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	[TB285 trade name][1]
Manufacturer of Prequalified Product	Mylan Laboratories Limited Plot No. H-12 & H-13 MIDC, Waluj Industrial Area Aurangabad 431 136 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (isoniazid, J04AC01)
Therapeutic indication	[TB285 trade name] is indicated for the treatment and prophylaxis of tuberculosis

1. Introduction

[TB285 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis*.

[TB285 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 Ingredient (API)

Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified isoniazid (up to 300 mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble.

Isoniazid has 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 isoniazid, used in the manufacture of Isoniazid Tablets BP 300 mg, is 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.

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

Other ingredients

Other ingredients used in the tablet formulation include mannitol, microcrystalline cellulose, croscarmellose sodium, povidone, pregelatinized starch, colloidal anhydrous silica and stearic acid, all being pharmacopoeial controlled. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, biconvex, beveled edge tablet debossed with M on one side and IS1 on the other side. The tablets are presented in HDPE bottles, with or without a silica gel desiccant contained in a plastic canister or sachet.

Two tablet strengths, proportionally similar in composition, were developed: 100 mg and 300 mg. The development, described below, focused on the higher strength.

The multisource product was developed as an immediate release, solid oral tablet dosage form that would be bioequivalent to the WHO PQTm recommended comparator product, Isoniazid 300 mg tablets of Sandoz marketed in the USA. The excipients selected are conventional for immediate release tablets and are included in the formulation at suitable levels for recognised purposes. The compatibility of the excipients with the API was demonstrated by API-excipient studies performed on binary mixtures.

Due to poor flow properties of isoniazid, an aqueous wet granulation process was selected for the manufacture of the tablets. The formulation and process parameters were optimised, targeting the profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

The two strengths showed similar – very rapidly – dissolution profiles in the main BCS media, forming the basis of a biowaiver for the lower strength.

Specifications

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API (IR, UV), uniformity of dosage units (by mass variation), dissolution (UV detection), assay (UV at release, HPLC during stability), related substances (HPLC), loss on drying 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 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 stable at both long term and accelerated storage conditions in all packaging configurations with a slight increase in 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 2016 according to internationally accepted guidelines.

Study title: A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of isoniazid tablets BP 300 mg of Mylan Laboratories Limited, India with Isoniazid Tablets USP 300 mg of Sandoz Inc. Princeton, NJ 08540, in normal healthy adult human subjects under fasting conditions (study no. C16262).

The objective of the study was to compare the bioavailability of the stated isoniazid 300 mg tablet manufactured for/by Mylan Laboratories Limited, India (test drug) with the reference formulation Isoniazid USP 300 mg Tablet (Sandoz Inc.) and to assess bioequivalence. The comparison was performed as a single-centre, open -label, randomised, 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 Isoniazid 300 mg
(isoniazid 300 mg)
Batch no. 3046450

Treatment R: Reference – 1 tablet Isoniazid USP 300 mg
(isoniazid 300 mg)
Batch no. ME150324

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 36 hours 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for isoniazid.

The study was performed with 28 participants; data generated from a total of 26 subjects were used 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} (hours)	0.92 ± 0.76	0.72 ± 0.63	-	-
C_{max} (ng/ml)	8323 ± 3637 (7754)	8647 ± 2418 (8358)	92.8	82.9–103.8
AUC_{0-t} (ng·hours/mL)	37158 ± 10194 (36439)	37958 ± 11017 (35186)	101.2	98.5–103.9
AUC_{0-inf} (ng·hours/mL)	38063 ± 10516 (35593)	37009 ± 10678 (36077)	101.0	98.4–103.7

*geometric mean

Conclusion
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 300 mg tablet (Mylan Laboratories Ltd) meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid USP 300 mg (Sandoz Inc.).

4. Summary of product safety and efficacy

[TB285 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, [TB285 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Isoniazid tablets USP 300 mg (Sandoz Inc) for which

benefits have been proven in terms of clinical efficacy.
The clinical safety of [TB285 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 [TB285 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB285 trade name] has been shown to be bioequivalent with Isoniazid tablets USP 300 mg (Sandoz Inc. Princeton, NJ, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB285 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 [TB285 trade name] was acceptable for the following indication:in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis*, including in regimens for drug-resistant tuberculosis.

It is also indicated as monotherapy or with other medicines for the prevention of tuberculosis in persons at risk and would allow inclusion of [TB285 trade name], manufactured at Mylan Laboratories Limited, Plot No. H-12 & H-13, MIDC, Waluj Industrial Area, Aurangandad – 431 136, Maharashtra, India in the list of prequalified medicinal products.