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	[TB405 trade name][*]
Manufacturer of Prequalified Product	S Kant Healthcare Plot No. 1802-1805 G.I.D.C. Phase III, Vapi 396 195 Gujarat, India Tel.: 91 260 6539518 Fax: 91 260 2430527 Email: regulatory@skant.com
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Drugs for treatment of tuberculosis, Hydrazides, Isoniazid (J04AC01)
Therapeutic indication	[TB405 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

[TB405 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 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 [TB405 trade name] is of good quality and manufactured in

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

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.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, crospovidone, colloidal anhydrous silica, aspartame, orange flavour and magnesium stearate. The excipients are supported by appropriate declarations and controlled by acceptable specifications. None of the excipients are of human or animal origin. TSE/BSE free certificates from the suppliers have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off white, round, uncoated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has a break-line on one side and is plain on the other side. The break line is intended for subdivision of tablet when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are packaged in aluminium strip packs.

The objective of the product development was to obtain a stable and robust dispersible tablet formulation, bioequivalent to the WHO recommended comparator product; Isoniazid USP 100 mg tablets (Teva Pharmaceuticals USA Inc.). The quality target product profile was defined based on the literature review and characterization of the comparator product. The critical quality attributes were satisfactorily identified. The excipients used were based on available literature, composition of the comparator product, manufacturer's previous knowledge of development of dispersible tablets and API-excipient compatibility studies. A sweetener and a flavouring agent were included to achieve palatability of the dispersible tablets. To achieve the target tablet characteristics a direct compression process was selected to manufacture the finished pharmaceutical product. Formulation trials were performed to optimize the concentration of excipients and process parameters, resulting in a product with the desired physicochemical characteristics including dissolution profile similarity with the comparator product. Appropriate in-process controls were set 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 are pharmacopoeial based and include tests for appearance, identification (IR or colour development tests), uniformity of mass, tablet dimensions (diameter and thickness), hardness, disintegration time, dispersion time, fineness of dispersion, water content, dissolution (UV detection), related substances (HPLC), assay (HPLC), uniformity of content (by weight variation) 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 data provided indicate that the product is stable at both storage conditions. 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.

An open label, balanced, randomized, two treatment, two sequence, two period, single oral dose, crossover, bioequivalence study of Isoniazid dispersible tablet 100 mg of S Kant Healthcare Limited, India with Isoniazid tablets USP 100 mg of Teva Pharmaceuticals USA, Inc, North Wales, PA 19454 in normal, healthy, adult, human subjects under fasting condition (study no. 0334-22).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg dispersible tablet manufactured by/for S Kant Healthcare Limited, India (test drug) with the reference formulation Isoniazid USP 100 mg tablets (Teva Pharmaceuticals USA, Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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. WIA22004.

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

The test dispersible tablet was dispersed in 30 mL water (+ 10 mL of rinsing water) and administered. The reference was administered with 240 mL water. A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 16h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 25 ng/mL for isoniazid.

The study was performed with 36 participants; data generated from a total of 34 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 (0.083 – 2.00)	0.63 (0.33 -1.75)	–	–
C_{max} (ng/mL)	1946 ± 576 (1860)	1880 ± 623 (1787)	104.1	95.3 – 113.6
AUC_{0-t} (ng·h/mL)	6845 ± 3314 (5825)	6571 ± 3349 (5540)	105.2	101.5 – 108.9
AUC_{0-inf} (ng·h/mL)	7072 ± 3463 --	6800 ± 3506 --	–	–

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

4. Summary of product safety and efficacy

[TB405 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, [TB405 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Isoniazid USP 100 mg tablet (Teva Pharmaceuticals USA, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB405 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 [TB405 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB405 trade name] has been shown to be bioequivalent with Isoniazid USP 100 mg tablet (Teva Pharmaceuticals USA, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB405 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 [TB405 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', and would allow inclusion of [TB405 trade name], manufactured at S Kant Healthcare plot No. 1802-1805, G.I.D.C. Phase III, Vapi 396 195, Gujarat, India in the list of prequalified medicinal products.