SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Protionamide 250 mg Tablets

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 tablets plain on both sides.

The tablets should not be divided.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indication**

Protionamide 250mg Tablets is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in adults and children weighing 25kg or more ( see section 4.2).

Protionamide 250mg Tablets is only indicated as a second-line antimycobacterial drug when resistance to or toxicity from first-line drugs has developed.


*Where necessary, information is supplemented with that from ethionamide, because it is chemically and pharmacologically similar to protionamide.*

4.2 **Posology and method of administration**

Protionamide 250mg Tablets should be prescribed by a physician experienced in the management of multidrug resistant tuberculosis.

Oral use.

Protionamide 250mg Tablets must always be given in combination with other antituberculosis agents.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Posology
The optimum daily dose is 15-20mg/kg. The usual dose is 500mg to 750 mg daily (up to 1g 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 (up to 1 gram per day). A single daily dose can sometimes be given at bedtime or with the main meal.

<table>
<thead>
<tr>
<th>Protionamide weight-based dosing scheme in combination therapy of tuberculosis</th>
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<tbody>
<tr>
<td><strong>Body weight</strong></td>
</tr>
<tr>
<td><strong>Children</strong></td>
</tr>
<tr>
<td>25-29 kg</td>
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<tr>
<td><strong>Adults</strong></td>
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<tr>
<td>30-45 kg</td>
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<tr>
<td>46-70 kg</td>
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<tr>
<td>&gt;70 kg</td>
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</tbody>
</table>

Method of administration
Protionamide 250mg Tablets may be taken with or without food. Intake with food or at bedtime may improve gastrointestinal tolerability (see also section 5.2).

In order to assess and improve tolerability, therapy may be initiated at a dose of 250 mg daily with gradual titration to optimal doses as tolerated by the patient. Doses should be increased by 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. 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).

Children weighing less than 25 kg:
For these patient groups other more suitable formulations containing the active substance are available.

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.

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, e.g. on the length of the interruption, the time during therapy (early or late) and the patient’s status.
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 special 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 250mg Tablets 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 thiamide antimycobacterials including protionamide. In some cases, these symptoms have improved with nicotinamide and pyridoxine substitution. 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 250mg Tablets. Blood glucose control in diabetes mellitus may be more difficult during protionamide treatment, including an increased risk of hypoglycaemia (see also section 4.5.).

Hypothyroidism
Periodic monitoring of thyroid function is recommended as hypothyroidism, with or without goitre, has been reported with during therapy with thiamide antimycobacterials such as protionamide.
**Allergic reactions**
Protionamide may cause severe allergic hypersensitivity reactions with rash and fever. If this occurs, Protionamide 250mg Tablets must be discontinued.

**Visual disturbances**
Since protionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with Protionamide 250mg Tablets.

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

Co-administration of rifampicin and thiamide antimycobacterials such as protionamide has been associated with a high frequency of hepatitis with jaundice, possibly fatal. 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, then the concentration of protionamide in the blood is raised. Therefore, the protionamide dose should be reduced (=halved and not exceed 500 mg).

Protionamide slows down the decomposition of isoniazid.

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 and use of protionamide should thus be avoided.

### 4.6 Pregnancy and lactation

**Pregnancy**

There are no or limited amount of data from the use of protionamide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Protionamide 250 mg Tablets should not be used during pregnancy, unless the clinical condition of the woman requires treatment with protionamide.

**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 250 mg Tablets 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 /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 250mg Tablets 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 (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) or very rare (≤1/10,000). 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.

**Blood and lymphatic system disorders**

*Not known:* thrombocytopenia.

**Metabolism and nutrition disorders**

*Not known:* pellagra-like syndrome, hypothyroidism, hypoglycaemia.

**Psychiatric disorders**

*Not known:* depression, confusion, difficulties concentrating, psychosis, suicide attempt.

**Nervous system disorders**

*Common:* headache, dizziness, drowsiness, asthenia, paresthaesia

*Not known:* encephalopathy, peripheral neuritis, olfactory disturbance.

**Cardiovascular disorders**

*Not known:* postural hypotension.

**Gastrointestinal disorders**

*Very common:* taste of metal or sulphur, dry mouth, increased salivation, anorexia, nausea

*Uncommon:* vomiting, heartburn, abdominal pain, feeling of fullness, diarrhoea, constipation, meteorism, swelling of the parotid

**Hepatobiliary disorders**

*Very common:* elevated serum transaminases

*Common:* hepatitis, jaundice.

*Not known:* Liver failure
Skin and subcutaneous tissue disorders

*Not known:* pellagroid reactions, photodermatoses, rhagades, stomatitis, acne, cheilitis, glossitis, alopecia

Reproductive system and breast disorders

*Not known:* gynaecomastia, menstrual disturbance, impotence.

Eye disorders

*Not known:* visual disturbances (e.g. diplopia, blurred vision, optic neuritis).

Ear disorders

*Not known:* ototoxicity.

Musculo-skeletal disorders

*Not known:* arthralgia, arthritis

Renal and urinary disorders

*Not known:* Urolithiasis

Respiratory, thoracic and mediastinal disorders

*Not known:* haemoptysis

Immune system disorders

*Not known:* allergic reactions

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

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

*Absorption*

Protionamide is nearly completely absorbed upon oral administration. Following single dose administration of Protionamide 250mg Tablets in healthy volunteers, the mean (±SD) protionamide *C*<sub>max</sub> was 1385 ng/ml (±510 ng/ml), the mean (±SD) AUC<sub>0-t</sub> was 4357 ng.h/ml (±1445 ng.h/ml). The mean (± SD) protionamide *t*<sub>max</sub> value was 1.19 (± 0.79) hours.
Metabolism
Protionamide is converted to active sulfoxide metabolites which then are metabolized to nicotinamide and nicotinic acid forms.

Distribution and elimination
Plasma protein binding is approximately 30%, and the volume of distribution has been reported to be approximately 80 litres. Protionamide has good penetration into the cerebrospinal fluid. Protionamide undergoes extensive hepatic metabolism into several different metabolites, with only approximately 1% of a given dose excreted unchanged in the urine. Protionamide-sulfoxide is the major metabolite; it has been reported to have antibacterial activity. The plasma half-life of protionamide is approximately 2-3 hours.

Special populations
Renal/hepatic impairment: Pharmacokinetic data are available neither for patients with renal impairment nor for patients with mild to moderate hepatic impairment (see section 4.2).

Children
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\text{max} values above a target concentration of 2.5\mu g/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 and talc.

Film coating: Hypromellose, Lake of quinoline yellow, polyethylene glycol, talc and 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
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.


6.6 Instructions for use and handling and disposal
No special requirements. Any unused product or waste material should be disposed off in accordance with local requirements.

7. SUPPLIER
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13 June 2014

10. DATE OF REVISION OF THE TEXT

REFERENCES
This document is based on information available at the following sources:
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WHO guidelines on the treatment of Tuberculosis:

Companion Handbook, 2014, available at:
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