# 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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

# 1. NAME OF THE MEDICINAL PRODUCT

[TB133 trade name]†

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg ethionamide

For excipients see 6.1

# 3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets are plain on both sides.

# 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

[TB133 trade name] must be given in combination with other tuberculosis medicines. Treatment with [TB133 trade name] should be started and monitored by a health care provider experienced in the management of multidrug-resistant *M. 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 recommended 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. The 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.

| **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.

*Children*

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

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

| Child's weight | Dose in mg | Number of 250-mg tablets |
|---|---|---|
| Less than 5 kg | [TB133 trade name] not suitable; use an alternative product to give suitable doses of the active ingredient | |
| 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 | ½ tablet 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 | |
| * The dose can be taken once daily. Alternatively, to improve tolerability, either the dose can be split into two doses or the single dose given separately from other tuberculosis medicines (see also section 5.2). | | |

For children and adults who cannot swallow tablets, ethionamide 125 mg dispersible tablets may be available.

*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***

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 may not be necessary in patients with renal impairment.

***Method of administration***

Oral administration.

[TB133 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, use of dispersible tablets is preferred. If dispersible tablets are not available, one tablet should be thoroughly crushed and the powder dispersed in 10 mL. 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 | | |

## 4.3 Contraindications

Hypersensitivity to ethionamide, protionamide or to any of the excipients of [TB133 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, [TB133 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 [TB133 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, [TB133 trade name] must be discontinued.

*Visual disturbances*

Since ethionamide may cause visual disturbances, ophthalmoscopy is recommended before and periodically during therapy with [TB133 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 is 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).

[TB133 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 [TB133 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 [TB133 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

Drowsiness or headache with [TB133 trade name] can impair the ability to perform skilled tasks. Patients should be warned not to drive or operate machinery if affected by these side effects.

## 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

The absorption characteristics of [TB133 trade name] have been determined after administration of tablets of [TB133 trade name] in healthy male volunteers under fed conditions as follows:

| **Pharmacokinetic variable** | **Arithmetic mean value ± standard deviation** |
|---|---|
| Maximum concentration ($C_{max}$) ng/mL | 2489 ± 752 |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL | 9161 ± 2161 |
| Time to attain maximum concentration ($t_{max}$) h | 0.966 ± 0.638 |

| | **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

*Core tablet:* maize starch
gelatin
sodium starch glycolate
colloidal anhydrous silica
gum acacia
purified talc
magnesium stearate
povidone

*Film coat*: hypromellose
titanium dioxide
purified talc
color quinoline yellow supra
diethyl phthalate

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

HDPE bottle: 48 months

Aluminium/Aluminium strip pack: 48 months

### 6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

### 6.5 Nature and contents of container

[TB133 trade name] is available in the following packs.

Aluminium/aluminium strip pack containing 10 tablets. Available in boxes of 9 x 10 and 10 x 10 tablets.

Plastic (HDPE) bottle containing 100 tablets. The tablets are packed in a plastic (LDPE) bag in a triple-laminated (3-layer) aluminium pouch. The bottle has a screw cap.

### 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)

TB133

## 9. DATE OF PREQUALIFICATION

21 December 2007

## 10. DATE OF REVISION OF THE TEXT

December 2024

***References***

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WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents (2022) https://www.who.int/publications/i/item/9789240046832 [Accessed 7 May 2022]

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
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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)
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*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:*

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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/prequal/medicines/prequalified/finished-pharmaceutical-products*