

# NEW ZEALAND DATA SHEET

## 1 PDP-PYRAZINAMIDE

pdp-Pyrazinamide 500mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg of pyrazinamide

## 3 PHARMACEUTICAL FORM

pdp-PYRAZINAMIDE is available as white round tablets, scored on one side with "PMS" on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

pdp-PYRAZINAMIDE is indicated in patients with active tuberculosis caused by *Mycobacterium tuberculosis*. pdp-PYRAZINAMIDE is not active against the atypical mycobacteria. pdp-PYRAZINAMIDE should be given only in combination with other effective anti-tuberculous agents.

### 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. pdp-PYRAZINAMIDE should be administered with at least one other effective anti-tuberculous medicine. The use of pdp-PYRAZINAMIDE in combination therapy does not modify the accepted dosages of other anti-tuberculous agents.

The tablet should not be divided.

### 4.3 Contraindications

- Patients who are hypersensitive to any component of this product;
- Patients with hepatic disease
- Patients with hyperuricaemia and/or gouty arthritis.
- Safety for use in children has not been established
- Nursing mothers. If use of this medicine is deemed essential, the patient should stop nursing.

## NEW ZEALAND DATA SHEET

### 4.4 Special warnings and precautions for use

pdp-PYRAZINAMIDE 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.

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. Adverse effects for pdp-PYRAZINAMIDE primarily involve the liver and vary from asymptomatic elevations of liver function tests to serious clinical manifestations of hepatic disease; therefore, liver function tests, especially alanine transaminase (ALT) and aspartate transaminase (AST) determinations, should be carried out prior to therapy, and then every two to four weeks during therapy. Therapy with pdp-PYRAZINAMIDE should be withdrawn and not reinstated if signs of hepatocellular damage occur.

Pre-treatment examinations should also include baseline serum uric acid determinations. pdp-Pyrazinamide inhibits renal excretion of urates, frequently resulting in hyperuricemia that is usually asymptomatic. If hyperuricaemia accompanied by an acute gouty arthritis occurs, therapy should be discontinued and not reinstated. pdp-PYRAZINAMIDE should be used with caution in patients with a history of gout or diabetes mellitus, as their management may become more difficult.

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

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

#### Use in Children

The safety of pdp-PYRAZINAMIDE for use in children has not been established. Because of its potential toxicity, the use of pdp-PYRAZINAMIDE in children should be avoided unless it is considered crucial.

### 4.5 Interaction with other medicines and other forms of interaction

Probenicid is known to block the excretion of pyrazinamide.

### 4.6 Fertility, pregnancy and lactation

Category B2

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

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

## NEW ZEALAND DATA SHEET

### 4.7 Effects on ability to drive and use machines

There is no data to suggest that pdp-PYRAZINAMIDE affects the ability to drive or use machines.

### 4.8 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. With a dose of 3g daily, hepatotoxicity occurs in approximately 15% 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

### 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.

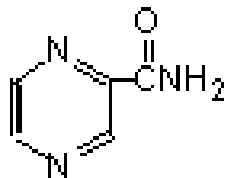
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# NEW ZEALAND DATA SHEET

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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



PYRAZINAMIDE-AFT tablets contain corn starch.

Pyrazinamide is a highly specific agent having a bactericidal effect on *Mycobacterium tuberculosis* but no activity against other mycobacteria or micro-organisms in vitro. Results of in vitro susceptibility testing with pyrazinamide are affected by the test media, inoculum size and pH. The MIC for *M. tuberculosis* is less than 20 µg/mL at pH 5.6 but it is almost completely inactive at a neutral pH. Pyrazinamide is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages.

The exact mechanism of action has not been fully elucidated but appears to partly depend on conversion of pyrazinamide to pyrazinoic acid. Susceptible strains of *Mycobacterium tuberculosis* produce pyrazinamidase which is an enzyme that deaminates pyrazinamide to pyrazinoic acid. The in vitro susceptibility of a given strain of the organism appears to correspond to its pyrazinamidase activity.

### 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 if 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

No relevant information.

## 6 PHARMACEUTICAL PARTICULARS

# NEW ZEALAND DATA SHEET

## 6.1 List of excipients

Colloidal silicon dioxide  
Microcrystalline cellulose  
Pregelatinised maize starch  
Starch  
Stearic acid

## 6.2 Incompatibilities

None known.

## 6.3 Shelf life

36 months.

## 6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture.

## 6.5 Nature and contents of container

Bottles of 100 tablets.

## 6.6 Special precautions for disposal

No special requirements.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

AFT Pharmaceuticals Ltd  
PO Box 33.203  
Takapuna  
Auckland  
Email:customer.service@aftpharm.com

## 9 DATE OF FIRST APPROVAL

12 October 2006

## 10 DATE OF REVISION OF THE TEXT

06 September 2018

## SUMMARY TABLE OF CHANGES

<b>Date</b>	<b>Section(s) Changed</b>	<b>Change (s)</b>
06 September 2018	All	Reformat consistent with new Medsafe Data Sheet Template.