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	[TB179 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceutical Limited Plot No. 25-27, Survey No. 366 Premier Industrial Estate Kachigam, Daman – 396 210 (UT) India
Active Pharmaceutical Ingredient(s) (API)	Isoniazid
Pharmaco-therapeutic group (ATC Code)	Antimycobacterials, hydrazides (J04AC01)
Therapeutic indication	[TB179 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*

1. Introduction

[TB179 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis.*
It is also indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis*.
[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[TB179 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)

Isoniazid is a class 3/1 API according to Biopharmaceutics Classification System (WHO Technical Report Series 937, Annex 8: *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*).

Isoniazid is described in the Ph.Int., Ph.Eur. and the USP and is considered well-established.

The API, which is obtained from approved API manufacturer, is adequately controlled by quality specifications which are pharmacopoeial based, with an additional in-house specification for residual solvents.

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

Based on the results of stability testing conducted according to the requirements of WHO, a retest period of 5 years was approved for isoniazid.

Other ingredients

Other ingredients used in the tablet formulation include calcium hydrogen phosphate, colloidal anhydrous silica, disodium edetate, magnesium stearate, maize starch and purified talc, which are all compendial. Magnesium stearate is of vegetable origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Isoniazid tablets are described in the Ph.Int., BP and USP and are considered well- established.

[TB179 trade name] is white, circular, biconvex, uncoated tablets having plain surface on both the sides. The tablets (1,000) are packed in an LDPE bag, which is further packed in a round, white opaque HDPE jar, tagger-sealed with an aluminium circular foil (soft tempered) laminated with LDPE film and closed with a polypropylene screw cap. The tablets are also presented in plain aluminium foil/white opaque PVDC coated PVC blister cards of 10 tablets.

The development of the final composition of [TB179 trade name] has been described and the compatibility of the API with the excipients demonstrated. The manufacturing process entails a conventional wet granulation followed by drying, lubrication, compression and packaging. Appropriate in-process controls have been set to ensure batch-to-batch reproducibility. Validation data presented on three production batches and batch analysis data demonstrate the consistency of the process and the quality of the product. The pharmacopoeial based specifications and analytical methods with validation are considered adequate for controlling the quality of this finished pharmaceutical product at release and during shelf life.

Specifications

The finished product specifications include tests for description, identification (IR and by colour development), average weight, friability, uniformity of dosage unit (by mass variation), disintegration time, dissolution (UV detection), assay (by titrimetry and HPLC), loss on drying, related substances (HPLC and TLC) and microbial limit test. The analytical methods have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/70%RH as long-term conditions and at accelerated conditions according to the requirements of WHO. At the time of the prequalification, a shelf-life of 24 months has been allowed for the FPP when stored at a temperature not above 30°C. The applicant committed to continue long-term testing on production scale batches for a period of time sufficient to cover the whole proposed shelf-life and to report any out-of-specification results immediately to WHO.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2005 according to internationally accepted guidelines.

An open label, randomized, two-treatment, two sequence, two period, two way crossover, single dose bioequivalence study of [TB179 trade name] manufactured by Macleods Pharmaceuticals Ltd., India comparing with three tablets of Isozid 100 mg (each containing isoniazid 100 mg) of Fatol

Arzneimittel GmbH, Schiffweiler, Germany, in healthy, adult, male, human subjects under fasting conditions (study no. BEQ-009-ISON-2005).

The objective of the study was to compare the bioavailability of the stated [TB179 trade name] manufactured by Macleods Pharmaceuticals Ltd., India (test drug) with the same dose of the reference tablet (Isozid, Fatol Arzneimittel) 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 two treatments in a randomized fashion:

Treatment T: Test – [TB179 trade name]
(isoniazid 300 mg)
Batch no. IB501.
Treatment R: Reference – 3 x Isozid® 100 mg tablet
(isoniazid 100 mg)
Batch no. 004114.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 16 samples within 24 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 were analyzed using a validated HPLC method. The limit of quantification was stated to be about 100 ng/mL for isoniazid.

The study was performed with 28 participants; data generated from a total of 24 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for isoniazid 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)	0.68 ± 0.30	0.79 ± 0.36	–	–
C_{max} (µg /mL)	7.27 ± 1.89 (7.05)	6.99 ± 1.86 (6.79)	103.9	95.3 – 113.3
AUC_{0-t} (ng·h/mL)	32.25 ± 12.49 (29.30)	32.11 ± 12.84 (28.82)	101.7	97.1 – 106.5
AUC_{0-inf} (ng·h/mL)	33.37 ± 12.79 (30.33)	33.08 ± 13.17 (29.69)	102.2	98.4 – 106.1

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding isoniazid. Accordingly, the test tablet [TB179 trade name] meets the criteria for bioequivalence with regard to rate and extent of absorption and is therefore bioequivalent to the reference 3 x Isozid® 100 mg tablet (Fatol Arzneimittel).

4. Summary of product safety and efficacy

[TB179 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, [TB179 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product 3 x Isozid® 100 mg tablet (Fatol Arzneimittel) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [TB179 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 [TB179 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB179 trade name] has been shown to be bioequivalent with 3 x Isozid® 100 mg tablet (Fatol Arzneimittel).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB179 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 [TB179 trade name] was acceptable for the following indication: 'treatment of tuberculosis caused by Mycobacterium tuberculosis', and would allow inclusion of [TB179 trade name], manufactured at Macleods Pharmaceutical Limited, Plot No. 25-27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396 210 (UT) Premier Industrial Estate, India, in the list of prequalified medicinal products.