SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pyrazinamide 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 500 mg pyrazinamide.

Excipient(s) with known effect: Lactose

Each 500mg tablet contains 124.5 mg of Lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
White, flat, circular bevelled edge, uncoated tablets with score line on one side and other side is plain.

The score line is only for aesthetic purposes/to facilitate swallowing of the tablets and not for subdivision of tablets, i.e. not for the purpose of providing part doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Pyrazinamide 500mg tablets is indicated in patients with active tuberculosis caused by *Mycobacterium tuberculosis*. Pyrazinamide should only be given in combination with other antituberculous agents. Pyrazinamide is not active against the atypical mycobacteria.

Consideration should be given to official guidance on the appropriate use of antituberculosis agents.

4.2 Posology and method of administration
Pyrazinamide should be administered under the supervision of a physician trained in the management of tuberculosis.

Posology
**Adults and adolescents**

Recommended dosage for standard unsupervised 2-month treatment

Under 50 kg bodyweight: maximum 1.5g Pyrazinamide = 3 Pyrazinamide 500 mg Tablets
Over 50kg bodyweight: maximum 2.0 g pyrazinamide = 4 Pyrazinamide 500 mg Tablets

Recommended dosage for intermittent supervised 2-month therapy (only if daily administration is not feasible)

Under 50 kg bodyweight: 2.0 g Pyrazinamide = 4 Pyrazinamide 500 mg Tablets 3 times a week.
Over 50 kg bodyweight: 2.5 g Pyrazinamide = 5 Pyrazinamide 500 mg Tablets 3 times a week.

**Children**

Recommended dosage for standard unsupervised 2-month treatment: 35 mg / kg body weight per day
Maximum daily dose: 1.5 g

Equivalent in children aged 4-10
0.5-1 g Pyrazinamide = 1-2 Pyrazinamide 500 mg Tablets

And in children aged 11-14
1-1.5 g Pyrazinamide = 2-3 Pyrazinamide 500 mg Tablets

Recommended dosage for intermittent supervised 2 month regimen (only if daily regimen not feasible):

Dosage 50 mg/kg body weight, three times weekly

**Method and duration of administration**

**Method of administration**
Pyrazinamide is used in combination with other antitubercular agents.

**Duration of administration**
In standard tuberculosis treatment, Pyrazinamide is given together with other antituberculosis medication during the initial phase of treatment over a total of 8 weeks. In order to prevent recurrent infection, Pyrazinamide treatment can be continued up to 3 months.

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**4.3 Contraindications**

Pyrazinamide is contraindicated in patients with
- severe hepatic impairment, acute liver disease (e.g. hepatitis) and up to 6 months after occurrence of hepatitis
- acute porphyria
- acute gouty arthritis
- Allergy to pyrazinamide or any of the excipients of Pyrazinamide 500 mg Tablets (See section 6.1)

4.4 Special warnings and precautions for use

Pre-treatment examinations should include renal function, hepatic function and particularly base-line uric acid determinations

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

Patients with a regularly high level of alcohol consumption or alcohol abuse and patients taking other potentially hepatotoxic medications or substances are particularly at risk. Patients with pre-existing impairment of the liver and higher susceptibility (e.g. with concomitant alcoholism) must undergo more frequent liver testing.

Patients or their carers should be told how to recognize signs of liver disease, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Patients suffering from gout should be prescribed this medication only if urgent treatment is required.

In patients with renal impairment, the medication should be prescribed in emergencies only. Here, pyrazinamide should be administered intermittently (see section 4.2). Liver and kidney function should be tested before initiating treatment.

Regular liver and kidney function tests should be carried out before and during treatment, at intervals of about 3 - 4 weeks.

High-dose treatment (above standard dosage) may interfere with insulin levels in diabetic patients.

Pyrazinamide inhibits excretion of urates, frequently resulting in hyperuricaemia which is usually asymptomatic. Infrequently, hyperuricaemia (see section 4.8) may cause arthralgia, especially in susceptible patients. Urea levels in the bloodstream should therefore monitored regularly (every 3 - 4 weeks). If hyperuricaemia accompanied by an acute gouty arthritis occurs, therapy should be discontinued and not reinstated. Massively elevated urea levels may require treatment with uricosurics, such as benzbromarone.
Close monitoring is advised to detect any increasing difficulty in the management of patients with a history of gout or diabetes mellitus. If hyperuricaemia accompanied by an acute gouty arthritis occurs, treatment with pyrazinamide should be discontinued.

Pyrazinamide treatment may elicit photosensitivity (see section 4.8). Patients treated with pyrazinamide should therefore not be exposed to strong sunlight.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Compared to fast acetylators, individuals known as slow acetylators have a higher risk of liver intoxication during combination treatment of Pyrazinamide, rifampicin and isoniazid.

Treatment with Pyrazinamide may affect the following lab parameters:
Bilirubin, urea levels, prothrombin time, serum-aminotransferase levels, thyroxin levels.

Pyrazinamide was found to interfere with the determination of serum iron with Ferrochem II.

4.5 Interaction with other medicinal products and other forms of interaction

Undesirable interaction may occur in combination with the following drugs:

Acetyl salicylic acid, ascorbic acid, radiocontrast agents containing iodine, gout medication that affects the excretion of urea, such as probenecid (Pyrazinamide antagonizes the effects of probenecid and sulfinpyrazone), blood glucose-lowering medication (accelerates lowering of blood sugar levels). Patients taking blood glucose-lowering medication and those taking gout medications must therefore be monitored more closely.

Pyrazinamide may reduce rifampicin blood levels (reduced bioavailability and enhanced rifampicin clearance). No further information available.
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.

Alcohol should not be taken during pyrazinamide treatment, as this could increase the risk of damage to the liver and significantly impair reactivity.

4.6 Fertility, Pregnancy and lactation

No sufficient clinical data on pregnant women exposed to Pyrazinamide exist. Animal studies do not suggest any detrimental effect on pregnancy, embryonic/foetal development, birth or postnatal development (see section 5.3).
Pyrazinamide is excreted into the breast milk of lactating mothers. Pyrazinamide should only be administered to pregnant and lactating women when the benefit clearly outweighs the risk.

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

Even when used appropriately, Pyrazinamide may impair a patient's reactions to such an extent that it affects the ability to drive, use machines or work without secure support.

4.8 **Undesirable effects**

<table>
<thead>
<tr>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1.000 to &lt;1/100)</th>
<th>Rare (≥1/10.000 to &lt;1/1.000)</th>
<th>Very rare (&lt;1/10.000)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of the blood and lymphatic system</td>
<td></td>
<td></td>
<td>Haematopoietic system disorders, sideroblastic anaemia, porphyria, thrombocytopenia with or without purpura, splenomegaly</td>
<td></td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td>Impairs adrenocortical function (17-ketosteroid-excretion in urine)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td>Pellagra</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Headache, dizziness, irritability, insomnia</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Loss of appetite, nausea,</td>
<td></td>
<td></td>
<td>Aggravation of peptic</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Frequentity</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/10.000 to &lt;1/1/000)</th>
<th>Rare (≥1/10.000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10.000)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sickness, vomiting, heartburn, abdominal spasms, weight loss</td>
<td></td>
<td></td>
<td></td>
<td>ulcer</td>
</tr>
</tbody>
</table>

**Hepatobiliary disorders**

- Raised serum transaminase levels, liver function disorders
- Hepatomegaly, jaundice, hepatic failure (which may be fatal)

**Skin and subcutaneous disorders**

- Photosensitivity (see Section 4.4)
- Erythema multiforme
- Flushing, dysuria, rash, urticaria, pruritus

**Renal and urinary disorders**

- Hyperuricaemia (see Section 4.4)
- Tubulo-interstitial nephritis

**General and administration site disorders**

- Hypertension
- Fever, malaise

**Musculoskeletal, connective tissue and bone disorders**

- Gout, arthralgia

**Immune system disorders**

- Angioedema

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**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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard
4.9 Overdose

Overdose symptoms
Specific pyrazinamide intoxication symptoms are not known. However, known undesired effects (see section 4.8) may be enhanced. Liver toxicity and hyperuricaemia may occur with overdosage.

In one study, flushing with pruritus on the entire skin surface was observed immediately after taking 4g of pyrazinamide, but disappeared after a few hours without any lasting effect.

Overdose treatment
In an emergency, intensive medical care is required, including gastric lavage. There is no specific antidote. Pyrazinamide and its metabolites are haemodialysable (see section 5.2).
General supportive measures should be employed. Liver function should be monitored closely, and a high-carbohydrate, low-fat diet employed. Care should be taken to avoid exposure of the patient to other potential hepatotoxic agents, including alcohol. Probenecid may be given for hyperuricaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Medication for the treatment of tuberculosis, ATC code: J04AK01

Mechanism of action
Under in vitro conditions, Pyrazinamide is hardly or not at all effective against most strains of Mycobacterium bovis and atypical mycobacteria. There is a cross-resistance to morphazinamide, a Pyrazinamide-derivative. No other cross-resistances to antitubercular agents are known.

The action mechanism of Pyrazinamide against tuberculosis pathogens is not known. Due to its similarity to nicotinamide, Pyrazinamide is intracellularly converted by nicotinic acid amidase (also known as pyrazinamidase) into pyrazinoic acid, which has an antimycobacterial effect.

Resistance mechanism
Acquired resistance of susceptible pathogens from clinical isolates is mainly caused by a mutation on the pncA gene. The gene encodes the enzyme pyrazinamidase, which converts pyrazinamide into its active bactericidal form pyrazinoic acid. The mutation on the pncA gene or its promoter region inhibits this process in bacteria.

Approximately 70 - 97 % of all pyrazinamide-resistant Mycobacterium tuberculosis isolates carry this mutation, whereas a small proportion of resistant strains (3-30 %) show no changes in the pncA gene and/or the
promoter region. Variable resistance rates and pyrazinamidase activity has been observed. The underlying mechanism of the resistance is not known.

Mycobacterium tuberculosis resistance to pyrazinamide develops rapidly in an *in vitro* situation and in patients treated solely with pyrazinamide.

**Resistance status**
The prevalence of acquired pyrazinamide resistance in tuberculosis caused by *Mycobacterium tuberculosis* - the most frequently found and reported pathogen - varies depending on time and location.

### 5.2 Pharmacokinetic properties

**Absorption**
Pyrazinamide is administered orally and absorbed rapidly by the gastrointestinal tract. Maximum serum levels (approx. 33 µg/mL after administration of 1.5 g of Pyrazinamide and approx. 65 µg/mL after administration of 3 g of Pyrazinamide) are reached after 1 - 3 hours.

**Distribution**
There are no consistent data on the distribution and penetration of Pyrazinamide.

**Biotransformation**
In humans, Pyrazinamide is mainly metabolised in the liver-microsomal P-450 cytochrome system converting pyrazinamide into pyrazinoic acid, which, in turn, is converted by xanthinoxidase into 5-hydroxy-pyrazinoic acid, the end product of the Pyrazinamide metabolism that is completely excreted through the kidneys. Other Pyrazinamide metabolites are probably less important.
The conversion of Pyrazinamide into pyrazinoic acid in humans is a slow process and, in connection with the relatively slow renal excretion, explains the fairly long half-life of Pyrazinamide (see below).

**Elimination**
Pyrazinamide is eliminated though renal excretion only. Over 24 hours, approximately 70 % of the oral Pyrazinamide dose is eliminated, predominantly through glomerular filtration. About 4 - 14 % are excreted unmodified, while the rest forms metabolites.

Elimination half life is between 4 and 17 hours with statistically significant individual differences.

**Linearity**
Within the range of 0.5 to 3 g, Pyrazinamide serum concentrations are directly proportionate to the dose.

**Pharmacokinetics in special populations:**
**Impaired renal function**

Studies in patients with renal failure have shown that Pyrazinamide, pyrazinoic acid, 5-hydroxy- Pyrazinamide and 5-hydroxy- pyrazinoic acid can be eliminated effectively through haemodialysis.

**Hepatic impairment**

In patients with hepatic failure, increased clearance and longer Pyrazinamide half-lives were observed, as well as an exposure (AUC) increased by a factor of 3 and a double pyrazinoic acid half-life.

See section 4.4 regarding monitoring requirements.

**Children**

Compared to adults, the proportion of children with incomplete or delayed Pyrazinamide absorption may be higher. No further information is available.

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**5.3 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, toxicity to reproduction and development.

In animal studies, Pyrazinamide proved to be a medication that was well absorbed and tolerated and of very low toxicity. Its toxicity is well below the toxicity of other antitubercular agents.

A dose of 3.0 g/kg body weight was lethal to approximately 30% of mice and rats. Significant reactions with signs of serious liver toxicity (increased amino transferase parameters and icterus) were observed in dogs with Pyrazinamide levels of 1.0 g/kg body weight. The reactions occurred just before the death of the animals, with extensive liver necrosis.

An oral dose of 1.5 g/kg body weight over several weeks was well tolerated by mice and rats. Many animal studies showed that a dose of 500 mg/kg body weight did not cause any (histologically) manifest liver damage.

The many studies show beyond doubt that Pyrazinamide only has toxic effects at very high doses of 1.5-3.0 g/kg body weight (depending on the animal species).

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**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose monohydrate, maize starch, pregelatinised starch, talc, colloidal anhydrous silica, hydrogenated castor oil.
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
PVC-PVDC/Aluminium Blister pack - 36 month
HDPE container pack - 48 months

After opening the HDPE container pack, the tablets can be used for six months (180 days).

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
Pyrazinamide 500 mg tablets are available as PVC-PVDC/aluminium blister packs & HDPE container with PP Cap pack in the following pack sizes:

- Blister pack containing 10, 14, 28, 30, 50, 56, 60, 90, 100, 120, 500 tablets
- HDPE container with PP cap containing 90, 1000 tablets

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom
8  MARKETING AUTHORISATION NUMBER(S)
    PL 20117/0014

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
    20/12/2013

10 DATE OF REVISION OF THE TEXT
    20/12/2013