

## 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.*

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\*[https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[TB206 trade name]†

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg protionamide.

Each film-coated tablet contains 1.38 mg sodium benzoate and 1.56 mg propylene glycol.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow circular, bevelled edged, biconvex film coated tablet plain on both sides.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[TB206 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

[TB206 trade name] must be given in combination with other tuberculosis medicines. Treatment with [TB206 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.

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

If protonamide is administered in combination with isoniazid, the daily dose of [TB206 trade name] should be halved. The maximum daily dose then should not exceed 500 mg protonamide.

### *Children*

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

<b>Child's weight</b>	<b>Dose in mg</b>	<b>Number of 250-mg tablets</b>
Less than 5 kg	[TB206 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*

Protonamide 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.

[TB206 trade name] may be taken with food or between meals. Taking it with food may improve gastrointestinal tolerability.

### *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 <sup>†</sup>	75 mg daily
7 kg to less than 10 kg	5 mL daily <sup>†</sup>	125 mg daily
<sup>†</sup> An oral syringe should be provided to measure volumes less than 10 ML		

#### 4.3 Contraindications

- Hypersensitivity to protonamide, ethionamide, isoniazid or to any of the excipients of [TB206 trade name] (see section 6.1).
- Severe hepatic impairment.

#### 4.4 Special warnings and precautions for use

##### *Resistance*

The use of protonamide 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 protonamide 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, protonamide 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 protonamide. 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 protonamide.

##### *Blood glucose*

Since protonamide treatment is associated with hypoglycaemia, blood glucose should be determined before therapy with [TB206 trade name] and periodically throughout therapy. Blood glucose control in diabetes mellitus may be more difficult during protonamide 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 protonamide.

##### *Allergic reactions*

Protonamide may cause severe allergic hypersensitivity reactions with rash and fever. If this occurs, [TB206 trade name] must be discontinued.

### *Visual disturbances*

Since protonamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with [TB206 trade name].

## **4.5 Interaction with other medicinal products and other forms of interaction**

Co-administration of rifampicin and thioamide antimycobacterials such as protonamide 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 protonamide and ethionamide, the action and effects of protonamide 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 protonamide.

## **4.6 Fertility, pregnancy and breastfeeding**

### *Pregnancy*

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

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

[TB206 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*

Protonamide may pass into breast milk of treated women. The effect of protonamide on breast-feeding infants is unknown. A decision must be made to whether discontinue breast-feeding or to discontinue protonamide 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 [TB206 trade name], the baby should be monitored for side effects of protonamide (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 protonamide 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 [TB206 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 protonamide 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 protonamide 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 protonamide 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. Protonamide is not dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, thiocarbamide derivatives

ATC code: J04AD01

Protonamide 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 protonamide 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. Protonamide is a prodrug that needs activation by mycobacterial enzymes. Drug resistance develops rapidly when protonamide is given as monotherapy. Protonamide and ethionamide are completely cross-resistant.

### 5.2 Pharmacokinetic properties

The absorption characteristics of [TB206 trade name] have been determined after administration of tablets of [TB206 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value $\pm$ standard deviation
Maximum concentration ( $C_{max}$ )	1385 $\pm$ 510 ng/mL
Area under the curve ( $AUC_{0-\infty}$ ), a measure of the extent of absorption	4497 $\pm$ 1450 ng.h/mL
Time to attain maximum concentration ( $t_{max}$ )	1.19 $\pm$ 0.79 hours

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

## Special populations

### *Renal impairment*

There are no pharmacokinetic data available for patients with renal impairment. Protonamide 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 protonamide in paediatric patients are scarce but the pharmacokinetics of protonamide 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 protonamide 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:* colloidal silicon dioxide  
corn (maize) starch  
dibasic calcium phosphate dihydrate  
magnesium stearate  
microcrystalline cellulose  
povidone  
propylene glycol  
sodium benzoate  
sodium starch glycolate  
talc



*Film coat:* hypromellose  
lake of quinoline yellow  
polyethylene glycol  
talc  
titanium dioxide

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**

Store below 30°C. Protect from light.

Store tablets in blisters in the provided carton.

## **6.5 Nature and contents of container**

### *HDPE bottle*

The primary pack is a polyethylene bag which is placed in HDPE bottle having polyethylene plain screw cap and aluminium tagger seal. 50 tablets per bottle.

Pack size: 50 tablets

### *Blisters*

Alu/PVC/PVdC blister card of 10 tablets. Such 10 blister cards are packed in a carton.

Pack size: 10 x 10's tablets.

Alu/PVC/PE/PVdC blister card of 10 tablets. Such 10 blister cards are packed in a carton.

Pack size: 10 x 10's tablets.

Alu/PVC/Aclar blister card of 28 tablets. Such 10 blister cards are packed in a carton.

Pack size: 10 x 28's tablets.

## **6.6 Special precautions for disposal and other handling**

No special requirements.

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

## **7. SUPPLIER**

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## **8. WHO REFERENCE NUMBER (WHO Prequalification Programme)**

TB206

## **9. DATE OF PREQUALIFICATION**

13 June 2014

## **10. DATE OF REVISION OF THE TEXT**

October 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).

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