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	[TB193 trade name]*
Manufacturer of Prequalified Product	Svizera Labs Private Ltd Plot D-16/6, TTC Industrial Area Turbhe Navi, Mumbai - 400 703, India
Active Pharmaceutical Ingredients (APIs)	Ethambutol hydrochloride, Isoniazid, Pyrazinamide, Rifampicin
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02)
Therapeutic indication	[TB193 trade name] is indicated for the initial treatment of tuberculosis, caused by *Mycobacterium tuberculosis*.

1. Introduction

[TB193 trade name] is indicated for the initial treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis*.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

[TB193 trade name] should be initiated by a health care provider experienced in the management 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 ethambutol hydrochloride (up to 400 mg oral dose), isoniazid (up to 300 mg oral dose) and pyrazinamide (up to 500 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 is 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.

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

Isoniazid and Pyrazinamide (CEPs)

CEPs (Certificates of Suitability) issued by the EDQM have been submitted for isoniazid and pyrazinamide, ensuring good manufacturing control and applicability of the respective Ph.Eur. monographs to control the quality of the APIs.

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

Finished pharmaceutical product (FPP)

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

Pharmaceutical development and manufacture

The product is a pinkish brown, oblong, biconvex, film-coated tablet with 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 desiccant in a white square HDPE bottle with aluminium induction seal and in white polypropylene cap (1000's) and in red 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 the APIs is partially achieved by the separate processing of rifampicin granules, isoniazid granules and pyrazinamide/ethambutol granules. Amounts of diluents and binders were varied and the effect on parameters such as bulk density and particle size were studied with respect to compressibility and dissolution. Granules were mixed with different concentrations of lubricants and compressed, and robustness of process, tablet quality, physical parameters and dissolution (all APIs) were studied. This was followed by process validation of three consecutive batches manufactured according to the chosen process. Appropriate in-process controls were set.

Specifications

The product specifications are pharmacopoeial based and 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), related substances (HPLC and TLC), assay (HPLC), organic volatile impurities and microbial limits.

Stability testing

Stability studies have been performed at 25°C/60%RH and 30°C/75%RH as long-term conditions and for six months at accelerated conditions. The data showed a notable decrease in the assay value of

rifampicin, and to lesser extent of the other APIs, 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 2010 according to internationally accepted guidelines.

A bioequivalence study comparing fixed-dose combination of Ethambutol Hydrochloride, Isoniazid, Pyrazinamide, Rifampicin tablet (containing ethambutol hydrochloride 275 mg, isoniazid 75 mg, pyrazinamide 400 mg and rifampicin 150 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) Fatol; Pyrazinamide (Lederle) tablet (containing pyrazinamide 500 mg) of RIEMSER Arzneimittel AG and Myambutol® 400 mg tablet (containing ethambutol hydrochloride 400 mg) of RIEMSER Arzneimittel AG, in 32 healthy adult human male subjects under fasting condition (study no. BBRC/EX/10/005).

The objective of the study was to compare the rate and extent of absorption of the stated fixed-dose combination tablet Ethambutol Hydrochloride/Isoniazid/Pyrazinamide/Rifampicin 275 mg/75 mg/400 mg/150 mg with the individual reference formulations— Myambutol® (Riemser Arzneimittel AG), Isozid® (Fatol Riemser Arzneimittel AG), Pyrazinamide (Lederle), and Rimactane® (Sandoz Pharmaceuticals 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 Ethambutol Hydrochloride/Isoniazid/ Pyrazinamide/Rifampicin 275 mg/75 mg/400 mg/150 mg (ethambutol hydrochloride 275 mg + isoniazid 75 mg + pyrazinamide 400 mg + rifampicin 150 mg) Batch No. SL1980
Treatment R:	Reference – 1 tablet Myambutol® (ethambutol 400 mg) Batch No. 808850
	Reference – 1 tablet Isozid® (isoniazid 100 mg) Batch No. 002079
	Reference – 1 tablet Pyrazinamide (Lederle) (pyrazinamide 500 mg) Batch no. 803100
	Reference – 1 capsule Rimactane® (rifampicin 150 mg) Batch No. 511386

A 6-day washout period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 samples within 72 hours after dosing) 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 ethambutol, isoniazid, pyrazinamide, and rifampicin in plasma

were analysed using a validated LC/MS/MS method. The limit of quantification was stated to be 100 ng/ml for ethambutol, 200 ng/ml for isoniazid, 1.0 µg/ml for pyrazinamide and 200 ng/ml for rifampicin. The differences in the ethambutol, isoniazid and pyrazinamide doses between the Reference and Test were taken into account in the analysis.

Arithmetic mean values (with standard deviation) and geometric mean values (AUC and C_{max}) of the pharmacokinetic variables for ethambutol, isoniazid, pyrazinamide, and rifampicin as well as statistical results are summarised in the following tables:

Ethambutol

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	2.45 ± 0.50	2.17 ± 0.25	–	–
C_{max} (µg/ml)	1.87 ± 0.35 (1.84)*	1.58 ± 0.22 (1.56)*	117.9	112.7–123.4
AUC_{0-t} (µg·hour/ml)	6.78 ± 1.70 (6.56)*	6.16 ± 1.51 (5.99)*	109.5	104.0–115.4
AUC_{0-inf} (µg·hour/ml)	8.24 ± 2.41 (7.90)*	7.13 ± 1.65 (6.96)*	113.5	106.0–121.5
* geometric mean				

Isoniazid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	1.08 ± 0.45	1.22 ± 0.66	–	–
C_{max} (µg/ml)	2.12 ± 0.69 (1.99)*	1.88 ± 0.61 (1.78)*	112.0	104.0–120.8
AUC_{0-t} (µg·hour/ml)	7.10 ± 3.38 (6.25)*	6.86 ± 2.98 (6.15)*	101.7	94.3–109.6
AUC_{0-inf} (µg·hour/ml)	8.99 ± 3.82 (8.15)*	8.10 ± 3.38 (7.37)*	110.5	101.3–120.6
* geometric mean				

Pyrazinamide

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	2.34 ± 0.36	2.49 ± 0.31	–	–
C_{max} (µg/ml)	23.4 ± 3.7 (23.2)*	21.7 ± 3.8 (21.4)*	108.4	101.7–115.6
AUC_{0-t} (µg·hour/ml)	181 ± 31 (179)*	171 ± 32 (168)*	106.4	98.7–114.7
AUC_{0-inf} (µg·hour/ml)	213 ± 35 (210)*	190 ± 36 (187)*	112.5	104.1–121.5

* geometric mean

Rifampicin

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD	Reference (R) arithmetic mean ± SD	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (hour)	1.83 ± 0.64	2.06 ± 0.96	–	–
C_{max} (µg/ml)	2.21 ± 1.34 (1.88)*	2.36 ± 1.32 (2.00)*	93.8	83.8–105.1
AUC_{0-t} (µg·hour/ml)	8.90 ± 4.94 (7.62)*	9.00 ± 4.93 (7.62)*	100.2	90.1–111.5
AUC_{0-inf} (µg·hour/ml)	10.37 ± 5.12 (9.22)*	10.33 ± 5.29 (9.23)*	100.1	90.8–110.4
* geometric mean				

Conclusion

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and C_{max} values for ethambutol, isoniazid, pyrazinamide, and rifampicin. Accordingly, the test fixed-dose combination [TB193 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the individual reference formulations (Myambutol® Riemser Arzneimittel AG, Isozid®, Fatol Riemser Arzneimittel AG, Pyrazinamide, Lederle, and Rimactane®, Sandoz Pharmaceuticals AG).

4. Summary of Product Safety and Efficacy

[TB193 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovators' products. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference products, Myambutol® (ethambutol tablets 400 mg), Isozid® (isoniazid tablets 100 mg), Pyrazinamide, (Lederle, pyrazinamide tablets 500 mg) and Rimactane® (rifampicin capsules 150 mg).

The clinical safety of this product is considered 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

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

Comparability between the references Myambutol® (Riemser Arzneimittel), Isozid®, (Fatol Riemser Arzneimittel), Pyrazinamide (Lederle), and Rimactane® (Sandoz Pharmaceuticals) and the test product [TB193 trade name] (Svizera) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Efficacy and Safety

Regarding clinical efficacy and safety, [TB193 trade name] is considered effective and safe when the guidance and restrictions presented 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 by consensus that the benefit–risk profile of [TB193 trade name] was acceptable for the following indication: "**initial treatment phase of tuberculosis caused by *Mycobacterium tuberculosis***" and has advised to inclusion of [TB193 trade name], manufactured at Svizera Labs Private Ltd, Plot D-16/6, TTC Industrial Area, Turbhe, Navi Mumbai, 400 703, India, in the list of prequalified medicinal products.