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	[TB192 trade name][*]
Manufacturer of Prequalified Product	Svizera Labs Pvt. Ltd Plot D-16/6, TTC Industrial Area, MIDC, Turbhe, New Mumbai – 400703 India
Active Pharmaceutical Ingredients (APIs)	Ethambutol hydrochloride/ Isoniazid/Rifampicin
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, drugs for treatment of tuberculosis(J04AK02 for ethambutol, J04AC01 for isoniazid, J04AB02 for rifampicin).
Therapeutic indication	[TB192 trade name]is indicated for the initial treatment phase of tuberculosis, caused by Mycobacterium tuberculosis.

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

1. Introduction

[TB192 trade name]is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis.*

[TB192 trade name] should be prescribed 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 of Medicines Programme (PQP) has identified ethambutol hydrochloride (up to 400 mg oral dose) and isoniazid (up to 300 mg oral dose) as BCS class 3 APIs. These APIs are thus BCS highly soluble.

Ethambutol hydrochloride
Ethambutol hydrochloride 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, specific optical rotation, pH, loss on drying, heavy metals, sulphated ash, assay, related substances (HPLC and TLC) and organic volatile impurities. Meso-ethambutol is controlled at a limit of 1.0% and 1,2-dichloroethane at a limit of 5 ppm.

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.

Isoniazid (CEP)
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.

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 collidal silicon dioxide, croscarmellose sodium, magnesium stearate, maize starch, microcrystalline cellulose, polyvinylpyrrolidone and purified talc. Magnesium stearate is of vegetable origin. The film coating contains hydroxypropyl methylcellulose, iron oxide red, purified talc and titanium dioxide.

Finished Pharmaceutical Product (FPP)

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

Pharmaceutical development and manufacture

The product is a brown coloured, circular, biconvex, film-coated tablet. The tablets are packed in a polypropylene bag, packed together with a silica gel desiccant in a white square HDPE bottle with aluminium induction seal and in white polypropylene cap (1000's) and in peach coloured 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, which is enhanced by the presence of ethambutol hydrochloride. In the tablet formulation, separation of rifampicin and isoniazid is partially achieved by the separate processing of rifampicin granules and isoniazid/ethambutol hydrochloride 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.

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 related substances (HPLC), assay (HPLC), organic volatile impurities and microbial limits.

Stability testing

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 SPmC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2011 according to internationally accepted guidelines.

A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampicin, Isoniazid and Ethambutol Hydrochloride tablet (containing rifampicin 150 mg, isoniazid 75 mg and ethambutol hydrochloride 275 mg) of Svizera Labs Pvt. Ltd., Mumbai, India with Rimactane® 150 capsules (containing rifampicin 150 mg) of Sandoz Pharmaceuticals AG, Steinhausen; Isozid® 100 mg tablet (containing isoniazid 100 mg) FatolRiemserArzneimittel AG and Myambutol® 400 mg tablet (containing ethambutol hydrochloride 400 mg) of RiemserArzneimittel AG, in 28 healthy adult human male subjects under fasting conditions (study no. BBRC/EX/10/010).

The objective of the study was to compare the rate and extent of absorption of the stated fixed dose combination tablet Rifampicin/Isoniazid/Ethambutol Hydrochloride 150/75/275 mg with the individual reference formulations (Rimactane®, Sandoz Pharmaceuticals AG,

Isozid®,FatolRiemserArzneimittel AG and Myambutol® RiemserArzneimittel AG).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 –1 tablet Rifampicin/Isoniazid/Ethambutol Hydrochloride 150/75/275 mg
(rifampicin 150 mg + isoniazid 75 mg + ethambutol 275 mg)
Batch no. SL56

Treatment R: Reference – 1 capsule Rimactane®
(rifampicin 150 mg)
Batch no. 511386
Reference – 1tablet Isozid®
(isoniazid 100 mg)
Batch no. 002079
Reference – 1tablet Myambutol®
(ethambutol400 mg)
Batch no. 808850

A 6 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 48 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, isoniazid andethambutol in plasma were analyzed using a validated LC/MS/MS method. The limit of quantification was stated to be 31 ng/ml for rifampicin, 55 ng/ml for isoniazid and 106 ng/ml for ethambutol.

The study was performed with 28 participants, data generated from a total of 28 subjects were utilized for analysis to establish pharmacokinetic parameters and assessbioequivalence. The difference in the administered dose of isoniazid and ethambutol was taken into account in the analysis.

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

Rifampicin

Pharmacokinetic Parameter	**Test formulation (T)** arithm.mean ± SD (geometric mean)	**Reference (R)** arithm. mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.33 ± 0.90	2.15 ± 1.02	-	-
C_{max} (µg/mL)	1.79 ± 0.55 (1.71)	1.93 ± 0.58 (1.85)	92.8	83.7 – 102.8
AUC_{0-t} (µg.h/mL)	9.10 ± 3.89 (8.44)	9.26 ± 3.87 (8.58)	98.4	86.3 – 112.2
AUC_{0-inf} (µg.h/mL)	9.78 ± 4.06 (9.08)	9.83 ± 3.85 (9.16)	99.1	87.7 – 111.9

Isoniazid

Pharmacokinetic Parameter	**Test formulation (T)** arrithm.mean± SD (geometric mean)	**Reference (R)** arrithm. mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	1.02 ± 0.61	1.36 ± 0.60	-	-
C_{max} (µg/mL)	1.44 ± 0.62 (1.30)	1.40 ± 0.57 (1.27)	102.3	93.6 – 111.8
AUC_{0-t} (µg.h/mL)	6.37 ± 3.42 (5.43)	6.30 ± 3.11 (5.43)	100.1	91.9 – 109.1
AUC_{0-inf} (µg.h/mL)	7.22 ± 3.69 (6.22)	7.20 ± 3.62 (6.07)	102.4	94.8 – 110.7

Ethambutol

Pharmacokinetic Parameter	**Test formulation (T)** arrithm.mean± SD (geometric mean)	**Reference (R)** arrithm. mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.88 ± 0.92	3.70 ± 0.88	-	-
C_{max} (µg/mL)	1.25 ± 0.35 (1.21)	1.15 ± 0.35 (1.11)	109.2	99.1 – 120.4
AUC_{0-t} (µg.h/mL)	5.72 ± 1.34 (5.57)	5.50 ± 1.51 (5.28)	105.5	94.4 – 117.9
AUC_{0-inf} (µg.h/mL)	7.06 ± 1.58 (6.92)	6.57 ± 1.84 (6.52)	106.2	97.1 – 116.3

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max}values regarding rifampicin, isoniazid and ethambutol. Accordingly, the test fixed dose combination Rifampicin/Isoniazid/Ethambutol Hydrochloride 150/75/275 mg tablets meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual reference formulations (Rimactane®, Sandoz Pharmaceuticals AG, Isozid®, FatolRiemserArzneimittel AG and Myambutol®RiemserArzneimittel AG).

4. Summary of product safety and efficacy

[TB192 trade name]has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the comparatorproducts. According to the submitted data on quality and bioavailability [TB192 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator products, administered as individual formulations, Rimactane® (Sandoz Pharmaceuticals AG), Isozid® (FatolRiemserArzneimittel AG), and Myambutol® (RiemserArzneimittel AG) 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 account. Reference is made tothe 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 [TB192 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB192 trade name]has shown to be bioequivalent to, administered as individual formulations, Rimactane® (rifampicin 150 mg capsules, Sandoz Pharmaceuticals AG), Isozid® (isoniazid 100 mg tablets, FatolRiemserArzneimittel AG),and Myambutol®400 mg (ethambutol 400 mg tablets, RiemserArzneimittel AG).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB192 trade name]is considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB192 trade name]was acceptable for the following indication: **"initial treatment phase of tuberculosis caused by *Mycobacterium tuberculosis*"**and has advised that the quality, efficacy and safety of [TB192 trade name] allow inclusion of [TB192 trade name], manufactured atSvizera Labs Pvt. Ltd, Plot D-16/6, TTC, MIDC Industrial Area Turbhe, New Mumbai – 400703, India,in the list of prequalified medicinal products.