▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

PYRAZINAMIDE–AFT (pyrazinamide)

Tablet

1 NAME OF THE MEDICINE

Pyrazinamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains 500 mg pyrazinamide.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White to off-white colour round tablet, one side impressed with “YSP” and the other side with a score.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pyrazinamide-AFT is indicated in adult patients of more than 12 years of age with active drug-sensitive tuberculosis caused by *Mycobacterium tuberculosis*. Pyrazinamide-AFT is an anti-tuberculosis agent used in combination with other anti- tuberculosis agents and is commonly used in the first 2 months of treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Usual dose: Pyrazinamide is administered orally, 15 to 30 mg/kg once daily.

Older regimens employed 3 or 4 divided doses daily, but most current recommendations are for once a day. Three grams per day should not be exceeded. The CDC recommendations do not exceed 2 g per day when given as a daily regimen.

Alternatively, a twice weekly dosing regimen (50 to 75 mg/kg twice weekly based on lean body weight) has been developed to promote patient compliance with a regimen on an outpatient basis. In studies evaluation the twice weekly regimen, doses of Pyrazinamide in excess of 3 g twice weekly have been administered. This exceeds the recommended maximum 3 g/daily dose. However, an increased incidence of adverse reactions has not been reported. Pyrazinamide-AFT should be administered with at least one other effective anti-tuberculous medicine. The use of Pyrazinamide-AFT in combination therapy does not modify the accepted dosages of other anti-tuberculous agents.

4.3 CONTRAINDICATIONS

- Patients who are hypersensitive to any component of this product.
- Patients with hepatic disease.
- Patients with hyperuricaemia and/or gouty arthritis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Laboratory tests

Pyrazinamide-AFT should be used only when close daily observation of the patient is possible, and when laboratory facilities are available for performing frequent liver function tests and blood uric acid determinations.

Baseline liver function studies [especially ALT (SGPT), AST (SGOT) determinations] and uric acid levels should be determined prior to therapy. Appropriate laboratory testing should be performed at periodic intervals and if any clinical signs of symptoms occur during therapy.

Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, pain or swelling of the joints.

Therapy with Pyrazinamide-AFT should be withdrawn and not reinstated if signs of hepatocellular damage occur.

Pre-treatment examinations should include *in vitro* sensitivity tests of recent cultures of *M. tuberculosis* from the patients as measured against the usual anti-tuberculous medicines.

Acute gouty arthritis

If hyperuricaemia accompanied by an acute gouty arthritis occurs, therapy should be discontinued and not reinstated. Pyrazinamide-AFT should be used with caution in patients with a history of gout or diabetes mellitus, as their management may become more difficult.

Renal insufficiency

In the presence of renal insufficiency reduction in size and/or frequency of dose is recommended.

Diabetes mellitus

Increased difficulty in controlling diabetes mellitus has been reported when diabetics are given pyrazinamide.

Nursing mothers

Pyrazinamide has been found in small amounts in breast milk. Therefore, it is advised that pyrazinamide be used with caution in nursing mothers taking into account the risks and benefit of treatment.

Use in children

There is less clinical information examining the use of pyrazinamide in children than in adults. Pyrazinamide should be used with caution in children when control of tuberculosis disease is necessary.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Probenicid is known to block the excretion of pyrazinamide.

Pyrazinamide and its active metabolite, pyrazinoic acid are metabolised by xanthine oxidase. Drugs that inhibit xanthine oxidase activity (such as allopurinol) may increase plasma concentrations of pyrazinamide and pyrazinoic acid.

Pyrazinamide inhibited the expression of hepatic transporters, BSEP and OATP1A1 in rats. It may reduce the elimination of drugs that are cleared by BSEP-mediated biliary excretion or OATP1A1 substrates that are predominantly cleared by hepatic metabolism.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In female rats, subclinical doses of pyrazinamide elicited significant disruption of endocrine balance (reduced levels of luteinizing hormones, prolactin and estrogen), and induced ovarian and uterine oxidative stress and histopathology of reproductive organs (erosion of uterine mucosa, and congestion and underdeveloped follicles in ovaries). In male mice, subclinical doses of pyrazinamide caused histological lesions in testes (including degeneration of seminiferous epithelium and Sertoli cells). Decreased volume and spermatogonia numbers, and epithelium desquamation and exfoliation of testes and testis and epididymis DNA fragmentation were reported in male rats treated with pyrazinamide at 2000 mg/kg/day (12 times the maximum recommended clinical dose [MRHD] per body surface area). Male rats dosed with pyrazinamide, isoniazid, rifampicin and ethambutol at 217, 62, 74.4 and 155 mg/kg/day PO, respectively, and mated with untreated females resulted in significantly lower fertility index and increased pre- and post-implantation losses than the control group.

Use in pregnancy

Category B2

There are no well-controlled studies in pregnant women. Pyrazinamide-AFT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In mice orally dosed with pyrazinamide at up to 3000 mg/kg/day (9 x the maximum recommended clinical dose [MRHD] per body surface area) during organogenesis, no effects on embryofetal development were observed (fetuses were only examined for external abnormalities, and not examined for visceral or skeletal abnormalities).

Use in lactation

Pyrazinamide is excreted in breast milk. If use of Pyrazinamide-AFT is deemed essential to a nursing mother, the patient should stop nursing.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no data to suggest that pyrazinamide affects the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequent adverse effect is hepatotoxicity. Transient increases in serum aminotransferase (transaminase) concentrations, jaundice, hepatitis and a syndrome of fever, anorexia, malaise, liver tenderness, hepatomegaly and splenomegaly have been reported. Rarely acute yellow atrophy of the liver and death have occurred. Hepatotoxicity appears to be dose related and may occur at any time during therapy. Hepatotoxicity occurs in approximately 10-25% of patients with jaundice occurring in 2-3%.

Pyrazinamide inhibits renal excretion of urates frequently resulting in hyperuricemia. This effect is usually asymptomatic but acute gout has occurred in some patients. Nongouty polyarthralgia reportedly occurs in up to 40% of patients. Urisuric agents administered concurrently may reduce pyrazinamide induced hyperuricemia. If hyperuricemia is severe or accompanied by acute gouty arthritis, treatment with pyrazinamide should be discontinued.

Mild arthralgia and myalgia have been reported frequently with pyrazinamide therapy.

Maculopapular rash, fever, acne, porphyria, dysuria, interstitial nephritis and photosensitivity with reddish-brown discolouration of the exposed skin have been reported rarely.

Hypersensitivity reactions including rash, urticaria and pruritus have been reported.

Gastrointestinal disturbances including aggravation of peptic ulcer, nausea, vomiting and anorexia have also occurred.

Thrombocytopenia and sideroblastic anaemia with erythroid hyperplasia, vacuolation of erythrocytes and increased serum iron concentrations have occurred rarely. Adverse effects on blood clotting mechanisms have also been reported rarely.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The stomach should be emptied by emesis or gastric lavage. Short acting barbiturates may be given for manifestations of CNS stimulation, analeptics for coma and artificial respiration and oxygen for respiratory failure, In the event of shock, a vasopressor agent, metaraminol bitartrate, should be given.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pyrazinamide (PZA) is a prodrug that is converted to the active form pyrazinoic acid (POA) by pyrazinamidase/nicotinamidase encoded by the pncA gene in M. tuberculosis. PZA is generally active only at an acid pH. The precise mechanism of action is unknown. Possible mechanisms of antibacterial activity include: (1) activation of the sigma factor (SigE)-dependent cell envelope stress response, (2) binding of POA to asparate decarboxylase (PanD), and (3) POA binding to ribosomal protein S1 (RpsA) of M. tuberculosis. Inhibition of fatty acid synthesis may also contribute to the activity of POA.

Resistance develops rapidly if pyrazinamide is used as sole antitubercular agent. Loss of pyrazinamidase activity, mutations in pncA, RpsA or pan D genes may confer PZA resistance.

5.2 PHARMACOKINETIC PROPERTIES

Pyrazinamide is readily absorbed from the gastro-intestinal tract with peak serum concentration being reached about 2 hours after taking the dose. Plasma concentrations of pyrazinoic acid, which is the major metabolite, are generally greater than those of pyrazinamide and peak 4-8 hours after dosing.

Pyrazinamide is widely distributed in body tissues and fluids including the liver, lungs and CSF. It is not known of pyrazinamide crosses the placenta but it is excreted in breast milk.

Pyrazinamide is metabolised primarily in the liver by hydrolysis to pyrazinoic acid which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidney mainly by glomerular filtration. Approximately 70% of a dose appears in the urine within 24 hours (mainly as metabolites with 4-14% as pyrazinamide)

The plasma half-life is 9-10 hours in patients with normal renal and hepatic function. The plasma half-life may be prolonged in patients with impaired renal or hepatic function.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Pyrazinamide was assessed for mutagenicity in Ames test, DNA damage by the comet assay and chromosome aberrations by the micronucleus assay and chromosomal aberration assay. Pyrazinamide was mutagenic in Ames bacterial assay. Increased bone marrow micronuclei were observed in mice after a single dose of pyrazinamide at ≥ 250 mg/kg IP. Chromosomal aberrations of bone marrow cells and DNA damage of spleen cells were increased in rats treated with pyrazinamide (132.65 mg/kg/day PO for 28 days) in combination with isoniazid and rifampicin. In another rat study, micronuclei in blood cells were not increased following treatment with pyrazinamide (189 mg/kg/day for 90 days) or pyrazinamide in combination with other anti-TB drugs, but DNA damage

was evident in liver, kidney and blood cells. Based on *in vivo* study findings, pyrazinamide is considered to be genotoxic.

Carcinogenicity

Carcinogenicity studies in mice and rats were conducted where pyrazinamide was administered in the diet of mice and rats for 78 weeks. The estimated daily dose was 0.75 or 1.5 g/kg (2-5 times the MRHD per body surface area) for the mouse, and 0.25 or 0.5 g/kg (1.5-3 times the MRHD per body surface area) for the rat. Pyrazinamide was not carcinogenic in rats or male mice. No conclusion was possible for female mice due to insufficient numbers of surviving control mice.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate

Colloidal anhydrous silica

Stearic acid

6.2 INCOMPATIBILITIES

None known.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

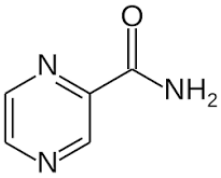
HDPE bottles of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Pyrazinamide (pyrazinoic acid amide, or pyrazixe carboxylamide), has the following structural formula:



CAS number: 98-96-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 SPONSOR

AFT Pharmaceuticals Pty Ltd.

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North Ryde, NSW 2113, Australia

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

2 May 2025

10 DATE OF REVISION

XXX

Summary table of changes

Section changed	Summary of new information