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	[TB361 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited At, Oxalis Labs Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient (API)	Clofazimine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials (J04BA01)
Therapeutic indication	[TB361 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB361 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. Clofazimine 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 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 which is the most stable polymorphic form is consistently produced.

The API specifications include tests for description, solubility, identification (IR and HPLC), loss on drying, residue on ignition, organic impurities (HPLC), assay (HPLC), residual solvents (GC), genotoxic impurities (HPLC), polymorphic identity (XRPD) and particle size distribution.

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.

* 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 castor oil polyoxyl hydrogenated, povidone, polysorbate 80, betadex (cyclodextrin), microcrystalline cellulose, colloidal silicon dioxide, crospovidone and sodium stearyl fumarate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains hypromellose, triacetin, titanium dioxide, iron oxide red and iron oxide yellow. None of the excipients are of animal or human origin. 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 light brown-coloured, circular-shaped, biconvex, film-coated tablet and plain on both sides. The tablets are packaged in clear PVC/PVDC-aluminium blister, plain aluminium foil laminated with polyethene film strip and round white HDPE container closed with white polypropylene child resistant closure with pulp and white printed liner.

Two strengths of clofazimine tablets proportionally similar in composition were developed: 50 mg and 100 mg. The development focused on the higher strength, which was used in the BE study against the WHO comparator product Lamprene®, (clofazimine 100 mg capsules). Once the formulation for the 100 mg strength was finalized, the 50 mg strength was pursued using dose-proportionality approach.

The objective of the development of the multisource product was to develop a stable and robust formulation of clofazimine tablets, which is bioequivalent to the WHO recommended comparator product, Lamprene® 100 mg Capsules. The selection of the excipients was primarily based on API-excipient compatibility studies and suitability to achieve the desired characteristics of the tablet. Betadex is used solely as diluent, and an inclusion complex is not formed. Based on the characteristics of the API, wet granulation process was selected as the manufacturing process.

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 include tests for description, identification (HPLC and UV-VIS) and colourants, average weight, loss on drying, dissolution (UV-VIS detection), uniformity of dosage units (by content uniformity), related substances (HPLC), residual solvents (GC), assay (HPLC) 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 accelerated conditions in the packages 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. The tablets must be protected from light.

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.

Single-dose, fed, in-vivo bioequivalence study of Clofazimine tablets 100 mg (Macleods Pharmaceuticals Ltd., India) to Lamprene® (clofazimine) soft gel capsules molle 100 mg (Novartis Pharma S.A.S. France) in healthy, adult, human subjects (study no. BEQ-2229-CLOF-2017).

The objective of the study was to compare the bioavailability of the stated Clofazemine 100 mg tablet manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Lamprene® (Novartis Pharma S.A.S.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Clofazimine 100 mg (clofazimine 100 mg) Batch no. NCG702D.

Treatment R: Reference – 1 tablet Lamprene® (clofazimine 100 mg) Batch no. GG0650.

A 60 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 30 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 clofazimine were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 4 ng/mL for clofazimine.

The study was performed with 24 participants; data generated from a total of 20 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)	5.80 ± 1.47	5.68 ± 1.42	–	–
C_{max} (ng/mL)	137 ± 62 (121)	135 ± 68 (125)	103.6	89.3 – 120.1
AUC_{0-72h} (ng·h/mL)	3216 ± 1036 (2989)	3223 ± 1135 (3023)	101.1	92.7 – 110.4

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 tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Lamprene® (Novartis Pharma S.A.S.).

A biowaiver was granted for the additional 50 mg tablet strength [TB361 trade name] (Macleods Pharmaceuticals Ltd., India) in accordance to the WHO guideline. In comparison with the 100 mg strength of the test product used in the bioequivalence study, [TB361 trade name] was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the API were determined to be the same.

4. Summary of product safety and efficacy

According to the submitted data on quality, [TB361 trade name] is a direct scale-down of Clofazemine 100 mg tablets (Macleods Pharmaceuticals Ltd.). The latter is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Lamprene® (Novartis Pharma S.A.S.) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [TB361 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 [TB361 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB361 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB361 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 [TB361 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 [TB361 trade name], manufactured at Oxalis Labs, G-Block, Village Theda, P.O. Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India, in the list of prequalified medicinal products.