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	[TB196 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited A-28/1, MIDC Industrial area Chikalthana Aurangabad 431210 India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AC01)
Therapeutic indication	[TB196 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB196 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. [TB196 trade name] is not indicated for use in patients with clinically significant hypersensitivity to isoniazid or to any of the components in the formulation and in patients with acute liver disease, drug induced hepatic disease and previous isoniazid-associated hepatic injury.

Therapy is recommended only on the advice of a physician experienced in the treatment of tuberculosis.

2. Assessment of quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

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

Isoniazid (reference number WHOAPI-086) 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 [TB196 trade name], 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.

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

Other ingredients

Other ingredients include colloidal anhydrous silica, maize starch, microcrystalline cellulose, sodium edetate and stearic acid. Stearic acid is of vegetable origin.

Finished pharmaceutical product (FPP)

Isoniazid tablets are described in the Ph.Int.and USP.

Pharmaceutical development and manufacture

The pharmaceutical product is a white to off-white circular, flat-faced, bevelled-edge, uncoated tablet, with 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. The tablets are packed in PVC/PVDC-aluminium blister packs and in an aluminium/VMCH laminated pouch which is further packed, together with a silica gel bag and cotton filler, in an HDPE container sealed with aluminium tagger.

The development of the final composition of the tablets has been described. The predevelopment studies indicated that isoniazid can form complexes with metals, hence it was decided to include a small amount of sodium edetate in the composition to act as chelating agent. It was also concluded from the predevelopment studies that excipients containing aldehyde and ketone groups should be avoided due to their tendency to react with the hydrazine group of the API. API-excipient studies indicated that magnesium stearate may not be compatible with isoniazid; hence stearic acid was selected as lubricant. Based on the flow properties and compressibility of the API, the wet granulation process was selected for manufacture of the tablets.

The process was optimized to obtain tablets that showed dissolution characteristics similar to the comparator product, Isozid® 100 mg. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three production scale batches demonstrated the consistency of the process and the quality of the product.

Specifications

The product specifications include tests for description, identification of the API, average weight, uniformity of weight, tablet thickness and hardness, friability, disintegration time, dissolution, related substances (HPLC), assay (HPLC), microbial limits and subdivision of tablets. The latter test may be removed from specifications once the divisibility has been established, using the variation procedure.

Stability testing

Stability studies have been performed at 30°C/65%RH as long-term conditions and for six months at accelerated conditions. The product proved to be quite stable at both storage conditions. Based on the available stability data, the proposed shelf life (60 months for both containers) and storage (below 30ºC) 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 was performed in 2011 according to internationally accepted guidelines.

An open-label, balanced, randomised, single-centre, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Isoniazid 100 mg tablets, manufactured by Lupin Limited, India and Isozid® 100 mg (isoniazid) tablets of Fatol Arzneimittel GmbH, Germany in healthy human adult male subjects, under fasting conditions (study no. S-11-237).

The objective of the study was to compare the bioavailability of the stated Isoniazid 100 mg tablet manufactured by Lupin Limited, India (test drug) with the same dose of the reference formulation (Isozid®, Fatol Arzneimittel GmbH) and to assess bioequivalence. The comparison was performed as a single-centre, open-label, randomised, crossover study in healthy male subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T: Test – 1 tablet Isoniazid 100 mg
(isoniazid 100 mg)
Batch no. CUI18003.

Treatment R: Reference – 1 tablet Isozid®
(isoniazid 100 mg)
Batch no. 001031.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 15 samples within 24 hours after the 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 152 ng/ml for isoniazid.

The study was performed with 32 participants; data generated from a total of 31 subjects were utilised 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)	0.83 ± 0.48	0.88 ± 0.38	–	–
C_{max} (µg/mL)	2.50 ± 0.65 (2.43)	2.57 ± 0.78 (2.47)	98.5	92.2 – 105.1
AUC_{0-t} (µg·h/mL)	10.01 ± 4.13 (8.97)	9.91 ± 4.36 (8.69)	103.2	98.9 – 107.8
AUC_{0-inf} (µg·h/mL)	11.17 ± 4.73 (10.02)	11.01 ± 4.66 (9.75)	102.7	98.4 – 107.3

4. Summary of product safety and efficacy

[TB196 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Isozid® 100 mg (Fatol Arzneimittel GmbH) 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 presented in the Summary of Product Characteristics are taken into consideration. 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 [TB196 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB196 trade name] has shown to be bioequivalent with Isozid® 100 mg (Fatol Arzneimittel GmbH).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB196 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB196 trade name] was acceptable for the following indication: "treatment of tuberculosis caused by *Mycobacterium tuberculosis*" and has advised that the quality, efficacy and safety of [TB196 trade name] allow inclusion of [TB196 trade name], manufactured at Lupin Limited, A-28/1, MIDC Industrial area, Chikalthana, 431 210 Aurangabad, India, in the list of prequalified medicinal products.