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:	[TB353 trade name][*]
Manufacturer of Prequalified Product:	Technolog Private Joint Stock Company 8, Stara prorizna street, Uman City Cherkassy Region, 20300 Ukraine
Active Pharmaceutical Ingredient (API):	Protionamide
Pharmaco-therapeutic group (ATC Code):	Antimycobacterials, combinations of drugs for treatment of MDR tuberculosis or lepra (ATC code: J04AD01)
Therapeutic indication:	[TB353 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.* [TB353 trade name] is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

1. Introduction

[TB353 trade name] is indicated in combination with other anti-tuberculosis agents for the treatment of multi-drug resistant tuberculosis caused by *Mycobacterium tuberculosis.*

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[TB353 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)

Protionamide has 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 API, used in the manufacture of [TB353 trade name] is 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: 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.

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

Additional user requirements in the FPP manufacturer's specifications for the BCS low soluble protionamide include tests for particle size distribution, with limits based on the data obtained for the API batch used in the manufacture of the FPP biobatch.

Other ingredients

Other ingredients used in the core tablet formulation include croscarmellose sodium, crospovidone, copovidone, colloidal anhydrous silica, hypromellose, lactose monohydrate, microcrystalline cellulose and magnesium stearate, all being pharmacopoeial controlled. The film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, macrogol and FD&C yellow #6 / sunset yellow FCF (E110). TSE/BSE free certificates have been provided for lactose monohydrate and magnesium stearate.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an orange coloured, round, biconvex film coated tablet. The tablets are packaged in a clear PVC-aluminium blister card.

The objective of the formulation development strategy was to develop a product with a quality profile similar to that of the WHO recommended comparator product, Peteha 250 mg film-coated tablets. The quality target product profile and critical quality attributes were established. The excipients were same as the composition of the WHO recommended comparator product. An aqueous wet granulation process was selected for the manufacture of the tablets. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification of API (HPLC, UV and visible absorption spectrophotometry) and colorants (UV and colour reaction), average mass, uniformity of mass, disintegration time, dissolution (HPLC detection), assay (HPLC), related substances (HPLC), uniformity of dosage units (mass variation), assay (HPLC), loss on drying, thickness of tablet and microbiological purity. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging intended for marketing of the product. The data showed that results for all parameters remained within acceptable limits, at both storage conditions. The data support the proposed shelf life at the storage conditions as stated in the SmPC.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2019 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of protionamide (Protech) coated tablets 250 mg of Private Joint Stock Company Technolog (Group of Pharmaceutical Companies Lekhim) Ukraine, with Peteha® (protionamide) film coated tablets 250 mg of Riemser Arzneimittel AG (Fatol Arzneimittel GmbH), Germany, in normal, healthy, adult, human subjects under fasting conditions (study no. ARL/18/366).

The objective of the study was to compare the bioavailability of the stated protionamide 250 mg tablet manufactured by/for Private Joint Stock Company Technolog, Ukraine (test drug) with the reference formulation Peteha® (Riemser Arzneimittel AG) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, 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 – 1 tablet Protionamide 250 mg (protionamide 250 mg) Batch no. 20216.
Treatment R: Reference – 1 tablet Peteha® 250 mg (protionamide 250 mg) Batch no. 047065.

A 12 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 16 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 protionamide were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 50 ng/ml for protionamide.

The study was performed with 32 participants; data generated from a total of 31 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Protionamide

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)	1.45 ± 0.86	1.57 ± 0.83	-	-
C_{max} (ng/mL)	1903 ± 889 (1734)	1648 ± 569 (1561)	111.1	102.5 – 120.4
AUC_{0-t} (ng. h/mL)	6107 ± 2203 (5768)	5713 ± 1650 (5494)	105.0	100.3 – 109.9
AUC_{0-inf} (ng h/mL)	6323 ± 2247 --	5921 ± 1668 --	-	-

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding protionamide. Accordingly, the test protionamide 250 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Peteha® (Riemser Arzneimittel AG).

4. Summary of Product Safety and Efficacy

[TB353 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. [TB353 trade name] has been established to be bioequivalent to the reference product Peteha® (Riemser Arzneimittel AG. The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [TB353 trade name] is used in accordance with the SmPC.

Bioequivalence

[TB353 trade name] is bioequivalent to the reference product Peteha® Riemser Arzneimittel AG.

Efficacy and Safety
Regarding clinical efficacy and safety, [TB353 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy, the team of assessors considered that the benefit–risk profile of [TB353 trade name] was acceptable for the following indication: "**for the treatment tuberculosis**", and has advised that the quality, efficacy and safety of [TB353 trade name] allow inclusion of [TB353 trade name] , manufactured at Technolog Private Joint Stock Company 8, Stara prorizna street, Uman City, Cherkassy Region, 20300, Ukraine in the list of prequalified medicinal products.