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

[TB159 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg pyrazinamide.
For the list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Tablets.
White, circular, flat bevelled edged uncoated tablets plain on both sides.
The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB159 trade name] is indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis* including in regimens for drug-resistant tuberculosis.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[TB159 trade name] must always been given in combination with other antituberculosis agents.

The therapy should be initiated by a health care provider experienced in the management of tuberculosis infection.

Dosing recommendations

The recommended weight-based daily dose for children and adolescents younger than 15 years is 30-40 mg/kg body weight; for patients older than 15 years it is 20-30 mg/kg body weight.

Weight	Daily dose
3 – <5 kg	0.25* tablet
5 – <7 kg	0.5* tablet
7 – <10 kg	0.75* tablet
10 – <16 kg	1 tablet
16 – <24 kg	2 tablets
24 – <30 kg	2.5* tablets
30 – <36 kg	3 tablets
36 – <46 kg	4 tablets
46 – <70 kg	4 tablets
>70 kg	5 tablets

* Fractioning of tablets into halves or quarters is not possible with [TB159 trade name]

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

When breaking of the tablet is required to allow for correct dosing, other formulations such as dispersible tablets containing lower amounts of pyrazinamide should preferably be used.

If such formulations are not available, an extemporaneous solution may be prepared by mixing the tablet(s) of [TB159 trade name] with drinking water and the following volumes of extemporaneous solution should then be taken, according to the patient's weight:

Child's weight	**Number of tablets to be mixed with water**	**Volume of water to be used**	**Volume (dose) of extemporaneous solution to be given**	**Equivalent to**
3 – <5 kg	1	10 mL of water	2.5 mL daily	0.25 tablet once daily (100 mg)
5 – <7 kg	1	10 mL of water	5 mL daily	0.5 tablet once daily (200 mg)
7 – <10 kg	1	10 mL of water	7.5 mL daily	0.75 tablet once daily (300 mg)
10 – <16 kg	1	10 mL of water	10 mL daily	1 tablet once daily (400 mg)
16 – <24 kg	2	20 mL of water	20 mL daily	2 tablets once daily (800 mg)
24 – <30 kg	3	30 mL of water	25 mL daily	2.5* tablets once daily (1000 mg)
30 – <36 kg	3	30 mL of water	30 mL daily	3 tablets once daily (1200 mg)
36 – <46 kg	4	40 mL of water	40 mL daily	4 tablets once daily (1600 mg)

For detailed instructions, see section 6.6 below: "Method of administration, extemporaneous formulation". For tuberculous meningitis different dosing regimens may apply. Current WHO treatment guidelines should be followed.

Special populations

Renal impairment

Dose adjustment is necessary in patients with CrCL <30 ml/min. It is recommended to administer the dose three times per week (not daily).

Patients on haemodialysis: On dialysis days, [TB159 trade name] should be administered after the dialysis session.

Hepatic impairment

Pyrazinamide must not be used in severe liver disease (see section 4.3).

Missed dose and vomiting after a dose

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to pyrazinamide and reduce its effectiveness.

The patient should take a missed dose if it was due fewer than 12 hours ago. If more than 12 hours have passed since the dose was due, the patient should omit the missed dose and take the next scheduled dose at the usual time. The patient should not take a double dose.

If the patient vomits within 1 hour of taking [TB159 trade name], the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.

Duration of therapy
In standard, first-line treatment of *Mycobacterium tuberculosis*, pyrazinamide is used during the first 2 months of therapy, in combination with two or three further medicines. However, the duration of 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) or the patient's status.

Method of administration
The recommended dose should be administered orally and the tablets should be swallowed whole. When only a part of a tablet is to be given, an extemporaneous formulation may be made.
[TB159 trade name] is unaffected by food and may be taken with food or between meals.
For instructions on preparing an extemporaneous formulation for children, see section 6.6.

4.3 Contraindications
[TB159 trade name] is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- severe liver impairment;
- acute gout;
- porphyria.

4.4 Special warnings and precautions for use
Patients started on [TB159 trade name] should have baseline serum uric acid and liver function determinations.
In patients with severe renal impairment (CrCl < 30 ml/min) the dose should be adjusted (see section 4.2).
Patients with impaired renal function, with a history of gout or with diabetes should be carefully monitored.
Whenever possible, the use of pyrazinamide should be avoided in patients with pre-existing hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity.
Patients at increased risk for hepatic impairment, such as drug-related hepatitis (e.g. patients with a high level of alcohol consumption) should be monitored closely.
In all patients, serum transaminase levels should be monitored during treatment with [TB159 trade name]. If transaminase levels exceed 5 times the ULN, with or without symptoms, or 3 times the ULN with jaundice and/or hepatitis symptoms, [TB159 trade name] should be discontinued and is not to be resumed.

Cross-sensitivity
Patients hypersensitive to ethionamide, isoniazid, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to [TB159 trade name].

4.5 Interaction with other medicinal products and other forms of interaction
Probenecid: There is a complex pharmacokinetic and pharmacodynamic two-way interaction between pyrazinamide and probenecid. The appropriate dose of probenecid in co-treatment has not been established. Therefore, concomitant use should be avoided.

Allopurinol: Co-administration increased the AUC of the active metabolite of pyrazinamide, pyrazinoic acid, by approximately 70%. Since pyrazinoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia.

Ofloxacin and levofloxacin: Co-treatment with pyrazinamide and either of these fluoroquinolones has been associated with a high frequency of adverse events (e.g., hepatic, gastrointestinal, musculoskeletal), leading to discontinuation of therapy; therefore, careful safety monitoring should be applied.

Sulfinpyrazone: Pyrazinamide antagonizes the effect of uricosuric agents such as probenecid and sulfinpyrazone.

Co-treatment with hepatotoxic drugs (e.g., rifampicin, isoniazid, ethionamide): Co-treatment may potentiate hepatotoxicity.
Pyrazinamide may interfere with urinary ketone determination tests that utilise the sodium nitroprusside method.
Pyrazinamide may reduce the contraceptive effects of oestrogens and should be avoided 3 days before and after oral typhoid vaccination since it may inactivate the vaccine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
There have been no well-controlled studies in pregnant women.
[TB159 trade name] should only be used if the potential benefit justifies the risk to the foetus.

Breastfeeding
Pyrazinamide is excreted in human milk. However, concentrations in breast milk are so low that breastfeeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants. No effects on the breastfed newborns/infants are anticipated.
[TB159 trade name] can be used during breastfeeding.

Fertility
No human data on the effect of [TB159 trade name] on fertility are available. Animal studies indicate that pyrazinamide has effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[TB159 trade name] is unlikely to affect the ability to drive and use machines.

4.8 Undesirable effects

The most important adverse effect of pyrazinamide is liver damage, ranging from asymptomatic increases of serum transaminases to symptomatic liver dysfunction, and in rare cases also fatal liver failure.
Adverse events considered at least possibly related to pyrazinamide treatment are listed below by body system, organ class and frequency: very common (more than 1 in 10); common (1/100 to 1/10); uncommon (1/1000 to 1/100); rare (1/10 000 to 1/1000); very rare (less than 1/10 000); and not known (cannot be estimated from the available data).

Nervous system disorders

Not known	headache, dizziness, nervousness, insomnia

Gastrointestinal disorders

Common	nausea, vomiting
Not known	abdominal cramps, anorexia

Hepatobiliary disorders

Very common	Increased liver enzymes
Uncommon	jaundice
Rare	liver failure

Metabolism and nutrition disorders
Very common hyperuricaemia
Very rare pellagra, aggravated porphyria

Renal and urinary disorders
Not known Interstitial nephritis

Skin and subcutaneous tissue disorders
Rare rash, photosensitivity reaction, urticaria

General disorders
Very common flushing
Not known malaise, fever, weight loss, allergic reactions

Blood and lymphatic systems disorders
Not known anaemia, thrombocytopenia, neutropenia

Musculoskeletal disorders
Very common arthralgia
Unknown gouty arthritis

Vascular disorders
Not known hypertension

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
Symptoms
Data on pyrazinamide overdosing are scarce. However, liver toxicity and hyperuricaemia might occur.
Treatment
Emesis and gastric lavage may be of value if undertaken within few hours. Further treatment is essentially symptomatic. Pyrazinamide is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimycobacterial. ATC code: J04AK01.
Properties: Pyrazinamide is bactericidal against intracellular mycobacterium tuberculosis.

Mechanism of action:
Pyrazinamide is a prodrug that is converted into its active form, pyrazinoic acid, by a mycobacterial enzyme, pyrazinamidase, as well as through hepatic metabolism. Pyrazinoic acid is bactericidal to *Mycobacterium tuberculosis* at acid pH values but not at neutral pH. The precise mechanism of action is unknown.
Pyrazinamide is inactive against atypical mycobacteria.
Resistance develops rapidly if pyrazinamide is used as sole antitubercular agent.

5.2 Pharmacokinetic properties

Absorption of [TB159 trade name]
The absorption characteristics of [TB159 trade name] have been determined after administration of one pyrazinamide 400 mg tablet in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
	Pyrazinamide
Maximum concentration (C_{max})	9.41 ± 2.62 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	114.1 ± 31.1 µg·h/mL
Time to attain maximum concentration (T_{max})	1.61 ± 0.94 h

*arithmetic mean

Pharmacokinetics of pyrazinamide

	Pyrazinamide
Absorption	
Absolute bioavailability	NA
Oral bioavailability	Almost completely absorbed.
Food effect	Absorption is not affected by food.
Distribution	
Volume of distribution (mean)	0.57 – 0.84 L/kg
Plasma proteinbinding *in vitro*	40 – 50%
Tissue distribution	Pyrazinamide is widely distributed to most fluid compartments and tissues. Within 5 h after administration, CSF concentrations are comparable to plasma concentrations. Excreted in human milk.
Metabolism	
	Pyrazinamide is hydrolysed by a microsomal deaminase to the active metabolite, pyrazinoic acid, which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazoinoic acid.
Elimination	
Elimination half life	about 10 h
Excreted in urine	70% within 24 h, of which 4 – 14% as unchanged drug and 30 – 40% as pyrazinoic acid
Pharmacokinetic linearity	Linear pharmacokinetics over 500 – 3000 mg

Special populations
Renal impairment
Pyrazinamide is excreted through renal elimination, mainly in the form of the active metabolite pyrazinoic acid. Hence, pyrazinamide doses should probably be reduced in patients with renal failure. A single-dose study in haemodialysis patients compared with healthy controls showed an approximately two-fold increase in pyrazinamide AUC and a 5-fold increase in the AUC of pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were estimated to be 26 and 22 hours, respectively.

Hepatic impairment
In a single dose, parallel group study comparing the pharmacokinetics of pyrazinamide in patients with severe liver disease (hypoalbuminaemia, increased INR, ascites, in most cases hyperbilirubinaemia) and healthy volunteers demonstrated a 40% reduction in pyrazinamide clearance and a 3-fold increase in the exposure to pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were increased by approximately 60% and 100%, respectively.

5.3 Preclinical safety data

Pyrazinamide was not mutagenic in the Ames test. Pyrazinamide induced chromosomal aberrations in human lymphocyte cell cultures. Pyrazinamide was not carcinogenic in rats or male mice when administered in daily doses of approximately 10-40 times the maximum recommended human dose; results in female mice could not be determined because of insufficient numbers of surviving mice in the control group.

Studies in rats with pyrazinamide showed reduced concentrations of follicle-stimulating and luteinizing hormones, estrogen, and prolactin. In mice, oral dose levels of pyrazinamide approximately 12 times those used therapeutically did not have adverse effects on sperm production. High dose level studies in rats also demonstrated decreased sperm production.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch,
Povidone
Sodium starch glycolate
Purified talc
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months for HDPE bottles and Alu/PVC blister packs.

60 months for Alu/PVDC silver-coated PVC blister packs.

6.4 Special precautions for storage

Do not store above 30ºC. Protect from moisture.

6.5 Nature and contents of container

Low density polyethylene bag further packed in HDPE container sealed with aluminium tagger. Pack size: 500 tablets.

Low density polyethylene bag further packed in HDPE container sealed with aluminium tagger. Pack size: 1000 tablets.

Alu/PVC blisters of 10 or 28 tablets. Such 3, 10 or 24 blisters are packed in a carton. Pack sizes: 30 (3x10), 84 (3x28), 100 (10x10), 240 (24x10), 280 (10x28) and 672 (24x28)

Alu/PVDC silver-coated PVC blisters of 10 or 28 tablets. Such 3, 10 or 24 blisters are packed in a box. Pack sizes: 30 (3x10), 84 (3x28), 100 (10x10), 240 (24x10), 280 (10x28) and 672 (24x28) tablets.

6.6 Special precautions for disposal and other handling

No special precautions for disposal. Any unused product or waste material should be disposed of in

accordance with local requirements.

Extemporaneous formulation for children

Two small bowls, drinking water, a teaspoon and an oral syringe are needed for preparing the extemporaneous formulation. The following steps should be applied:

1. The required number of tablets (see dosing table above) should be disintegrated in a small bowl by adding the required amount of drinking water and stirring gently.
2. The required portion of the mixture (see dosing table above) should be withdrawn with the syringe.
3. The withdrawn mixture should be mixed with additional liquid or semi-solid food to improve palatability.
4. The mixture should be administered immediately to the child.
5. Any unused mixture must be discarded.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB159

9. DATE OF PREQUALIFICATION

23 March 2007

10. DATE OF REVISION OF THE TEXT

July 2022.
Section 6.3 updated in May 2023

References

WHO consolidated guidelines on tuberculosis, Module 5: Management of tuberculosis in children and adolescents 2022. https://apps.who.int/iris/rest/bitstreams/1414329/retrieve

WHO, Geneva 2022. WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. https://apps.who.int/iris/rest/bitstreams/1414333/retrieve

WHO consolidated guidelines on tuberculosis, Module 4: Treatment Drug-resistant tuberculosis treatment 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/332397/9789240007048-eng.pdf

WHO operational handbook on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment (2020), Available at: https://apps.who.int/iris/bitstream/handle/10665/332398/9789240006997-eng.pdf

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. Available at: https://doi.org/10.1183/13993003.03300-2020

WHO consolidated guidelines on drug-resistant tuberculosis treatment (2019), World Health Organization, Geneva. Available at: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/ (accessed 21 May 2019)

WHO, Geneva 2010 Guidelines for treatment of tuberculosis. Fourth edition: http://www.who.int/tb/publications/2010/9789241547833/en/

SmPC for Zinamide 500 mg Tablets, available at: https://www.medicines.org.uk/emc/product/5273/smpc#gref (accessed on 24 January 2022)

Section 4.6 and 5.3

Briggs, Gerald G., author: Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk / Gerald G. Briggs, Roger K. Freeman, Sumner J. Yaffe. — Tenth edition.

Drug and Lactation Database (LactMed). Available at: https://www.ncbi.nlm.nih.gov/books/NBK501547/ (accessed 23 January 2022)

REPROTOX® is a service of The Reproductive Toxicology Center, A Non-Profit Foundation located at:2737 Devonshire Pl NW #120 Washington DC 20008-3459 (2018) Available at:https://reprotox.org/contact (accessed 23 January 2022)

Section 5.1

Schön T, Juréen P, Chryssanthou E, Giske CG, Sturegård E, Kahlmeter G, Hoffner S, Ängeby KA. Wild-type distributions of seven oral second-line drugs against *Mycobacterium tuberculosis*. The International Journal of Tuberculosis and Lung Disease 2011;15(4):502-509.

Lee M, Cho SN, et al. Linezolid for XDR-TB — Final Study Outcomes N. Engl. J. Med. 2016;373(3):290-291.

Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893–902.

Section 5.2

Journal of pharmaceutical sciences, vol. 97, no. 9, September 2008. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Pyrazinamide

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