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

[TB206 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg protionamide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB206 trade name]is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children.

[TB206 trade name] is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.

Consideration should be given to official treatment guidelines for tuberculosis, e.g., those of WHO.

4.2 Posology and method of administration

[TB206 trade name] should be prescribed by a health care provider experienced in the management of multidrug resistant tuberculosis.

Oral use.

Protionamide must always be given in combination with other antituberculosis agents.

Posology

The optimum daily dose is 15-20 mg/kg. The usual dose is 500 mg to 750 mg daily (up to 1 g daily), depending on body weight and tolerance. This daily dose can be taken either at a single occasion or split up in two doses over the day to improve tolerability.

In children the recommended doses of 15–20 mg/kg/day is usually divided into 2–3 doses. A single daily dose can sometimes be given at bedtime or with the main meal.

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

Protionamide weight-based dosing scheme in combination therapy of tuberculosis:

Body weight	Number of tablets per day (dose)
Children	
10-16 kg	1 tablet (250 mg/day)
24-34 kg	2 tablets (500 mg/day)
> 34 kg	Use adult doses
Adults	
30-45 kg	2 tablets (500 mg/day)
45-70 kg	3 tablets (750 mg/day)
> 70 kg	4 tablets (1000 mg/day)

Method of administration

[TB206 trade name] may be taken with or without food. Intake with food or at bedtime may improve gastrointestinal tolerability (see Section 5.2).

To assess and improve tolerability, therapy may be initiated at a dose of 125-250 mg daily with gradual titration to optimal doses as tolerated by the patient. Doses should be increased by 125-250 mg increments over a few days until the full dose is reached.

It is recommended that all patients should receive pyridoxine (vitamin B6) while taking protionamide. The suggested dose for adults is 100 mg and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day).

Duration of therapy

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

If therapy is interrupted, the treatment schedule should be extended to a later completion date depending on the length of the interruption, the time during therapy (early or late) and the patient's status.

Hepatic and renal impairment

Protionamide is almost completely metabolised in the liver by the CYP450 system, though it is not known which of the CYP enzymes are responsible. Its use should be avoided in patients with severe hepatic impairment. No data are available for patients with mild to moderate hepatic impairment. Very little protionamide is excreted renally, and dose adjustments are not expected to be necessary in patients with renal impairment.

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.

4.3 Contraindications

- Hypersensitivity to protionamide/ethionamide or to any of the excipients
- 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 suitable other antituberculous drug or drugs, the choice being based on results of susceptibility testing. However, therapy may be initiated prior to receiving the results of susceptibility tests, as deemed appropriate by the physician.

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 been reported 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 five times the ULN, with or without symptoms, or three times the ULN with jaundice and/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 which drug (or drugs) is (are) responsible for the hepatotoxicity.

An increased risk of hepatotoxicity has been described in patients with diabetes mellitus.

Neurologic 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 has been associated with hypoglycaemia, blood glucose should be determined prior to and periodically throughout therapy with protionamide. Blood glucose control in diabetes mellitus may be more difficult during protionamide treatment, including an increased risk of hypoglycaemia (see Section 4.5).

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, protionamide must be discontinued.

Visual disturbances

Since protionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with protionamide.

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 reported. 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 test abnormalities, as well as clinical signs and symptoms of liver dysfunction.

If protionamide and isoniazid are given concomitantly, the concentration of protionamide in the blood is raised. The dose of protionamide should be reduced by 50%, not to exceed 500 mg when taken with isoniazid.

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

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

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

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

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

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

Protionamide should not be used during pregnancy, unless the anticipated benefits to the woman are considered to outweigh the risk of harm to the fetus.

Lactation

Protionamide has been identified in breastfed newborns/infants of treated women. The effect of protionamide on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from protionamide therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Supplementary pyridoxine (vitamin B6) is recommended both for the breastfeeding mother and the infant.

Fertility

There are no data on the effects of protionamide or its metabolites on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

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 reaction profile of protionamide 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, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/10 to < 1/100), or uncommon (≥ 1/100 to < 1/1000). 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, estimates of frequency cannot be made. These events have been included for their potential causal connection to protionamide, taking also into account their seriousness and the number of reports.

Organ system	Very common	Common	Uncommon	Not known
Blood and lymphatic system disorders				Thrombocytopenia
Metabolism and nutrition disorders				Pellagra-like syndrome; hypothyroidism; hypoglycaemia
Psychiatric disorders				Depression; confusion; psychosis; suicidality
Nervous system disorders		Headache; dizziness; drowsiness; asthenia; paresthesia		Encephalopathy; peripheral neuropathy; olfactory disturbance
Cardiovascular disorders				Postural hypotension
Gastrointestinal disorders	Metallic taste; dry mouth; anorexia; nausea		Vomiting; heartburn; abdominal pain;	Stomatitis; glossitis

Organ system	Very common	Common	Uncommon	Not known
			diarrhoea; constipation; parotid swelling	
Hepatobiliary disorders	Elevated hepatic transaminases	Hepatitis; jaundice		Liver failure
Skin and subcutaneous tissue disorders				Pellagroid reactions; photodermatoses; acne; alopecia
Reproductive system and breast disorders				Gynaecomastia; menstrual disturbance; impotence
Eye disorders				Visual disturbance; optic neuritis
Ear disorders				Ototoxicity
Musculoskeletal disorders				Arthralgia; arthritis
Renal and urinary tract disorders				Urolithiasis
Respiratory, thoracic and mediastinal disorders				Haemoptysis
Immune system disorders				Allergic reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Cases of severe overdosage have not been described in the literature. In case of overdose, treatment should be symptomatic. Protionamide is not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thioamide anti-mycobacterial agent

ATC code: J04AD01

Protionamide is bacteriostatic against *M. tuberculosis* at therapeutic concentrations but may be bactericidal at higher concentrations. Protionamide 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 peptide synthesis in susceptible organisms. 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 [TB206 trade name] have been determined after administration of one protionamide 250mg film-coated tablets in healthy volunteers in the fasting state as follows:

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

*arithmetic mean

Absorption	
Oral bioavailability	Nearly complete absorption after oral administration
Food effect	No effect
C_{max}	1729 ± 768 ng/mL
AUC_{0-t}	5661 ± 1679 ng·hr/mL
T_{max}	1.20 ± 0.62 hours
Distribution	
Volume of distribution (mean)	Approximately 80 liters
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	Approximately 1%
% 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. One study in children aged 0-12 years showed that a daily dose of 15-20 mg/kg yielded C_{max} values above a target concentration of 2.5µg/ml in the majority of patients. This target concentration was based on published expert opinion. Exposures tended to be lower in younger patients, particularly in those < 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: 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

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.

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

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References

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