

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pyrazinamide 150mg tablets

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 can not be divided into equal halves.

4. CLINICAL PARTICULARS**Therapeutic indications:**

Pyrazinamide 150mg Dispersible Tablets is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis* in children.

Consideration should be given to official guidelines on treatment of tuberculosis, e.g. by WHO.

This product is intended for use in children. Nonetheless information is provided on adult health issues such as pregnancy and lactation, to allow full access to all relevant information.

Posology and method of administration

Oral use

Pyrazinamide 150mg Dispersible Tablets must always been given in combination with other antituberculosis agents.

Daily regimen**Children:**

35 mg/kg (30-40 mg/kg) body weight as a single daily dose.

Number of Pyrazinamide 150mg Dispersible Tablets for daily treatment according to weight bands

Weight in kg	4-6	7-10	11-14	15-19	20-24
Number of tablets per day	1	2	3	4	5

Intermittent regimen

35 mg/kg (30-40 mg/kg) body weight 3 times a week.

Pyrazinamide 150mg Dispersible Tablets should preferably be taken without food.

The required number of Pyrazinamide 150mg Dispersible Tablets should be dispersed in approximately 50 ml 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.

Pyrazinamide 150mg Dispersible Tablets is not suitable for patients weighing less than 4 kg.

Renal impairment:

Dose adjustment is necessary in patients with CrCL <30 ml/min. It is recommended to administer 20-30 mg/kg per dose three times per week (not daily).

Patients on haemodialysis: On dialysis days, Pyrazinamide 150mg Dispersible Tablets should be administered after the dialysis session.

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

Children and adolescents: Appropriate studies on the relationship of age to the effects of pyrazinamide have not been performed in the paediatric population. However, no paediatrics-specific problems have been documented to date.

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 drugs. However, the duration of antituberculous 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 (see e.g. WHO guidelines on treatment of TB).

Contraindications

Pyrazinamide 150mg Dispersible Tablets is contraindicated in patients with

- hypersensitivity to the active substance or to any of the excipients,
- severe liver impairment or
- acute gout.

Special warnings and special precautions for use

Patients started on Pyrazinamide 150mg Dispersible Tablets 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 preexisting 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 followed closely.

In all patients, serum transaminase levels should be monitored during treatment with Pyrazinamide 150mg Dispersible Tablets. If transaminase levels exceed five times the ULN, with or without symptoms, or three times the ULN with jaundice and/or hepatitis symptoms, Pyrazinamide 150mg Dispersible Tablets 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 Pyrazinamide 150mg Dispersible Tablets.

Warning on special excipients:

Contains a source of phenylalanine. May be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in children below 12 weeks of age. Therefore aspartame containing medicinal products should be used with caution in this age group.

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% (6). 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 (8,9). When co-treatment is deemed necessary, careful safety monitoring should be applied.

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.

Pregnancy and lactation

No adverse effects of pyrazinamide on the fetus have been reported. However, it is to be used only when the benefits outweigh the potential risks.

Pyrazinamide is excreted into the breast milk of lactating mothers. No adverse effects in the baby have been reported.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Pyrazinamide 150mg Dispersible Tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

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 (4). Adverse events considered at least possibly related to pyrazinamide treatment are listed below by body system, organ class and frequency. Frequency estimates are in many cases not based on adequately sized randomised trials, but on published data generated during post-approval use. Often, no frequency data can be given. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100, <1/10$), uncommon ($\geq 1/1000, <1/100$), rare ($\geq 1/10000, <1/1000$), very rare ($<1/10000$), 'not known'.

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.

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; there is no specific antidote. Pyrazinamide is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial
ATC Code for Pyrazinamide: 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 (13). The precise mechanism of action is unknown. Pyrazinamide is inactive against atypical mycobacteria (13). Resistance develops rapidly if pyrazinamide is used as sole antitubercular agent.

Pharmacokinetic properties

Absorption:

Pyrazinamide is almost completely absorbed from the gastrointestinal tract. Following single dose administration of ten tablets Pyrazinamide 150mg Dispersible Tablets in healthy volunteers, the mean (SD) pyrazinamide C_{max} value was 38.9 µg/ml (±7.2) and the corresponding values for AUC_{0-t} was 499 µg*hr/ml (±68) and AUC_{0-inf} was 520 µg*hr/ml (±76). The mean pyrazinamide t_{max} value was 1.03 (± 0.71) hours.

Distribution:

Pyrazinamide is widely distributed to most fluid compartments and tissues. The volume of distribution has been reported as 0.57-0.84 l/kg (10). The plasma protein binding of pyrazinamide is low, approximately 10-20%.

Metabolism:

Pyrazinamide is hydrolysed by a microsomal deaminase to the active metabolite, pyrazinoic acid, which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid.

Elimination:

Pyrazinamide is eliminated renally, mostly in the form of various metabolites. Approximately 3% of a pyrazinamide dose is eliminated unchanged (14). The half-life of pyrazinamide is approximately 10 hours. The half-life for the active metabolite pyrazinoic acid after a single dose is approximately 10-20 hours.

Pharmacokinetics in special populations

Impaired renal function: 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 twofold 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 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 threefold increase in the exposure to pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were increased by approximately 60% and 100%, respectively.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or reproduction toxicity.

6. PHARMACEUTICAL PARTICULARS

List of Excipients

Maize starch, sodium starch glycolate, povidone, microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal anhydrous silica, strawberry flavour, aspartame, purified talc, magnesium stearate

Incompatibilities

Not applicable

Shelf life

36 months

Special precautions for storage

Store below 30°C, in dry place. Protect from light.

Keep out of the reach and sight of children.

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.

Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME) MARKETING AUTHORISATION NUMBER

04067/4029/NMR/2017

9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 27, 2021

10. DATE OF REVISION OF THE TEXT:

February 2019

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