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:	[TB359 trade name][*]
Manufacturer of Prequalified Product:	Macleods Pharmaceuticals Limited At Oxalis Labs, G Block -Tablet Section Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101, India
Active Pharmaceutical Ingredient (API):	Isoniazid
Pharmaco-therapeutic group (ATC Code):	Drugs for treatment of tuberculosis, Hydrazides, Isoniazid (J04AC01)
Therapeutic indication:	[TB359 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.* It is also indicated either alone or in combination with other anti-tuberculosis agents for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB359 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.*
It is also indicated either alone or in combination with other anti-tuberculosis agents for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*.
[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[TB359 trade name] should be initiated by a health care provider experienced in the management of tuberculosis.

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 Ingredients (APIs)

Isoniazid has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [TB359 trade name] is of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file

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

(APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, colloidal anhydrous silica, povidone, saccharin sodium, crospovidone, magnesium stearate and raspberry flavour. The commercially sourced proprietary raspberry flavour which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, circular, flat faced, beveled edge uncoated tablet with a break line on one side and plain on 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 packaged in Alu/Alu strips.

The objective of the product development was to obtain a stable and robust formulation of isoniazid 100mg dispersible tablets, bioequivalent to the WHO recommended comparator product, isoniazid 100mg tablets (Sandoz U.S.). Based on the properties of the active pharmaceutical ingredient, literature search, excipients that are used in the comparator product, as well as other excipients that are commonly used in dispersible tablets, the composition was finalized. Compatibility studies which were conducted showed that the API was compatible with the selected excipients. Formulation trials were performed to optimise the concentration of excipients and process parameters. Wet granulation process using organic solvent to form light and porous granules, was selected to manufacture the finished pharmaceutical product. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification (HPLC and UV), average weight, friability, hardness, disintegration time (NMT 3minutes), loss on drying, fineness of dispersion, uniformity of dosage units (by weight variation), dissolution (UV detection), related substances (HPLC), residual solvent (GC), assay (HPLC) and microbial limits.

Stability testing

Stability studies have been performed at 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 product proved to be quite stable, with no significant change or negative trend observed. 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 Bio-Equivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

Single dose fasting in-vivo bioequivalence study of Isoniazid dispersible tablets 100 mg (Macleods Pharmaceuticals Ltd., India) to Isoniazid® 100 mg tablets (Barr Laboratories Inc, USA) in healthy, adult, human subjects (study no. BEQ-2597-ISON-2019).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg dispersible tablet manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Isoniazid® 100 mg tablets (Barr Laboratories Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects

under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T:	Test – 1 dispersible tablet Isoniazid 100 mg (isoniazid 100 mg) Batch no. NID801A.
Treatment R:	Reference – 1 tablet Isoniazid® 100 mg (isoniazid 100 mg) Batch no. 34033104A

An 8 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 24h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for isoniazid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 49 ng/ml for isoniazid.

The study was performed with 24 participants; data generated from a total of 23 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.62 ± 0.51	0.66 ± 0.45	-	-
C_{max} (ng/ml)	2650 ± 1037 (2436)	2680 ± 999 (2478)	98.3	85.0 – 113.7
AUC_{0-t} (ng.h/ml)	8466 ± 4302 (6987)	8122 ± 4090 (6772)	103.2	99.1 – 107.4
AUC_{0-inf} (ng.h/ml)	8775 ± 4395 --	8384 ± 4174 --	-	-

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid. Accordingly, the test Isoniazid 100 mg dispersible tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid® 100 mg tablet (Barr Laboratories Inc.).

4. Summary of Product Safety and Efficacy

[TB359 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, [TB359 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Isoniazid 100 mg tablets (Barr Laboratories Inc, USA) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB359 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 [TB359 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB359 trade name] has been shown to be bioequivalent with Isoniazid® 100 mg tablets (Barr Laboratories Inc, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB359 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 [TB359 trade name] was acceptable for the following indication: "for the treatment and prevention of tuberculosis", and has advised that the quality, efficacy and safety of [TB359 trade name] allow inclusion of [TB359 trade name], manufactured at Macleods Pharmaceuticals Limited, At Oxalis Labs, G Block -Tablet Section, Village Theda, P.O. Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India in the list of prequalified medicinal products.