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	[MA177 trade name]*
Manufacturer of Prequalified Product	KBN-Zhejiang Pharmaceutical Co., Ltd. 340 Yunhai Road, Economy Development Zone Jiaxing City Zhejiang Province China
Active Pharmaceutical Ingredient(s) (API)	Dihydroartemisinin/Piperaquine (as phosphate)
Pharmaco-therapeutic group (ATC Code)	Artemisinin and derivatives, combinations ATC code: P01BF05
Therapeutic indication	[MA177 trade name] is indicated for the treatment of uncomplicated malaria. [MA177 trade name] is active against all Plasmodium parasites that cause malaria in humans.

1. Introduction

[MA177 trade name] is indicated for the treatment of uncomplicated malaria. [MA177 trade name] is active against all Plasmodium parasites that cause malaria in humans.

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.

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)

Dihydroartemisinin and piperaquine phosphate (piperaquine tetraphosphate tetrahydrate) 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 [MA177 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 core tablet formulation include maize starch, dextrin, hypromellose, sodium starch glycolate and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl ethanol, titanium dioxide, talc, macrogol/ polyethylene glycol, FD&C blue #2/indigo carmine aluminium lake, lecithin (soya), FD&C blue #1/brilliant blue FCF aluminium lake and FD&C yellow #6/sunset yellow FCF aluminium lake. Magnesium stearate is of vegetable origin. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a blue, round, biconvex film-coated tablets with 'D•C' debossed one side and a break line 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 presented in plastic (PVC) on aluminium foil blister cards.

The objective of the product development was to formulate a stable fixed dose combination tablet, which is bioequivalent to the WHO comparator product Eurartesim®. The excipients were chosen and finalized based on the excipients used in the comparator product and API-excipient compatibility studies. As the product is well established by the manufacturer, the formulation and product development were supported by annual product quality review covering sufficient batches. Ethanol is used in the wet granulation manufacturing process, to dissolve hypromellose and the residual limit is in accordance with ICH Q3C. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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 APIs (HPLC and TLC), related substances (HPLC), assay (HPLC), water content (KF), weight variation, dissolution of dihydroartemisinin (HPLC detection), dissolution of piperaquine phosphate (UV detection), uniformity of dihydroartemisinin content, residual solvent (GC) and microbial limits. The test procedures have been adequately validated.

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 conditions and for six months at 40°C/75%RH as accelerated storage conditions. Degradation was observed for dihydroartemisinin at long-term storage conditions, with significant changes for assay and degradation products observed at accelerated condition. 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 and humidity.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2020 according to internationally accepted guidelines.

A randomized, balanced, single dose, two-treatment, two-period, crossover oral bioavailability/ bioequivalence study for piperaquine and dihydroartemisinin in fixed dose combination of [MA177 trade name] (dihydroartemisinin 40 mg and piperaquine tetraphosphate 320 mg) tablets of KBN-Zhejiang Pharmaceutical Co., Ltd. China (test), with Eurartesim® (dihydroartemisinin 40 mg and piperaquine tetraphosphate 320 mg) film-coated tablets, manufactured by Alfasigma S.p.A. Italy (reference) in healthy, adult, human subjects under fasting condition (study no. ARL/20/040).

The objective of the study was to compare the bioavailability of the stated [MA177 trade name] manufactured for/by KBN-Zhejiang Pharmaceutical Co., Ltd. China (test drug) with the reference formulation Eurartesim® (dihydroartemisinin/piperaquine) tablets 40/320 mg (Alfasigma S.p.A.) 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 tablet [MA177 trade name] (dihydroartemisinin 40 mg + piperaquine 320 mg) Batch no.: 200603
Treatment R:	References – 1 tablet Eurartesim® 40/320 mg (dihydroartemisinin 40 mg + piperaquine 320 mg) Batch no.: 190242

A 76-days wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 dihydroartemisinin and piperaquine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 1 ng/mL for dihydroartemisinin and about 0.3 ng/mL for piperaquine.

The study was performed with 162 participants; data generated from a total of 144 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Dihydroartemisinin

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 (ANOVA log)
t_{max} (h)	1.37 ± 0.77	1.48 ± 0.88	–	–
C_{max} (ng/mL)	266 ± 133 (235)	243 ± 114 (217)	108.2	100.8 – 116.0
AUC_{0-t} (ng·h/mL)	539 ± 229 (489)	563 ± 243 (510)	95.8	91.0 – 100.8
AUC_{0-inf} (ng·h/mL)	542 ± 229 (493)	567 ± 224 (514)	95.8	91.1 – 100.8

Piperaquine

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)	3.49 ± 1.36	3.61 ± 1.17	–	–
C_{max} (µg/mL)	123 ± 85 (100)	129 ± 78 (110)	90.9	83.8 – 98.7
$AUC_{0\text{-}72h}$ (µg ·h/mL)	2029 ± 926 (1835)	2134 ± 902 (1953)	94.0	89.1 – 99.1

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dihydroartemisinin and piperaquine. Accordingly, the test fixed dose combination tablet [MA177 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Eurartesim® 40/320 mg tablet (Alfasigma S.p.A.).

4. Summary of product safety and efficacy

[MA177 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, [MA177 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Eurartesim® (Alfasigma S.p.A. Italy) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [MA177 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 [MA177 trade name] is used in accordance with the SmPC.

Bioequivalence

[MA177 trade name] has been shown to be bioequivalent with Eurartesim® (Alfasigma S.p.A. Italy).

Efficacy and Safety

Regarding clinical efficacy and safety, [MA177 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 [MA177 trade name] was acceptable for the following indication: 'treatment of uncomplicated malaria', and would allow inclusion of [MA177 trade name], manufactured at KBN-Zhejiang Pharmaceutical Co. Limited, 340 Yunhai Road, Economy Development Zone, Jiaxing City, Zhejiang Province, China in the list of prequalified medicinal products.