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	[TB364 trade name]*
Manufacturer of Prequalified Product	Suheung Co. Ltd. Osong Plant (Head Office) 61, Osongsaengmyeong-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea Dong-A ST Co. Ltd. Cheonan Plant (2F Section B, 3F, 4F Section B) 200-23, Baekseokgongdan 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do, Republic of Korea
Active Pharmaceutical Ingredient(s) (API)	Clofazimine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials (J04BA01)
Therapeutic indication	[TB364 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB364 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. [TB364 trade name] is indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance.

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)

Clofazimine, 3-(p-chloroanilino)-10-(p-chlorophenyl)-2,10- dihydro-2-(isopropylimino)-phenazine, is manufactured in a reddish-brown crystalline form. The structure of clofazimine was confirmed by the route of synthesis and spectrometric data. Clofazimine is known to exhibit polymorphism and exists in several forms. Form I is consistently produced.

The API specifications include tests for appearance, solubility, identification (IR and HPLC), loss on drying, residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), polymorphic identity (pXRD), platinum content (ICP-OES), residual solvents (GC), and particle size distribution.

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

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

The capsule fill contains soybean oil, canola oil, hydrogenated vegetable oil, white beeswax, lecithin and butylated hydroxytoluene. The capsule shell contains gelatin, glycerin, ethyl vanillin, black iron oxide, red iron oxide, methylparaben and propylparaben. TSE/BSE free certificates from the suppliers have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a brown opaque, oval soft capsule filled with brick red to brown suspension. The capsules are packaged in a white HDPE bottle with 1g silica gel stick and closed with white low density polyethylene cap.

The objective of the development of the multisource product was to obtain a stable and robust formulation, which is bioequivalent to the WHO recommended comparator product, Lamprene® 100mg soft gelatin capsules. The selection of the excipients was primarily based on the comparator product and API-excipient compatibility studies. The finished pharmaceutical product is manufactured by a conventional pharmaceutical manufacturing process for soft capsules which involves preparation of capsule content, preparation of capsule shell, encapsulation and drying. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, identification (HPLC and UV), colourant and polymorphic identity, assay (HPLC), related substances (HPLC), uniformity of dosage units (by mass uniformity), disintegration, time for capsule to rupture, water content of shell, preservative content, particle size distribution and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 25^0C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the package proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with a slight increase of degradation products, though within agreed limits. 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 2017/2018 according to internationally accepted guidelines.

A randomized, open label, balanced, three-sequence, two-treatment, three-period, partial replicate design bioequivalence study of Dong-A Clofazimine solution in soft gel capsule 100 mg of Dong-A ST Co. Ltd., India with Lamprene® (clofazimine) soft gelatin capsules 100 mg of Novartis Pharmaceuticals Corporation in normal, healthy, adult, male and female human subjects under fed conditions (ARL/16/119).

The objective of the study was to compare the bioavailability of the stated Clofazimine 100 mg capsule manufactured by/for Dong-A St Co. Ltd., Republic of Korea (test drug) with the reference

formulation Lamprene® (Novartis Pharmaceuticals Co.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, partial replicate, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion, of which the Reference was administered twice:

Treatment T:	Test – 1 capsule Clofazimine 100 mg (clofazimine 100 mg) Batch no. FLP1706001.
Treatment R:	Reference – 1 capsule Lamprene® (clofazimine 100 mg) Batch no. GZ1889.

A 60 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 clofazimine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 2 ng/ml for clofazimine.

The study was performed with 108 participants; data generated from a total of 95 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Clofazimine

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)	6.15 ± 2.56	5.85 ± 1.46	–	–
C_{max} (ng/mL)	162 ± 88 (141)	148 ± 73 (130)	108.5	101.5 – 116.0
$AUC_{0\text{-}72h}$ (ng·h/mL)	3227 ± 1263 (2999)	2970 ± 1055 (2794)	107.3	102.5 – 112.4

The results of the study show that preset acceptance limits of 80-125% are met by both AUC and C_{max} values regarding clofazimine. Accordingly, the test Clofazimine 100 mg capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Lamprene® (Novartis Pharmaceuticals Co.).

4. Summary of product safety and efficacy

[TB364 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, [TB364 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Lamprene® (Novartis Pharmaceuticals Co.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB364 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 [TB364 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB364 trade name] has been shown to be bioequivalent with Lamprene® (Novartis Pharmaceuticals Co.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB364 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 [TB364 trade name] was acceptable for the following indication: 'in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis', and would allow inclusion of [TB364 trade name], manufactured at Suheung Co.Ltd. and Dong-A ST Co. Ltd., Chungcheongnam-do, Republic of Korea, in the list of prequalified medicinal products.