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

[TB352 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 125 mg ethionamide.

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

Yellow-coloured, circular, flat-faced, beveled edge, uncoated tablet, debossed with "E" above "125" on one face and plain on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ethionamide 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

[TB352 trade name] must be given in combination with other tuberculosis medicines. Treatment with [TB352 trade name] should be initiated and monitored by a health care provider experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

Posology

Ethionamide 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 optimum daily adult dose is 15–20 mg/kg. The usual dose is 750 to 1000 mg daily, depending on body weight and tolerance, as specified in the table below. This daily dose can be taken either as a single dose or split in two doses over the day to improve tolerability.

Bodyweight	**Dose in mg**	**Number of 125-mg dispersible tablets**	**Volume of water to disperse dose**, see Method of administration, below
46–69.9 kg	750 mg daily	6 tablets daily	50 mL
Over 70 kg	1000 mg daily	8 tablets daily	50 mL

To assess and improve tolerability, therapy may be started at a dose of 250 mg daily, and the dose increased in 250-mg increments over a few days towards the optimal 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.

Medicines containing a higher amount of ethionamide may be more suitable for adults.

Children

The dose can be taken either once daily or split up in two doses over the day to improve tolerability (see also section 5.2). 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 125-mg dispersible tablets**	**Volume of water to disperse dose**, see Method of administration, below
3–4.9 kg	37.5 mg daily	See Method of administration, below, for giving fractions of tablets	
5–6.9 kg	87.5 mg daily		
7–9.9 kg	125 mg daily	1 tablet daily	10 mL*
10–15.9 kg	250 mg daily	2 tablets daily	20 mL
16–23.9 kg	375 mg daily	3 tablets daily	20 mL
24–45.9 kg	500 mg daily	4 tablets daily	40 mL
Over 46 kg	As for adults		
* See Method of administration below if the daily dose is to be divided or if a volume of less than 10 mL is considered appropriate			

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 *Mycobacterium 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, time 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

Ethionamide 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. Very little ethionamide is excreted renally, and dose adjustments are not expected to be necessary in patients with renal impairment.

Method of administration

Oral administration.

[TB352 trade name] may be taken with food or between meals. Taking it with food may improve gastrointestinal tolerability.

Adults

The required number of [TB352 trade name] should be dispersed in about 50 mL water and thoroughly mixed. The entire mixture should be swallowed. The mixture (tablets dispersed in water) should be used within 10 minutes. The cup or glass that contained the mixture should then be rinsed with a small amount of water and the contents swallowed to ensure that the entire dose is taken.

Children weighing 7 kg or more

The required number of [TB352 trade name] should be dispersed in a small amount of water (see table above) and thoroughly mixed. The entire mixture (water and tablets) should be swallowed immediately. The cup or glass that contained the mixture should then be rinsed with a small amount of water and the contents swallowed to ensure the entire dose is taken.

If the health care provider considers that a volume less than 10 mL is appropriate for dispersing the tablet or if the daily dose is to be divided, then the health care provider should give full instructions on dispersing the tablet in the chosen volume of water and drawing up an appropriate volume of the mixture to give the correct dose.

An oral syringe should be provided to measure volumes less than 10 mL.

Children less than 7 kg

For children weighing less than 7 kg, one tablet should be dispersed in 10 mL water and thoroughly mixed. 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**
3–4.9 kg	3 mL daily†	37.5 mg daily
5–6.9 kg	7 mL daily†	87.5 mg daily
† An oral syringe should be provided to measure volumes less than 10 mL		

4.3 Contraindications

Hypersensitivity to ethionamide, protionamide or to any of the excipients of [TB352 trade name] (see section 6.1).

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Resistance

The use of ethionamide alone in the treatment of tuberculosis results in rapid development of resistance. It is essential, therefore, to co-administer other suitable tuberculosis 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 ethionamide treatment. Baseline liver function should be checked before 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, [TB352 trade name] and other potentially hepatotoxic co-administered drugs should be discontinued temporarily until the abnormalities have resolved. These medicines may then be reintroduced sequentially to determine which drug (or drugs) is (are) responsible for the hepatotoxicity.

The risk of hepatotoxicity is increased 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 ethionamide. In some cases, these symptoms have improved with nicotinamide and pyridoxine supplementation. Therefore, concurrent administration of pyridoxine is recommended to prevent neurotoxic effects of ethionamide.

Blood glucose

Since ethionamide is associated with hypoglycaemia, blood glucose should be checked before therapy with [TB352 trade name] and periodically throughout therapy. Blood glucose control in diabetes mellitus may be more difficult during ethionamide treatment and the risk of hypoglycaemia may be increased.

Hypothyroidism

Periodic monitoring of thyroid function is recommended as hypothyroidism, with or without goitre, has been reported with ethionamide therapy.

Allergic reactions

Ethionamide may cause severe allergic hypersensitivity reactions with rash and fever. If this occurs, [TB352 trade name] must be discontinued.

Visual disturbances

Since ethionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with [TB352 trade name].

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of ethionamide and rifampicin is associated with a high frequency of hepatitis with jaundice. In one study, hepatitis occurred in 4.5% of patients co-treated with rifampicin and ethionamide. The mortality in this subset of patients was 26%. Co-administration should be avoided unless the benefits outweigh the risks, and if both are used, the patient should be regularly monitored for liver function abnormalities, as well as signs and symptoms of liver dysfunction.

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

A reversible pellagra-like encephalopathy can occur when ethionamide and cycloserine are co-administered. This may be caused by disturbances in pyridoxine metabolism.

Excessive use of ethanol during ethionamide therapy can precipitate a psychotic reaction and should thus be avoided.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There little information on the use of ethionamide in pregnant women. Some data indicate an excess of congenital malformations when ethionamide is given to pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

[TB352 trade name] should not be used during pregnancy or by women who are likely to become pregnant during therapy unless the clinical condition of the woman requires treatment with ethionamide.

Breast-feeding

It is not known if ethionamide passes into human milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue [TB352 trade name] 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 [TB352 trade name], the baby should be monitored for side effects of ethionamide (see section 4.8).

Fertility

No data on the effect of ethionamide on fertility are available.

4.7 Effects on ability to drive and use machines

No studies on the effects of [TB352 trade name] on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of [TB352 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 ethionamide are listed below by body system, organ class and absolute frequency. 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), rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000).

In addition, adverse events identified during post-approval use of ethionamide 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 ethionamide, 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	psychotic reactions

Nervous system disorders

Common	headache, dizziness, drowsiness, asthenia, paraesthesia
Not known	encephalopathy, peripheral neuritis, olfactory disturbance

Cardiovascular disorders

Not known	postural hypotension

Gastrointestinal disorders

Very common	epigastric discomfort, abdominal pain, anorexia, nausea, vomiting, diarrhoea
Not known	metallic taste and sulphurous belching, increased salivation, taste disorders

Hepatobiliary disorders

Very common	elevated serum transaminases
Common	hepatitis, jaundice

Skin and subcutaneous tissue disorders

Not known	rash, urticaria, acne, photosensitivity, stomatitis, alopecia, purpura

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

General disorders and administration site conditions

Not known	hypersensitivity reaction (rash, fever)

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 little published information on severe ethionamide overdoses. In case of overdose, treatment should be symptomatic. Ethionamide is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for treatment of tuberculosis (thiocarbamide derivatives)
ATC code: J04AD03

Ethionamide is bacteriostatic against *M. tuberculosis* at therapeutic concentrations but may be bactericidal at higher concentrations. Ethionamide is also active against *M. kansasii, M. leprae* and some strains of *M. avium*-complex. Ethionamide inhibits the synthesis mycolic acids that are the major lipid component of mycobacterial cell walls. Drug resistance develops rapidly when ethionamide is given as monotherapy.

5.2 Pharmacokinetic properties

Absorption of [TB352 trade name]

The absorption characteristics of [TB352 trade name] have been determined after administration of two (2) tablets in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Arithmetic mean value (± standard deviation)**
Maximum concentration (C_{max})	2.669 ± 1.063 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	9.027 ± 1.837µg.h/mL
Time to attain maximum concentration (tmax)	1.13 (0.17 – 3.0) h #

median (range)

	Ethionamide
Absorption	
Absolute bioavailability	Almost 100%
Oral Bioavailability	Almost 100%
Food effect	No relevant food effect.
Distribution	
Volume of distribution (mean)	Approximately 94 L
Plasma protein binding in vitro	Approximately 30%
Tissue distribution	Widely distributed into body tissues and fluids with concentrations in plasma and various organs being approximately equal. Also distributed in CNS

Metabolism	
	Extensive hepatic metabolism into several different metabolites
Active metabolite	Ethionamide sulfoxide
Elimination	
General note	Ethionamide is mainly cleared through the liver
Mean systemic clearance (Cl/F)	56–72 hours
Terminal half life	1.7–2.1 hours
% of dose excreted in urine	Approximately 1% unchanged
% of dose excreted in faeces	Not available
Pharmacokinetic linearity	Not available
Drug interactions (in vitro)	Not available
Special populations	
Renal impairment	No pharmacokinetic data available
Hepatic impairment	No pharmacokinetic data available

Children

Data on the pharmacokinetics of ethionamide in children 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 2.5 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

Genotoxicity/carcinogenicity

Ethionamide did not exhibit a genotoxic potential *in vitro*.

Ethionamide was not carcinogenic in either rats or mice.

Reproductive toxicity

Animal studies with ethionamide indicate that the drug has a teratogenic potential in rabbits and rats. The doses used in these studies were considerably higher than those recommended in humans.

There are no other preclinical data of relevance to the prescriber in addition to those summarised in other sections of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, povidone, polysorbate, pineapple flavour, sucralose and magnesium stearate.

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
48 months

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Blister pack
[TB352 trade name] is available in clear PVC/PE/PVdC-Alu blisters of 14 tablets or 10 tablets. Such 3 or 10 blisters are packed in a carton.

Strip pack
[TB352 trade name] is also available in plain Alu-Alu strips. Each strip contains 10 tablets. Such 3 or 10 strips are packed in a carton.

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.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB352

9. DATE OF PREQUALIFICATION

23 July 2019

10. DATE OF REVISION OF THE TEXT

April 2023

References

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Mirzayev F, Viney K, Linh NN, *et al*. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. *Eur Respir J* 2020; in press
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Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis
https://www.who.int/publications/i/item/9789241548809 [Accessed 11 May 2022]

Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition
http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf

Mechanism of action

North JE, Jackson M, Lee ER. New Approaches to Target the Mycolic Acid Biosynthesis Pathway for the Development of Tuberculosis Therapeutics. Curr Pharm Des. 2014; 20(27)
https://dx.doi.org/10.2174/13816128196661311182036 41 [Accessed 7 May 2022]

Tissue distribution:

Bennett, J., et al (2015). "38 - Antimycobacterial Agents". Mandell, Douglas, and Bennett's principles and practice of infectious diseases.
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Food effect and clearance data:

Auclair B, Nix DE, Adam RD, et al. Pharmacokinetics of ethionamide administered under fasting conditions or with orange juice, food, or antacids. Antimicrob Agents Chemother. 2001; 45(3): 810–814
https://doi.org/10.1128/AAC.45.3.810-814.2001 [Accessed 7 May 2022]

Pediatric pharmacokinetics:

Thee S, Seifart HI, Rosenkranz B, et al. Pharmacokinetics of ethionamide in children. Antimicrob Agents Chemother, 2011; 55(10): 4594–4600
https://doi.org/10.1128/AAC.00379-11 [Accessed 7 May 2022]

Transport and metabolism:

Drugbank: Ethionamide
https://www.drugbank.ca/drugs/DB00609 [Accessed 17 September 2019]

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