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	[TB407 trade name][*]
Manufacturer of Prequalified Product	Cadila Pharmaceuticals Limited 1389, Trasad Road, Dholka- 382 225, District: Ahmedabad, Gujarat, India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Drugs for treatment of tuberculosis, Hydrazides, Isoniazid (J04AC01)
Therapeutic indication	[TB407 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis*, including in regimens for drug-resistant tuberculosis.

1. Introduction

[TB407 trade name] is indicated 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. Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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)

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 the API, used in the manufacture of [TB407 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 (APIMF) to verify compliance with WHO norms and standards, and inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

[*] 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, aspartame, colloidal silicon dioxide, banana flavour and magnesium stearate, all of which are 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 light yellow, round, uncoated tablet. It is flat on the top and bottom with a bevelled edge. The tablet has a break line on one side and a score line on the 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 either aluminium blisters or strips.

The objective of the product development was to obtain a stable and robust, immediate-release dispersible tablet that is bioequivalent to the WHO recommended comparator product isoniazid 100 mg tablets of Teva Pharmaceuticals, USA Inc. The quality target product profile was defined based on the physicochemical properties of the API and characteristics of the comparator product. The selection of excipients was based on their wide use in the manufacture of this type of solid oral dosage form, composition of the comparator product and API-excipient compatibility data. A sweetener and flavouring agent were used to improve the taste of the dispersible tablets. Due to the poor flow properties of the isoniazid API, and the manufacturer's experience with isoniazid 300 mg tablets, a wet granulation manufacturing process was selected to obtain readily compressible granules. Formulation trials were performed to optimise the concentration of excipients and process parameters. Appropriate in-process controls have been established to ensure batch-to-batch reproducibility.

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 finished product specifications include tests for description, identification of API (chemical reactions), average weight, uniformity of weight, hardness, disintegration time, water content (KF), fineness of dispersion, dissolution (UV detection), uniformity of dosage units (by mass variation), related substances (HPLC), 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 at these storage conditions with no apparent negative trend in the proposed packaging configurations. 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 2023 according to internationally accepted guidelines.

A randomized, open-label, two-treatment, two-period, two-sequence, single-dose, two-way crossover bioequivalence study of isoniazid dispersible tablet 100 mg of Cadila Pharmaceuticals Ltd., India with isoniazid tablet USP 100 mg of Teva Pharmaceuticals, USA Inc, North Wales PA 19454, in healthy, adult, human subjects under fasting condition (study no. 22-014).

The objective of the study was to compare the bioavailability of the stated isoniazid 100 mg dispersible tablet manufactured by/for Cadila Pharmaceuticals Ltd., India (test drug) with the reference formulation isoniazid tablet USP 100 mg (Teva Pharmaceuticals USA, 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 tablet 100 mg (isoniazid 100 mg) Batch no. ET9343002A.

Treatment R: Reference – 1 tablet isoniazid USP 100 mg (isoniazid 100 mg) Batch no. CKMSW.

The test dispersible tablet was dispersed in 50 mL water (+ 190 mL of rinsing water) and administered. The reference was administered with 240 mL water. An 8-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 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 40 participants; data generated from a total of 40 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.50 (0.17 – 2.50)	0.67 (0.33 – 3.50)	–	–
C_{max} (µg /mL)	1.90 ± 0.55 (1.82)	1.81 ± 0.69 (1.68)	108.3	98.3 – 119.4
AUC_{0-t} (µg h/mL)	6.18 ± 3.44 (5.18)	5.95 ± 3.44 (4.92)	105.3	101.7 – 109.0
AUC_{0-inf} (µg h/mL)	6.44 ± 3.57 (5.41)	6.25 ± 3.58 (5.19)	104.2	100.9 – 107.7

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 tablet USP 100 mg (Teva Pharmaceuticals USA, Inc).

4. Summary of product safety and efficacy

[TB407 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, [TB407 trade name] is pharmaceutically and therapeutically equivalent and thus

interchangeable with the comparator product isoniazid USP 100 mg (Teva Pharmaceuticals USA, Inc) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB407 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 [TB407 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB407 trade name] has been shown to be bioequivalent with isoniazid USP 100 mg (Teva Pharmaceuticals USA, Inc)

Efficacy and Safety

Regarding clinical efficacy and safety, [TB407 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 [TB407 trade name] was acceptable for the following indication: '[TB407 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis*, including in regimens for drug-resistant tuberculosis.', and would allow inclusion of [TB407 trade name], manufactured at Cadila Pharmaceuticals Limited, 1389 Trasad Road, Dholka – 382 225, District: Ahmedabad, Gujarat, India in the list of prequalified medicinal products.