WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB353 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains protionamide 250 mg

Each tablet contains 20.9 mg of lactose monohydrate

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

[TB353 trade name] are orange coloured, round, biconvex film-coated tablets with a scoreline on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB353 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis due to *Mycobacterium tuberculosis.*

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

4.2 Posology and method of administration

[TB353 trade name] must be given in combination with other tuberculosis medicines. Treatment with [TB353 trade name] should be started and monitored by a health care provider experienced in the management of multidrug-resistant *M. tuberculosis*.

Posology

Protionamide may be used in non-standard regimens for treating tuberculous meningitis; up-to-date WHO treatment guidelines should be followed. The recommendations below are for standard regimens.

Adults

The recommended daily dose is 15–20 mg/kg. The usual dose is 750 mg to 1000 mg daily, depending on body weight and tolerance. This daily dose can be taken as a single daily dose. Alternatively, to improve tolerability, either the dose can be split into two doses or the single dose given separately from other tuberculosis medicines.

The recommended doses for adults are shown below:

Body weight	**Dose in mg**	**Number of 250 mg tablets**
46 to less than 70 kg	750 mg daily	3 tablets daily
70 kg or more	1000 mg daily	4 tablets daily

To assess and improve tolerability, therapy may be started at a dose of 250 mg daily, and the dose increased by 250 mg increments over a few days towards the recommended doses, as tolerated by the patient. The usual maximum dose is 1000 mg daily.

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

If protionamide is administered in combination with isoniazid, the daily dose of [TB353 trade name] should be halved. The maximum daily dose then should not exceed 500 mg protionamide.

Children

The following dose recommendations for children are based on a dose of 15–20 mg/kg daily:

Child's weight	**Dose in mg**	**Number of 250-mg tablets**
Less than 5 kg	[TB353 trade name] not suitable; use an alternative product to give suitable doses of the active substance	
5 kg to less than 7 kg	See Method of administration, below, for giving fractions of tablets	
7 kg to less than 10 kg	125 mg daily	See Method of administration, below, for giving fractions of tablets
10 kg to less than 16 kg	250 mg daily	1 tablet daily
16 kg to less than 46 kg	500 mg daily	2 tablets daily
Over 46 kg	As for adults	

Duration of therapy

The duration of tuberculosis treatment depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility of *M. tuberculosis* isolates from the patient or the suspected source case.

If therapy is interrupted, the treatment schedule should be extended. The period of extension will depend on, for example, the duration of interruption, timing of interruption during therapy (early or late) and the patient's status.

Missed doses

When a dose is missed and this is noticed within 6 hours, the missed dose should be taken as soon as possible. The next regular dose should be taken as scheduled. If noticed later, then the normal dose should be taken when it is due. No double dose should be taken to make up for forgotten individual doses.

Hepatic and renal impairment

Protionamide is almost completely metabolised in the liver. It should not be used in patients with severe hepatic impairment. No data are available for patients with mild to moderate hepatic impairment.

It is not known if dose adjustment is required in renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/minute) should be monitored for side effects and the dose reduced if necessary.

Method of administration

Oral administration.

[TB353 trade name] may be taken with food or between meals. Taking it with food may improve gastrointestinal tolerability.

4.3 Contraindications

- Hypersensitivity to protionamide, ethionamide, isoniazid or to any of the excipients of [TB353 trade name] (see section 6.1).
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Resistance

The use of protionamide alone in the treatment of tuberculosis results in rapid development of resistance. It is essential, therefore, to co-administer other suitable tuberculous medicines, the choice being based on susceptibility testing.

Liver toxicity

Toxic hepatitis, obstructive jaundice, acute hepatic necrosis, as well as modest elevations of hepatic transaminase levels, bilirubin, and alkaline phosphatase with or without jaundice, have occurred during protionamide treatment. Baseline liver function tests should be performed prior to therapy, and serum transaminases should be monitored every 2-4 weeks during therapy. If transaminase levels exceed 5 times the upper limit of normal (ULN), with or without symptoms, or 3 times the ULN with jaundice or hepatitis symptoms, protionamide and other potentially hepatotoxic co-administered drugs should be discontinued temporarily until the laboratory abnormalities have resolved. These medications may then be reintroduced sequentially to determine the drug (or drugs) responsible for the hepatotoxicity.

The risk of hepatotoxicity is increased in patients with diabetes mellitus and in chronic alcohol abuse.

Neurological effects

Psychotic disturbances, encephalopathy, peripheral and optic neuritis, as well as a pellagra-like syndrome have been reported with thioamide antimycobacterials including protionamide. In some cases, these symptoms have improved with nicotinamide and pyridoxine supplementation. Therefore, concurrent administration of pyridoxine is strongly recommended to prevent neurotoxic effects of protionamide.

Blood glucose

Since protionamide treatment is associated with hypoglycaemia, blood glucose should be determined before therapy with [TB353 trade name] and periodically throughout therapy. Blood glucose control in diabetes mellitus may be more difficult during protionamide treatment, including an increased risk of hypoglycaemia.

Hypothyroidism

Periodic monitoring of thyroid function is recommended as hypothyroidism, with or without goitre, has been reported during therapy with thioamide antimycobacterials such as protionamide.

Allergic reactions

Protionamide may cause severe allergic hypersensitivity reactions with rash and fever. If this occurs, [TB353 trade name] must be discontinued.

Visual disturbances

Since protionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with [TB353 trade name].

Excipients

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of rifampicin and thioamide antimycobacterials such as protionamide has been associated with a high frequency of hepatitis with some fatalities. Co-administration should be avoided unless the benefits are considered to outweigh the risks, and if so, the patient should be regularly monitored for liver function abnormalities, as well as for signs and symptoms of liver dysfunction.

Due to the structural similarity of protionamide and ethionamide, the action and effects of protionamide and ethionamide can be assumed to be similar. Co-administration of ethionamide and isoniazid increased the serum concentration of the latter in both rapid and slow acetylators. If co-administration is necessary, supplemental pyridoxine should be given; also, the patient should be monitored for adverse effects of isoniazid (peripheral neuritis, hepatotoxicity, encephalopathy).

A reversible pellagra-like encephalopathy has occurred when ethionamide and cycloserine were co-administered. This may have been caused by disturbances in pyridoxine metabolism.

Excessive use of alcohol during ethionamide therapy has been reported to precipitate a psychotic reaction. Alcohol should be avoided while taking protionamide.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are limited data from the use of protionamide in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

[TB353 trade name] should not be used during pregnancy or by women who are likely to become pregnant during therapy; an alternative tuberculosis medicine should be selected instead.

Breast-feeding

Protionamide may pass into breast milk of treated women. The effect of protionamide on breast-feeding infants is unknown. A decision must be made to whether discontinue breast-feeding or to discontinue protionamide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

In case of breast-feeding during treatment with [TB353 trade name], the baby should be monitored for side effects of protionamide (see section 4.8).

Supplementary pyridoxine (vitamin B6) is recommended both for the breast-feeding mother and the infant.

Fertility

There are no data on the effects of protionamide or its metabolites on human fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse effects of [TB353 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events considered to be at least possibly related to treatment with protionamide are listed below by body system or organs. Frequencies are defined as very common (up to 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100) or rare (in less than 1 in 1000). In addition, adverse events identified during post-approval use of protionamide are listed (frequency category: 'not known'). Since they are reported voluntarily from a population of unknown size, frequency cannot be estimated. These events have been included for their potential causal connection to protionamide, taking also into account their seriousness and the number of reports.

Blood and lymphatic system disorders

Not known	anaemia, methaemoglobinaemia, hypoprothrombinaemia and hypofibrinogenaemia

Metabolism and nutrition disorders

Rare	hypoglycaemia

Endocrine disorders

Rare	hypothyroidism

Psychiatric disorders

Uncommon	poor concentration, confusion, psychiatric disorders such as depressive reactions, excitation, psychosis
Not known	suicide attempts

Nervous system disorders

Common	headache, dizziness
Rare	convulsive paroxysm, sleep disorders
Not known	algodystrophy

Cardiovascular disorders

Not known	postural hypotension

Gastrointestinal disorders

Very common	metallic taste, dry mouth or excessive salivation, anorexia, nausea
Uncommon	vomiting, heartburn, abdominal pain, feeling of fullness, diarrhoea, constipation, meteorism
Not known	parotid swelling, stomatitis, glossitis

Hepatobiliary disorders

Common	elevated serum transaminases
Rare	jaundice
Not known	hepatitis, liver failure

Skin and subcutaneous tissue disorders

Not known	pellagroid reactions, photodermatoses, rhagades, acne, alopecia, cheilitis

Reproductive system and breast disorders

Rare	gynaecomastia, menstrual disturbance

Eye disorders

Not known	blurred vision, ocular paralysis, impaired vision

Ear disorders

Not known	hearing impairment, tinnitus

Musculoskeletal disorders

Not known	arthralgia, arthritis, amyosthenia

Renal and urinary tract disorders

Not known	urolithiasis

Respiratory, thoracic and mediastinal disorders

Not known	haemoptysis

Immune system disorders

Not known	allergic reactions

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is a lack of information on protionamide overdose. In case of an overdose, the patient should be clinically assessed, bearing in mind the side effects listed in section 4.8; management should be symptomatic. Protionamide is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, thiocarbamide derivatives

ATC code: J04AD01

Protionamide is bacteriostatic against *M. tuberculosis* at therapeutic concentrations but may be bactericidal at higher concentrations. It is also active against *M. kansasii, M. leprae* and some strains of *M. avium*-complex.

The exact mechanism of action of protionamide has not been fully elucidated, but the drug appears to inhibit the synthesis of mycolic acids that are the major lipid component of mycobacterial cell walls. Protionamide is a prodrug that needs activation by mycobacterial enzymes. Drug resistance develops rapidly when protionamide is given as monotherapy. Protionamide and ethionamide are completely cross-resistant.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB353 trade name] have been determined after administration of one (1) tablet of [TB353 trade name] in healthy volunteers as follows:

Pharmacokinetic Parameter	**Arithmetic mean ± standard deviation**
Time to attain maximum concentration t_{max} (h)	1.45 ± 0.86
Maximum concentration C_{max} (ng/mL)	1903 ± 889
Area under the curve, a measure of the extent of absorption $AUC_{0\text{-}96h}$ (ng·h/mL)	6323 ± 2247

Pharmacokinetics of protionamide

Absorption	
Oral bioavailability	Nearly complete absorption after oral administration
Food effect	No effect
Distribution	
Volume of distribution (mean)	Approximately 80 L
Plasma protein binding in vitro	Approximately 30%
Tissue distribution	Concentrations close to serum concentrations reached in the lungs, tuberculous lesions, and CSF

Metabolism	
	Metabolised by flavin-containing monooxygenase (FMO) to active sulfoxide metabolites which are then metabolised to nicotinamide and nicotinic acid forms
Active metabolites	Protionamide sulfoxide
Elimination	
Plasma half-life	Approximately 2 to 3 hours
% of dose excreted in urine	Mainly excreted in the urine as protionamide and metabolites
% of dose excreted in faeces	Minimal

Special populations

Renal impairment

There are no pharmacokinetic data available for patients with renal impairment. Protionamide is not removed by haemodialysis.

Hepatic impairment

There are no pharmacokinetic data available for patients with mild to moderate hepatic impairment (see Section 4.2).

Paediatric patients

Data on the pharmacokinetics of protionamide in paediatric patients are scarce but the pharmacokinetics of protionamide and ethionamide are thought to be similar. One study in children aged 0–12 years showed that a daily ethionamide dose of 15–20 mg/kg yielded C_{max} values above a target concentration of 2.5 μg/mL in most patients. This target concentration was based on published expert opinion. Exposures tended to be lower in younger patients, particularly in those under 2 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Animal studies conducted with protionamide indicate that the drug had embryotoxic and teratogenic effects in mice, rabbits, and rats. There were no studies on effects on male and female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Croscarmellose sodium
Crospovidone
Copovidone
Colloidal anhydrous silica
Hypromellose
Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate

Film coat: Hypromellose
Lactose monohydrate

Titanium dioxide

Macrogol

FD&C yellow #6 / Sunset yellow FCF (E110)

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store tablets in blisters in the provided carton to protect from light.

6.5 Nature and contents of container

Blister pack

Clear PVC-aluminium blister card. 10 tablets are packed in a blister card.

Pack sizes:

- 5 blister cards are packed in a carton. (5 x 10 tablets)
- 10 blister cards are packed in a carton. (10 x 10 tablets)

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration - extemporaneous formulation for children

Children weighing less than 10 kg

For children weighing less than 10 kg, one tablet should be thoroughly crushed, and the powder dispersed in 10 mL of water. The child should be given a proportion of the mixture as follows:

Child's weight	**Volume to be given after dispersing 1 tablet in 10 mL water**	**Dose in mg**
5 kg to less than 7 kg	3 mL daily†	75 mg daily
7 kg to less than 10 kg	5 mL daily†	125 mg daily
† An oral syringe should be provided to measure volumes less than 10 mL		

7. SUPPLIER

LEKHIM Joint Stock Company

23, Shota Rustaveli Street

Kyiv, 01033

Ukraine

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB353

9. DATE OF PREQUALIFICATION

08 September 2021

10. DATE OF REVISION OF THE TEXT

November 2023

References

WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240063129 accessed 4 July 2023).

WHO operational handbook on tuberculosis. Module 4: treatment: drug-resistant tuberculosis treatment. 2022 update. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240065116, accessed 4 July 2023).

WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents, Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240046832, accessed 4 July 2022).

PETEHA (protionamide 250 mg tablets) summary of product characteristics. World Health Organization: September 2014 (https://extranet.who.int/pqweb/sites/default/files/TB345Part4v01.pdf, accessed 4 July 2022).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines