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	[TB302 trade name]*
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Unit II, Phase II Plot No 25-27 Survey No 366 Premier Industrial Estate Kachigam, Daman, 369 210 India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid / rifampicin
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, combinations of drugs for treatment of tuberculosis (rifampicin and isoniazid: J04AM02)
Therapeutic indication	[TB302 trade name] is indicated for the continuation phase of treatment of tuberculosis, caused by *Mycobacterium tuberculosis* in children weighing less than 25 kg

1. Introduction

[TB302 trade name] is indicated for the continuation phase of treatment of tuberculosis, caused by *Mycobacterium tuberculosis* in children weighing less than 25 kg

[TB302 trade name] should be initiated 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 Ingredient (API)

Rifampicin

Rifampicin API is described in the Ph.Int, Ph.Eur and the USP, and is considered well-established in the WHO Prequalification Programme. Compacted rifampicin is used in the manufacture of the dispersible tablets.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification of the API and of its crystal form (XRPD), pH, loss on drying, heavy metals, sulfated

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

ash, related substances (HPLC), assay (UV/HPLC), crystallinity, bulk density residual solvents and particle size distribution.
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
Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified isoniazid up to 300 mg oral dose as a BCS class 3 API. The API is thus regarded highly soluble in terms of the BCS.
Isoniazid is described in the Ph.Int, Ph.Eur and USP and is considered well-established in the WHO PQTm.
The API specifications, which are pharmacopoeial based, include tests for description, solubility, identification (m.p., IR), appearance and pH of solution, hydrazine and related substances (TLC), heavy metals, loss on drying, sulfated ash, assay (titrimetric/HPLC), related substances (HPLC), residual solvents, manganese (AAS), metal impurities (molybdenum, nickel, chromium and vanadium with ICPMS) and particle size.
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 tablet formulation include microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, aspartame, Trusil raspberry flavour and magnesium stearate. BSE/TSE risk-free declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
The product is a brick-red mottled, circular, uncoated biconvex tablet, having a deep score on one side and plain surface on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The tablets are packed in Alu-Alu strips or in an LDPE bag put in a triple laminated sachet contained in an HDPE bottle.

The pharmaceutical development was based on previous experience in this area and focussed on overcoming the inherent stability problems encountered with this 2-FDC tablet dosage form. According to literature rifampicin is not only prone to hydrolysis and oxidation, but it can also react (indirectly though acid degradation or directly) with isoniazid to form a hydrazone. This hydrazone is described in the Ph.Int. monograph of rifampicin and isoniazid dispersible tablets. The selection of the excipients was based on their suitability to achieve the desired characteristics of the formulation and their compatibility with rifampicin and isoniazid. Aspartame and strawberry flavour were selected as sweetener and flavouring agent, respectively.

The manufacture involves a non-aqueous wet granulation processes for isoniazid, while rifampicin is introduced extra-granularly. Quick dispersion of the tablets is achieved through inclusion of intra- and extra-granular disintegrants. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications
The product specifications include tests for description; identification of the APIs (HPLC, TLC); average weight; hardness; friability; disintegration time (≤ 3 min.); fineness of dispersion; loss on drying; dissolution (HPLC detection); uniformity of dosage units (by content uniformity); related substances (HPLC); assay (HPLC); residual solvent; and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for 6 months at 40°C/75%RH as accelerated conditions in both pack types proposed for marketing of the product. The data showed little change and were well within the agreed specifications at these storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage period (after first opening) as indicated in the product information for the HDPE bottle packs is supported by stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2016 according to internationally accepted guidelines.

Study title: Single dose fasting in-vivo bioequivalence study of fixed dose combination of rifampicin 75 mg and isoniazid 50 mg dispersible tablets (Macleods Pharmaceuticals Ltd., India) in comparison with separate formulation of rifampicine Sandoz® (rifampicin) capsules 150 mg (Sandoz B.V. Netherlands) and isoniazid tablets USP 100 mg (Sandoz Inc., USA) in healthy, adult, human subjects (study no. BEQ-1680-RiIs(F)-2015).

The objective of the study was to compare the bioavailability of the stated [TB302 trade name] manufactured for/by Macleods Pharmaceuticals Ltd., India (test drug) with the individual reference formulations rifampicin Sandoz® 150 mg capsules (Sandoz Inc.) and isoniazid 100 mg tablets USP (Sandoz Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: *Test* – 2 tablets [TB302 trade name]
(rifampicin 150 mg + isoniazid 100 mg)
Batch no. ERE6402C

Treatment R: *Reference* – 1 capsule Rifampicin Sandoz® 150 mg
(rifampicin 150 mg)
Batch no. FX0544
– 1 tablet Isoniazid 100 mg
(isoniazid 100 mg)
Batch no. ME140742

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 16 samples within 24 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for rifampicin and isoniazid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/mL for rifampicin as well as for isoniazid.

The study was performed with 40 participants. Data generated from a total of 35 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.20 ± 0.50	1.71 ± 0.68	–	–
C_{max} (ng/mL)	2160 ± 516 (2103)	2161 ± 588 (2099)	100.2	94.7 – 105.9
AUC_{0-t} (ng·h/mL)	10495 ± 2153 (10309)	10573 ± 2497 (10279)	100.3	96.5 – 104.2
AUC_{0-inf} (ng·h/mL)	10950 ± 2180 (NA[#])	10996 ± 2512 (NA[#])	--	--

not analysed

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)	0.57 ± 0.34	0.74 ± 0.55	–	–
C_{max} (ng/mL)	2043 ± 739 (1924)	2134 ± 994 (1980)	97.1	88.4 – 106.7
AUC_{0-t} (ng·h/mL)	7348 ± 3733 (6149)	7384 ± 3822 (6108)	100.7	98.0 – 103.4
AUC_{0-inf} (ng·h/mL)	7653 ± 3889 (NA#)	7707 ± 3956 (NA#)	--	--

not analysed

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 [TB302 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the individual references rifampicine Sandoz® 150 mg capsules (Sandoz Inc.) and isoniazid 100 mg tablets USP (Sandoz Inc.).

4. Summary of product safety and efficacy

[TB302 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, [TB302 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product rifampicin Sandoz® 150 mg capsules (Sandoz Inc.) and isoniazid 100 mg tablets USP (Sandoz Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB302 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 [TB302 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB302 trade name] has been shown to be bioequivalent with rifampicin Sandoz® 150 mg capsules (Sandoz Inc.) and isoniazid 100 mg tablets USP (Sandoz Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB302 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 [TB302 trade name] was acceptable for the following indication: 'for the continuation phase of treatment of tuberculosis, caused by Mycobacterium tuberculosis in children weighing less than 25 kg', and would allow inclusion of [TB302 trade name], manufactured at Macleods Pharmaceuticals Limited, Unit II, Phase II, Plot no. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman 369210, India in the list of prequalified medicinal products.