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	[TB307 trade name][*]
Manufacturer of Prequalified Product	Macleods Pharmaceuticals Limited Block N2, Village Theda, Post Office Lodhimajra, Tehsil Baddi, District Solan, Himachal Pradesh – 174101 India Tel: +91-1795 661400 Fax:+91-1795 661452
Active Pharmaceutical Ingredients (APIs)	Pyrazinamide
Pharmaco-therapeutic group (ATC Code)	Antimycobacterial (J04AK01)
Therapeutic indication	[TB307 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in children.

1. Introduction

[TB307 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant tuberculosis.

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

[TB307 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)

Based on scientific principles the WHO Prequalification Team – Medicines (PQTm) has identified pyrazinamide up to 500 mg oral dose as a BCS class 3 API. The API is thus BCS highly soluble. Pyrazinamide used in the manufacturer of Pyrazinamide 150mg Dispersible Tablets has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that pyrazinamide, used in the manufacture of Pyrazinamide 150mg Dispersible Tablets, is of good quality and manufactured in

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

accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients used in the tablet formulation include maize starch, sodium starch glycolate, povidone, microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal anhydrous silica, strawberry flavour, aspartame, purified talc and magnesium stearate. None of the excipients are derived from animal source.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, circular, biconvex uncoated tablet having plain on both sides. The tablets are presented in in a triple laminated sachet packed in an HDPE bottle.

The objective of the development activities was to obtain a formulation of Pyrazinamide Dispersible Tablets that would match the dissolution properties and pharmacokinetics of the comparator product, Pyrazinamide Tablet USP 500 mg of Dava Pharmaceuticals marketed in the USA. The selection of excipients was based on their suitability to achieve the desired characteristics of the formulation and was supported by API-excipient compatibility studies. As the dosage form is a dispersible tablet, sweeteners and flavouring agents may play an important role in the formulation for the patient acceptance. With aspartame as sweetener and strawberry cream flavour the reconstituted preparation (tablets dispersed in water) was considered to be acceptable by a taste panel of the manufacturer.

Pyrazinamide exhibits poor flow characteristics; hence the wet granulation approach was selected in order to obtain granules suitable for a fast speed tableting machine. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product in the BCS media. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications are pharmacopoeial based and include tests for tablet description, identification (IR, HPLC), average weight, uniformity of dosage units (by weight variation), hardness, friability, disintegration time, fineness of dispersion, related substances (TLC and HPLC), assay (HPLC), dissolution (UV detection), loss on drying and microbial limits.

Stability testing

Stability studies have been conducted at 30□C/75%RH (zone IVb) as long-term storage condition and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions with no apparent degradation observed and only slight increasing trends for friability and water content, though well within justified limits. The product should be protected from light. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The reconstituted preparation (tablets dispersed in water) should be used within 10 minutes.
The reconstituted preparation (tablets dispersed in water) should be used within 10 minutes.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2014 according to internationally accepted guidelines.

Bioequivalence study of ten tablets as single dose of Pyrazinamide Tablets BP 150 mg (dispersible tablets) manufactured by Macleods Pharmaceuticals Ltd., India in comparison with three tablets of Pyrazinamide tablets USP 500 mg manufactured for Dava Pharmaceuticals, Inc., USA in healthy, adult, human subjects under fasting condition (study no. BEQ-1105-PYRA-2013).

The objective of the study was to compare the bioavailability of the stated Pyrazinamide BP 150 mg tablet manufactured by/for Macleods Pharmaceuticals Ltd., India (test drug) with the reference formulation Pyrazinamide USP 500 mg tablet (Dava Pharmaceuticals, 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 two treatments in a randomized fashion:

Treatment T:	Test – 10 tablets Pyrazinamide BP 150 mg (pyrazinamide 1500 mg) Batch no. BPC1301A.
Treatment R:	Reference – 3 tablets Pyrazinamide USP 500 mg (pyrazinamide 1500 mg) Batch no. 70052A.

A 7 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for pyrazinamide were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 497 ng/ml for pyrazinamide.

The study was performed with 24 participants; data generated from a total of 17 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for pyrazinamide as well as statistical results are summarised in the following table:

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} (h)	1.03 ± 0.71	1.61 ± 0.86	-	-
C_{max} (µg/ml)	38.9 ± 7.2 (38.3)	36.2 ± 4.5 (35.9)	106.6	99.0 – 114.7
AUC_{0-t} (µg.h/ml)	499 ± 68 (496)	514 ± 77 (509)	97.4	93.7 – 101.2
AUC_{0-inf} (µg.h/ml)	520 ± 76 (516)	532 ± 80 (527)	97.9	95.0 – 101.0

* geometric mean

Conclusion

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding pyrazinamide. Accordingly, the test tablet Pyrazinamide BP 150 mg meets the

criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Pyrazinamide USP 500 mg tablet (Dava Pharmaceuticals, Inc.).

4. Summary of Product Safety and Efficacy

[TB307 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent to the reference Pyrazinamide USP 500 mg tablet (Dava Pharmaceuticals, Inc.).

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 consideration. Reference is made to the SPC (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 SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

[TB307 trade name] has shown to be bioequivalent with Pyrazinamide USP 500 mg tablet (Dava Pharmaceuticals, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [TB307 trade name] is considered effective and safe to use when the guidance and restrictions 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 [TB307 trade name] was acceptable for the following indication: **"in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in children"** and has advised that the quality, efficacy and safety of [TB307 trade name] allow inclusion of [TB307 trade name], manufactured at Macleods Pharmaceuticals Limited, Block N2, Village Theda, Post Office Lodhimajra, Tehsil Baddi, District Solan, Himachal Pradesh – 174101, India, in the list of prequalified medicinal products.