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

[TB015 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg pyrazinamide.

Excipient with known effect:
Each tablet contains 0.8 mg methyl paraben. See section 4-4.
For the full list of excipients, section 6-1.

3. PHARMACEUTICAL FORM

Tablets.
[TB015 trade name] are white, smooth, round, biconvex uncoated tablets with a break line on side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB015 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

[TB015 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.

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

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 [TB015 trade name]

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 [TB015 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, [TB015 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 [TB015 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.

[TB015 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

[TB015 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 [TB015 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 [TB015 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, [TB015 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 [TB015 trade name].

Excipients
This medicine contains methyl paraben. May cause allergic reactions (possibly delayed).

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.

[TB015 trade name] should only be used if the potential benefit justifies the risk to the fetus.

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.

[TB015 trade name] can be used during breastfeeding.

Fertility

No human data on the effect of [TB015 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

[TB015 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

The absorption characteristics of [TB015 trade name] have been determined after administration of one (1) pyrazinamide 400 mg tablet in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation**
	Pyrazinamide
Maximum concentration (C_{max})	15.2 ± 3.1 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	149 ± 29 µg·h/mL
Time to attain maximum concentration (T_{max})	0.89 ± 0.54 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 protein binding *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

Starch
Gum acacia
Methyl paraben/ methyl p-hydroxybenzoate
Purified talc
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs
PVC -printed aluminium blister. Each blister card contains 10 tablets. Such 10 blister cards are packed in a carton. Pack size: 10 x 10 tablets.
PVC/PVDC -printed aluminium blister. Each blister card contains 28 tablets. Such 24 blister cards are packed in a carton. Pack size: 24 x 28 tablets.

HDPE Bottle
1000 tablets are packed in a transparent polypropylene bag placed in a HDPE bottle with a cap.

6.6 Special precautions for disposal and other handling

No special precautions.

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)

TB015

9. DATE OF PREQUALIFICATION

13 November 2003

10. DATE OF REVISION OF THE TEXT

October 2022

References

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Section 4.6 and 5.3

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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

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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

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