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** | [TB276 trade name]* |
| **Manufacturer of Prequalified Product** | Cadila Pharmaceuticals Limited<br>Main Pharma Block<br>1389, Trasad Road<br>Dholka – 382225, Ahmedabad<br>Gujarat State, INDIA |
| **Active Pharmaceutical Ingredient(s) (API)** | Isoniazid |
| **Pharmaco-therapeutic group (ATC Code)** | Antimycobacterials, hydrazides (isoniazid, J04AC01) |
| **Therapeutic indication** | [TB276 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.* |

## 1. Introduction

[TB276 trade name] is indicated for the treatment of tuberculosis, caused by *Mycobacterium tuberculosis.* [TB276 trade name] tablets 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)*

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 is described in the Ph.Int., Ph.Eur. and USP and is considered well-established in the Prequalification Programme. The APIMF of isoniazid has been accepted through WHO's APIMF procedure. Isoniazid is manufactured from 4-cyanopyridine.

The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification (m.p. and IR), appearance of solution, pH, hydrazine and related substances (TLC), heavy metals, loss on drying, sulfated ash, assay, related substances (HPLC), residual solvents, bulk density and particle size (by sieve analysis).

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 tablet formulation include microcrystalline cellulose, maize starch, crospovidone, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. TSE/BSE free certifications were provided for all excipients

**Finished pharmaceutical product (FPP*)***

*Pharmaceutical development and manufacture*
The multisource product is a white to off-white, circular, biconvex, uncoated tablet, plain on both sides. The tablets are presented in PVC/PVDC-Alu blister packs and in a triple laminated pouch packed in an HDPE bottle.

The development of the final composition of multisource product has been described. The objective of the development activities was to formulate a stable, robust formulation of Isoniazid 300 mg Tablets which would be bioequivalent to the WHO PQTm recommended comparator product, Isoniazid 300 mg tablets of Sandoz marketed in the USA. The excipients selected are well established and commonly used in the manufacture of isoniazid tablets. Considering the physicochemical properties of isoniazid, it was decided to employ the wet granulation process for the manufacture of the tablets. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product in the BCS media. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

*Specifications*
The finished product specifications are pharmacopoeial based and include tests for tablet description, identification (IR), average weight, uniformity of weight, hardness, friability, disintegration time, dissolution, assay (HPLC), loss on drying, related substances (TLC and HPLC) and microbial limits.

*Stability testing*
Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions with no apparent negative trend in the proposed packaging configurations. The product should be protected from light. 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 2013 according to internationally accepted guidelines.

A randomized, open-label, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study of Isoniazid tablets BP 300 mg of Cadila Pharmaceuticals Ltd., India with Isoniazid tablets USP 300 mg manufactured by Epic Pharma, LLC Laurelton, NY 11413 and distributed by Sandoz Inc., Princeton, NJ 08540 in healthy, adult, human subjects under fasting condition (study no. 13-002).

The objective of the study was to compare the bioavailability of the stated Isoniazid BP 300 mg tablet manufactured by/for Cadila Pharmaceuticals Ltd., India (test drug) with the reference formulation Isoniazid tablet USP 300 mg (Sandoz 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 tablet Isoniazid BP 300 mg (isoniazid 300 mg) Batch no. ET089E2002.

Treatment R: Reference – 1 tablet Isoniazid USP 300 mg (isoniazid 300 mg) Batch no. ME120933.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 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 50 ng/ml for isoniazid.

The study was performed with 36 participants; data generated from a total of 35 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:

| 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) | 0.68 ± 0.39 | 0.79 ± 0.46 | - | - |
| $C_{max}$ (µg/ml) | 7.46 ± 2.38 (6.24) | 6.88 ± 2.86 (7.12) | 114.1 | 106.7 – 122.1 |
| $AUC_{0-t}$ (µg.h/ml) | 30.9 ± 13.5 (26.8) | 31.8 ± 16.6 (28.2) | 105.1 | 101.1 – 109.3 |
| $AUC_{0-inf}$ (µg.h/ml) | 31.6 ± 13.7 (27.4) | 32.5 ± 16.9 (28.8) | 105.0 | 100.9 – 109.2 |

* 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 tablet Isoniazid BP 300 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Isoniazid tablets USP 300 mg (Sandoz Inc.).

## 4. Summary of product safety and efficacy

[TB267 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability, [TB267 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the reference product Isoniazid tablets USP 300 mg (Sandoz Inc) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made 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 [TB267 trade name] is used in accordance with the SmPC.

### *Bioequivalence*

[TB267 trade name] has been shown to be bioequivalent with Isoniazid tablets USP 300 mg (Sandoz Inc. Princeton, USA).

### *Efficacy and Safety*

Regarding clinical efficacy and safety, [TB267 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 [TB267 trade name] was acceptable for the following indication: **"treatment of tuberculosis caused by *Mycobacterium tuberculosis*"**, and would allow inclusion of [TB267 trade name], manufactured at Cadila Pharmaceuticals Limited, Main Pharma Block, 1389, Trasad Road, Dholka – 382225, Ahmedabad, Gujarat State, India, in the list of prequalified medicinal products.