block N2, Village Theda, P. O. Lodhi Majra, Tehsil Baddi, Distt. Solan, Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient(s) (API)	Primaquine (as phosphate)
Pharmaco-therapeutic group (ATC Code)	Aminoquinoline anti-protozoal agent. ATC code: P01BA03
Therapeutic indication	[MA176 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

[MA176 trade name] is indicated in combination with either artemisinin-based combination therapy (ACT) or chloroquine for the radical cure 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.

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)

Data provided in the dossier show that primaquine phosphate, is an orange-red crystalline powder. Solubility data provided indicate that the API is highly soluble according to the BCS. Primaquine phosphate possesses a stereogenic carbon centre and hence shows stereoisomerism. It exists as both R and S enantiomers, but only preparations containing the racemic mixture are commercially available.

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

Polymorphism has not been reported in the literature for primaquine phosphate. The manufacturer of the API consistently produces the racemic mixture (RS).

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR, HPLC and pyrophosphate), loss on drying, related substances (HPLC), assay (HPLC), heavy metals, residual solvents (GC), bulk density and particle size distribution (laser diffraction).

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, lactose monohydrate, pregelatinized starch, povidone and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/ polyethylene glycol, talc, polysorbate and iron oxide red. All the excipients are conventional pharmaceutical ingredients included in the formulation at suitable levels and for recognised purposes. TSE/BSE free certificates have been provided for the excipients. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin, respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pink, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a score line on one side and is plain on the other side. The tablets are packaged in either aluminium (OPA/Alu/PVC laminate) on aluminium foil blister cards or HDPE bottles with childproof plastic (polypropylene) screw caps.

The objective of the product development was to obtain a stable and robust formulation of primaquine (as phosphate) 15 mg film-coated tablets which is bioequivalent to the WHO recommended comparator product, Primaquine phosphate 15 mg tablets (Sanofi Aventis U.S. LLC). The composition was based on the properties of the API and the excipients that are used in the comparator product. Compatibility studies showed that the API was compatible with the selected excipients. Based on the physicochemical characteristics (in particular poor flowability) of the API, a non-aqueous wet granulation process was selected for the manufacture of the FFP. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the API (HPLC and UV) and colourants, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), subdivision of tablets, loss on drying, residual solvent (GC) and microbial limits.

Stability testing

Stability studies have been performed at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The data showed degradation at both long-term storage conditions in both primary pack types, to the extent that only the storage condition ‘Do not store above 25°C” is supported. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable. The in-use storage period after first opening of the HDPE bottle is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

No bioequivalence study has been performed. Instead, a BCS based biowaiver has been applied. In accordance with the WHO guidance and criteria for BCS based biowaivers, supporting data have been provided regarding solubility, permeability, formulation comparability and in vitro dissolution.

Based upon the solubility and permeability data, primaquine can be considered a BCS Class I drug. Comparability between the reference Primaquine® 15 mg tablet (Sanofi-Aventis) and the test Primaquine 15 mg tablet (Macleods Pharmaceuticals Limited) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1.2, 4.5 and 6.8 have been shown. Accordingly, the test tablet Primaquine 15 mg tablet (Macleods Pharmaceuticals Limited) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the respective reference Primaquine® 15 mg tablet (Sanofi-Aventis).

4. Summary of product safety and efficacy

[MA176 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, [MA176 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Primaquine® 15 mg tablet (Sanofi-Aventis) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA176 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 [MA176 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA176 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. Hence, [MA176 trade name] and Primaquine® 15 mg tablet (Sanofi-Aventis) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [MA176 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, in vitro dissolution, safety and efficacy the team of assessors considered that the benefit–risk profile of [MA176 trade name] was acceptable for the following indication: '**in combination with either artemisinin-based combination therapy (ACT) or chloroquine for the radical cure 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'**, and would allow inclusion of [MA176 trade name], manufactured at

Macleods Pharmaceuticals Limited, Block N2, Village Theda, P. O. Lodhi Majra, Tehsil Baddi, Distt. Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.