SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zinamide Tablets 500mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of 'Zinamide' contains 500 mg of pyrazinamide Ph Eur.

Excipients with known effect
Each tablet of 'Zinamide' contains 150.6 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White tablets, with one side scored and marked 'GP 504'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

'Zinamide' is indicated in patients with active tuberculosis caused by *Mycobacterium tuberculosis*. 'Zinamide' is not active against the atypical mycobacteria. 'Zinamide' should only be given in combination with other antituberculous agents.

4.2. Posology and method of administration

Recommended dosage for standard unsupervised 2-month treatment:
Adults: Under 50kg bodyweight: maximum of 3 tablets or 1.5g daily. 50kg and over bodyweight: maximum of 4 tablets or 2g daily.
Children: 35mg/kg daily.

Recommended dosage for intermittent supervised 2-month treatment:
Adults: Under 50kg bodyweight: maximum of 4 tablets or 2g 3 times a week. 50kg and over bodyweight: maximum of 5 tablets or 2.5g 3 times a week.
Children: 50mg/kg 3 times a week.

Zinamide' should be administered with at least one other effective antituberculous drug. The use of 'Zinamide' in combination therapy does not modify the accepted dosages of other antituberculous agents.

Use in the elderly: The general considerations outlined above should also apply to elderly patients.

Immunocompromised patients: Multi-resistant *M. tuberculosis* may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed *M. Tuberculosis* infection sensitive to first-line drugs should be treated with a standard 6 month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms and specialist advice is needed.

In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

4.3. Contraindications

'Zinamide' is contra-indicated in patients with:

- hypersensitivity to pyrazinamide or to any of the excipients
- hepatic disease
- hyperuricaemia and/or gouty arthritis
- acute porphyria.

'Zinamide' is also contra-indicated in breast-feeding mothers (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

'Zinamide' should only be used 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 patient as measured against the usual antituberculous drugs. Side effects for 'Zinamide' 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 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 'Zinamide' should be withdrawn and not reinstated if signs of hepatocellular damage occur.

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.

Reduction in the size and/or frequency of dose is recommended for patients with renal insufficiency.

Pre-treatment examinations should include renal function, hepatic function and particularly base-line uric acid determinations. Pyrazinamide inhibits excretion of urates, frequently resulting in hyperuricaemia which is usually asymptomatic. If hyperuricaemia accompanied by an acute gouty arthritis occurs, therapy should be discontinued and not reinstated. Close monitoring is advised to detect any increasing difficulty in the management of patients with a history of gout or diabetes mellitus.

Zinamide should be used with caution in pregnant women.

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

4.5. Interaction with other medicinal products and other forms of interaction

Pyrazinamide antagonizes the effect of uricosuric agents such as probenecid and sulfinpyrazone. 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. Pregnancy and lactation

Pregnancy: There have been no well-controlled studies in pregnant women. 'Zinamide' should only be used if the potential benefit justifies the risk to the foetus.

Lactation: 'Zinamide' is contra-indicated in breast-feeding mothers. If its use is deemed essential, the patient should stop breast-feeding.

4.7 Effects on ability to drive and use machines

There are no data to suggest that 'Zinamide' affects the ability to drive or use machines.

4.8. Undesirable effects

A hepatic reaction is the most common side effect of 'Zinamide' and may occur at any time during therapy. This varies from a symptomless abnormality of hepatic cell function, detectable only by laboratory tests, through a mild syndrome of fever, anorexia, malaise, liver tenderness, hepatomegaly and spleenomegaly, to more serious reactions such as clinical jaundice, and rare cases of hepatic failure and death.

Other side effects-active gout, sideroblastic anaemia, arthralgias, anorexia, nausea and vomiting, flushing, dysuria, malaise, fever, rash, hypersensitivity reactions such as urticaria and pruritus, aggravation of peptic ulcer and occasionally photosensitivity.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Liver toxicity and hyperuricaemia may occur with overdosage.

The stomach should be emptied by gastric lavage if necessary.

There is no specific antidote. 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. Benzodiazepines may be given if there is evidence of central nervous system stimulation.

Probenecid may be given for hyperuricaemia.

The plasma half-life of pyrazinamide is about nine to ten hours.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, other drugs for treatment of tuberculosis. ATC code: J04AK01.

Pyrazinamide exhibits tuberculostatic activity *in vitro* only at slightly acidic pH. The growth of tubercle bacilli within monocytes *in vitro* is completely inhibited by pyrazinamide at a concentration of 12.5 μg/ml.

Pyrazinamide is active only at an acid pH, and it is therefore active mainly on the tubercle bacilli located within the cell. It is these bacteria which are probably responsible for microbial persistance and thus for relapses after chemotherapy has stopped.

Pyrazinamide has low bacterial activity compared with isoniazide. It is thought that when these are used in combination, isoniazide is the key bactericidal drug, whilst pyrazinamide has a sterilising role, acting on a special bacterial population inhibited by the acid environment inside the macrophage or the walls of tuberculous cavities.

5.2 Pharmacokinetic properties

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak concentrations occur about 2 hours after an oral dose and have been reported to be 33 µg per ml after 1.5 g and 59 µg per ml after 3 g.

Serum concentrations then decline, with a plasma half-life of about 9-10 hours.

About 30% of the dose is excreted in the urine as pyrazinoic acid and 4% as unchanged pyrazinamide within 24 hours.

5.3 Preclinical safety data

No relevant information.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, maize starch, magnesium stearate, silicon dioxide, and purified water.

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months for bottles
36 months for blisters

6.4 Special precautions for storage

Store at temperatures below 25°C.

6.5 Nature and contents of container

Amber glass bottles or HDPE bottles containing 100 tablets and PVC/Al blister packs containing 30 or 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals Limited
T/A Genus Pharmaceuticals
Linthwaite
Huddersfield
HD7 5QH, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0206

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 October 2007
Date of latest renewal: 13 February 2009

10 DATE OF REVISION OF THE TEXT

15/09/2020