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	[TB189 trade name]*
Manufacturer of Prequalified Product	Svizera Labs Private Limited Plot D-16/6, TTC, Industrial Area Turbhe, Navi Mumbai – 400703 India
Active Pharmaceutical Ingredient(s) (API)	isoniazid and rifampicin
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02).
Therapeutic indication	[TB189 trade name] is indicated for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB189 trade name] is indicated for the treatment of tuberculosis, caused by Mycobacterium tuberculosis. [See Part 4 Summary of Product Characteristics (SmPC), for full indications].

[TB189 trade name] should be initiated by a health care provider experienced in the management oftuberculosis.

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)

Isoniazid

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. Isoniazid is thus BCS highly soluble A CEP (Certificate of Suitability) issued by the EDQM has been submitted for isoniazid, ensuring good manufacturing control and applicability of the Ph.Eur. monograph to control the quality of the API.

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

Rifampicin

Rifampicin API is described in the Ph.Int., Ph.Eur. and the USP, and considered well-established in the WHO PQP.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification, crystallinity, pH, loss on drying, heavy metals, sulphated ash, related substances (HPLC), assay, residual solvents, particle size distribution and tapped density.

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.

Other ingredients

Other ingredients used in the core tablet formulation include colloidal silicon dioxide, magnesium stearate, maize starch, microcrystalline cellulose, povidone, purified talc and sodium starch glycolate. Magnesium stearate is of vegetable origin. The film coating contains colour lake Ponceau 4R (Cochineal Red A), hydroxypropyl methylcellulose, purified talc and titanium dioxide.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Rifampicin and isoniazid tablets are described in the Ph.Int. The Ph.Int. monograph includes a test for rifampicin related substances.

[TB189 trade name] are brownish red coloured, circular, biconvex, film-coated tablets having a break-line on one side. The break-line is non-functional. The tablets are packed in a polypropylene bag, packed together with a silica gel sachet in a white HDPE jar with white polypropylene cap (1000's) and in green PVDC/aluminium blisters cards.

The product was already well established for the manufacturer by the time of submission. All excipients are conventional excipients commonly used in solid oral dosage forms. Dichloromethane and isopropyl alcohol are used as solvents in the preparation of the film coating. A particular concern is the known interaction between isoniazid and rifampicin to form the hydrazone. In the tablet formulation, separation of the two APIs is partially achieved by the separate processing of rifampicin granules and isoniazid granules. Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data on three consecutive production batches demonstrated the consistency of the process and the quality of the product.

Specifications

The product specifications include tests for description, intactness of coating, identification of the APIs and colorants, average and uniformity of weight, loss on drying, disintegration time, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), rifampicin and isoniazid related substances (HPLC), assay (HPLC), organic volatile impurities and microbial limits.

Stabilitytesting

Stability studies have been performed at 25°C/60%RH as long-term conditions and for six months at accelerated conditions. The data showed a notable decrease in the assay value of rifampicin, with a concomitant increase in rifampicin related degradation products, though remaining within agreed limits, at all storage conditions in both pack types. An in-use period of 30 days has been demonstrated for the bulk bottle pack. 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 2010 according to internationally accepted guidelines.

A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampicin and Isoniazid Tablets (containing rifampicin 150 mg and isoniazid 75 mg) of Svizera Labs Mumbai, India with Rifinah® 150/300 mg (isoniazid and rifampicin) tablets (containing isoniazid 150 mg and rifampicin 300 mg) manufactured by Gruppo LepetitSpA, Italy; marketed by Sanofi-Aventis, UK, in 28 healthy adult human male subjects (study no. BBRC/EX/10/001).

The objective of the study was to compare the rate and extent of absorption of the stated fixed dose combination Rifampicin/Isoniazid 150/75 mg tablets with the same dose of the reference formulation (Rifinah®, Sanofi-Aventis). The comparison was performed as a randomized, two-treatment, two-period, single-dose, crossover study in healthy male subjects under fasting conditions. Subjects were assigned to receive the following two treatments:

Treatment T: Test – 2 tablets Rifampicin/Isoniazid 150/75 mg

(rifampicin 300 mg + isoniazid 150 mg)

Batch no. SL434

Treatment R: Reference – 1 tablet Rifinah®

(rifampicin 300 mg + isoniazid 150 mg)

Batch no. A9362

A 3 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 24 h post dose) were taken during each study period to obtain bioavailability characteristics AUC_{inf}, AUC_{0-t}, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for rifampicin and isoniazid in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 200 ng/ml for rifampicin as well as isoniazid.

The study was performed with 28 participants, data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Geometric means (AUC, C_{max}) and arithmetic means (± sd), for rifampicin and isoniazid as well as statistical results are summarised in the following table:

Rifampicin

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)	1.85 ± 0.92	2.25 ± 0.88	–	–
C_{max} (µg/mL)	6.67 ± 1.80 (6.22)*	6.09 ± 1.48 (5.71)*	108.9	100.1 – 118.4
AUC_{0-t} (µg·h/mL)	32.0 ± 13.0 (29.6)*	30.6 ± 10.0 (28.9) *	102.4	94.0 – 111.4
AUC_{0-inf} (µg·h/mL)	34.9 ± 13.9 (32.4)*	33.1 ± 10.7 (31.3) *	103.5	95.8 – 111.8

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)	1.13 ± 0.70	1.24 ± 0.70	–	–
C_{max} (µg/mL)	2.83 ± 1.26 (2.52)*	2.82 ± 1.35 (2.50)*	101.0	89.5 – 114.1
AUC_{0-t} (µg·h/mL)	9.61 ± 5.77 (8.13)*	10.1 ± 6.9 (8.25) *	98.5	88.2 – 110.0
AUC_{0-inf} (µg·h/mL)	10.6 ± 6.1 (9.13)*	11.3 ± 7.9 (9.20)*	99.3	88.9 – 110.8

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding rifampicin and isoniazid. Accordingly, the test fixed dose combination tablet Rifampicin/Isoniazid 150/75 mg tablets (Svizera Labs Mumbai, India), meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference Rifinah®150/300 mg tablets (Sanofi-Aventis).

4. Summary of product safety and efficacy

[TB189 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, [TB189 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Rifinah® 150/300 mg tablets (Sanofi-Aventis) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB189 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 [TB189 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB189 trade name] has been shown to be bioequivalent with Rifinah® 150/300 mg tablets (Sanofi-Aventis).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB189 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 [TB189 trade name] was acceptable for the following indication: ' treatment of tuberculosis caused by *Mycobacterium tuberculosis*{indication}', and would allow inclusion of [TB189 trade name], manufactured at Svizera Labs Private Limited, Plot D-16/6, TTC, Industrial Area, Turbhe, Navi Mumbai – 400703, India in the list of prequalified medicinal products.