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	[TB369 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited At Oxalis Labs, Village Theda P.O. Lodhimajra Tehsil Baddi, Dist. Solan Himachal Pradesh, 174101 India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid and rifapentine
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (J04AM02)
Therapeutic indication	[TB369 trade name] is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg.

1. Introduction

[TB369 trade name] is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg.

Consideration should be given to current official treatment guidelines for tuberculosis including those of WHO.

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 and rifapentine have 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 APIs, used in the manufacture of [TB369 trade name] are of good quality and manufactured in accordance with WHO Good Manufacturing Practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components:

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

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 core tablet formulation include microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, iron oxide red, povidone, low-substituted hydroxypropyl cellulose, sodium starch glycolate, sodium ascorbate, EDTA disodium, sodium lauryl sulfate, hydroxypropyl cellulose and calcium stearate. The seal coat contains hypromellose, while the commercially sourced proprietary film-coating mixture contains hypromellose, macrogol/ polyethylene glycol, titanium dioxide, iron oxide red and talc. TSE/BSE free certificates from the suppliers have been provided with regards to all the excipients. None of the excipients are derived from human or animal sources.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a reddish-brown coloured, capsule-shaped, biconvex, film-coated tablet debossed with "J" and "21" on either side of the scoreline on one side and plain on the other side. The scoreline is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility data. The tablets are packaged in Alu/Alu strips.

The objective of the product development was to obtain a stable and robust formulation of isoniazid/rifapentine tablets, bioequivalent to the individual WHO recommended comparator products, Isozid® (isoniazid) 100 mg tablets and Priftin® (rifapentine) 150 mg tablets. The comparator products were characterized and on that basis a quality target product profile was defined and critical quality attributes identified. Based on the physicochemical properties and compatibility of the APIs, a bilayer tablet approach with each API in a separate layer was selected for development. Since rifapentine is prone to oxidation, sodium ascorbate was included as anti-oxidant based on its presence in the comparator product. Rifapentine is a low soluble API; hence, micronized API was selected for the development. Based on the physicochemical properties of rifapentine, a dry granulation process was selected for manufacturing of the rifapentine layer. Due to poor compressibility of isoniazid API, a non-aqueous granulation process was selected for the manufacturing of the isoniazid layer. Compatibility studies which were conducted showed that the APIs were compatible with each other and also with the selected excipients. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

A risk assessment has been performed and a risk for nitrosamine impurities has been identified within the FPP manufacture. Confirmatory testing has been performed and cyclopentyl-4-nitrosopiperazine (CPNP) impurity was identified. A test for this impurity has been included in the FPP specifications.

Specifications

The finished product specifications include tests for description, identification of APIs (HPLC and TLC) and colourants, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection), related substances (HPLC), residual solvent (GC), assay (HPLC), antioxidant content (HPLC), subdivision of tablets, cyclopentyl-4-nitrosopiperazine content (LC-MS/MS $\leq$ 25ppm) 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 indicates 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 2018 according to internationally accepted guidelines:

Single dose fed in-vivo bioequivalence study of fixed dose combination of Rifapentine and Isoniazid tablets 300 mg/300 mg (Macleods Pharmaceuticals Ltd., India) to separate formulations of two tablets of Priftin® (rifapentine) tablets 150 mg (Sanofi-Aventis U.S. LLC, USA) and three tablets of Isozid® (isoniazid) tablets 100 mg (RIEMSER Pharma GmbH., Germany) in healthy, adult, human subjects (study no. BEQ-2349-RfIs (F)-2018).

The objective of the study was to compare the bioavailability of the stated Isoniazid/Rifapentine 300/300 mg FDC tablet manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulations Isozid® 100 mg tablet (Riemser Pharma GmbH) and Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet Isoniazid/Rifapentine 300/300 mg
(isoniazid 300 mg + rifapentine 300 mg)
Batch no.: NIE803C

Treatment R: References
– 3 tablets Isozid® 100 mg
(isoniazid 300 mg)
Batch no. 001046

– 2 tablets Priftin® 150 mg
(rifapentine 300 mg)
Batch no. A7010

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 29 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for isoniazid and rifapentine were analyzed using a validated LC-MS/MS methods. The limit of quantification was stated to be about 50 ng/ml for isoniazid and about 200 ng/ml for rifapentine.

The study was performed with 42 participants; data generated from a total of 41 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for isoniazid and rifapentine as well as statistical results are summarised in the following tables:

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)	2.51 ± 0.83	2.56 ± 0.69	–	–
C_{max} (ng/mL)	3737 ± 1205 (3214)	3449 ± 1175 (3484)	108.4	103.4 – 113.7
AUC_{0-t} (ng·h/mL)	22941 ± 11549 (18541)	22485 ± 11456 (18964)	102.3	99.7 – 104.9
AUC_{0-inf} (ng·h/mL)	23525 ± 11704 –	23033 ± 11604 –	–	–

Rifapentine

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)	5.42 ± 0.87	5.44 ± 0.70	–	–
C_{max} (µg/mL)	8.85 ± 1.84 (9.67)	9.86 ± 1.99 (8.63)	89.3	85.9 – 92.9
AUC_{0-t} (µg·h/mL)	217 ± 49 (230)	236 ± 46 (210)	91.3	87.5 – 95.3
AUC_{0-inf} (µg·h/mL)	229 ± 51 –	250 ± 52 –	–	–

The results of the study show that preset acceptance limits of 80–125 % are met by both AUC and C_{max} values regarding isoniazid and rifapentine. Accordingly, the test Isoniazid/Rifapentine 300/300 mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the references Isozid® 100 mg (Riemser Pharma GmbH) and Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC).

4. Summary of product safety and efficacy

[TB369 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator products. According to the submitted data on quality and bioavailability, [TB369 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Isozid® 100 mg (Riemser Pharma GmbH) and Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC), for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB369 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 [TB369 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB369 trade name] has been shown to be bioequivalent with the references Isozid® 100 mg (Riemser Pharma GmbH) and Priftin® 150 mg tablet (Sanofi-Aventis U.S. LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB369 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 [TB369 trade name] was acceptable for the following indication: 'prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg', and would allow inclusion of [TB369 trade name], manufactured at Macleods Pharmaceuticals Limited (At Oxalis Labs), Village Theda, P.O. Lodhimajra, Tehsil Baddi, Dist. Solan, Himachal Pradesh, 174101, India, in the list of prequalified medicinal products.