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

[TB307 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pyrazinamide 150 mg

Each tablet contains 2 mg of aspartame.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, circular, biconvex, uncoated tablets having break line on one side and plain surface on other side.

The tablet cannot be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB307 trade name] is indicated in children under 15 years of age 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.

This product is intended for use in children. Nevertheless, information is included on risks relevant to adults (for example, use in liver disease, pregnancy and breastfeeding); this provides access to the full information.

4.2 Posology and method of administration

Posology

[TB307 trade name] must always be 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 for patients less than 15 years of age (children and adolescents)

The recommended weight-based daily dose is 30–40 mg/kg body weight.

Weight	Daily dose
3 – <5 kg	0.5 tablet
5 – <7 kg	1 tablet
7 – <10 kg	2 tablets
10 – <16 kg	3 tablets
16 – <24 kg	5 tablets
24 – <30 kg	–*
30 – <36 kg	–*
36 – <46 kg	–*

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

* In these patients, other formulations containing higher amounts of pyrazinamide should be used.

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, [TB307 trade name] should be administered after the dialysis session.

Hepatic impairment

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

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.

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 [TB307 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.

Method of administration

Oral use. [TB307 trade name] is unaffected by food and may be taken with food or between meals.

The required number of [TB307 trade name] should be dispersed in approximately 50 ml of water and the entire mixture should be swallowed. The mixture (tablets dispersed in water) should be used within 10 minutes. An additional volume of water should then be consumed immediately. When administering the dose to patients weighing between 3 kg and 5 kg, only give half of the mixture prepared using 1 tablet. Discard any remaining mixture.

4.3 Contraindications

[TB307 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 [TB307 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 [TB307 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, [TB307 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 [TB307 trade name].

Excipients

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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.

[TB307 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.

[TB307 trade name] can be used during breastfeeding.

Fertility

No human data on the effect of [TB307 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

[TB307 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 [TB307 name] have been determined after administration of tablets of [TB307 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation** (*)
Maximum concentration (C_{max}) ng/ml	38.9 ± 7.2 (38.3)
Area under the curve (AUC_{0-t}), a measure of the extent of absorption ng.hour/ml	499 ± 68 (496)
Time to attain maximum concentration (t_{max}) hour	1.03 ± 0.71

*geometric 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
Sodium starch glycolate
Povidone
Microcrystalline cellulose
Croscarmellose sodium
Crospovidone
Colloidal anhydrous silica
Strawberry flavour
Aspartame
Purified talc
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, in dry place. Protect from light.
Keep this medicine out of the reach and sight of children.

6.5 Nature and contents of container

100 Tablets are packed in a triple laminated sachet and then placed in a round, white, HDPE container with PP closure.

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

Macleods Pharmaceuticals Limited
304, Atlanta Arcade,
Marol Church road
Andheri (East),
Mumbai – 400 059
India

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB307

9. DATE OF PREQUALIFICATION

7 December 2016

10. DATE OF REVISION OF THE TEXT

September 2022

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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.

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Section 5.1

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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