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	[TB388 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited F-4 & F-12, MIDC, Malegaon Sinnar, Nashik-422113 Maharashtra, India
Active Pharmaceutical Ingredient (API)	Delamanid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, antibiotics, ATC code: J04AK06
Therapeutic indication	Treatment of drug-resistant tuberculosis

1. Introduction

[TB388 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

It is recommended that [TB388 trade name] is administered by directly observed therapy (DOT).

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 delamanid, (2R)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo [2,1-b][1,3]oxazole, is available as white to pale yellow crystals or crystalline powder. The chemical structure has been verified using elemental and spectroscopic analysis (MS, UV,1H-NMR and 13C-NMR). Solubility data provided indicate that the API is critically insoluble according to the BCS.

According to the information provided by the applicant, delamanid does not exhibit polymorphism. The API has been confirmed to exist as a crystalline form according to the x-ray powder diffraction (XRPD) data provided.

The API specifications include tests for description, identification (UV and IR), related compounds (HPLC), optical purity (HPLC), residual solvent (GC), loss on drying, residue on ignition and assay (HPLC).

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 hypromellose phthalate, povidone, all-rac- α-tocopherol, microcrystalline cellulose, colloidal hydrated silica, lactose monohydrate, sodium starch glycolate, carmellose calcium and magnesium stearate.

The film-coating mixture contains hypromellose, macrogol /polyethylene glycol, titanium dioxide, iron oxide yellow (E172) and talc. The excipients are all being pharmacopoeial controlled. TSE/BSE free certificates from the suppliers have been provided with regard to the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round, film-coated tablet debossed with "DLM" and "50" on one side and plain on the other side. The tablets are packaged in cold form aluminium (Alu /Alu) blisters.

The application was based on technology transfer involving Otsuka Pharmaceuticals Co Ltd, the innovator, acting as the sending unit and Mylan Laboratories Limited, the applicant acting as the receiving unit.

In order to improve the solubility and thereby enhance the bioavailability, a spray-drying technology has been developed and employed for [TB388 trade name]. The applicant receives the solid-solid dispersion (spray dried dispersion), manufactured at the same site used for the innovator product, for subsequent blending, compression, coating, and packaging.

The transfer was supported based on jointly executed transfer protocol and technical agreement describing the responsibilities of each party. As well, dissolution profile similarity of the receiving batches against a sending unit batch was demonstrated. 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 product specifications include tests for tablet description, identification of API (HPLC with diode array detection), identification of tocopherol (HPLC) and colorant, related substances (HPLC), uniformity of dosage units (by content uniformity), dissolution (by UV detection), assay (HPLC), tocopherol content (HPLC, water content (KF), crystallinity content (by XRPD ≤ 5%) and microbial limits. The analytical procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at these storage conditions and showed only slight increase in degradation products, though within justified limits. Based on the available stability data, the proposed shelf life and storage conditions of the FPP as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

Chemistry, manufacturing and control of [TB388] are based on technology transfer of the innovator product, Deltyba (Otsuka Novel Products GmbH). Therefore, the need for a bioequivalence study has been waived and the similarity of the dissolution profiles is sufficient as proof of bioequivalence.

4. Summary of product safety and efficacy

[TB388 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, [TB388 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Deltyba (Otsuka Novel Products GmbH) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB388 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 [TB388 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB388 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, [TB388 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, safety and efficacy, the team of assessors considered that the benefit–risk profile of [TB388 trade name] was acceptable for the following indication: 'in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis* when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability', and would allow inclusion of [TB388 trade name], manufactured at Mylan Laboratories Limited, Sinnar, Nashik-422113, Maharashtra, India, in the list of prequalified medicinal products.