

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Pyrazinamide Atb 500 mg tablets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 500 mg of pyrazinamide

Full list of excipients see Section 6.1.

### **3. PHARMACEUTICAL FORM**

Tablet

Yellowish-white, round, flat, marked on one side with "PZ".

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Pyrazinamide Atb tablets is indicated in:

- Treatment of new cases of pulmonary tuberculosis in association with major antituberculosis drugs (rifampicin, isoniazid and ethambutol) during the first two months of treatment for conversion of sputum culture from positive to negative and reducing the treatment period (6 months).
- Treatment of pulmonary and extra-pulmonary tuberculosis caused by bacilli resistant to isoniazid and/or rifampicin, in combination with other anti-tuberculosis drugs.

#### **4.2 Posology and method of administration**

Pyrazinamide Atb is always used in combination with other anti-tuberculosis drugs to avoid rapid installation of resistance.

*Adults:* 3 - 4 tablets of 500 mg per day, a single dose (average 30 mg per kg of bodyweight per day).

*Children:* 20 mg/kg/day, a single dose, in cases where no satisfactory alternative.

#### **4.3 Contraindications**

- Hypersensitivity to pyrazinamide or any of the excipients listed in section 6.1
- Hepatic failure
- In case of hyperuricaemia (the inhibitory effect of pyrazinamide on the excretion of uric acid should be taken into account)
- Renal failure, except when absolutely necessary
- Porphyria
- Pregnancy.

#### **4.4 Special warnings and precautions for use**

Pyrazinamide hepatotoxicity should be taken into account (see also section 4.8). Pyrazinamide should be administered only after the initial evaluation of the patient, and only if the clinical and biological parameters can be monitored periodically.

Pyrazinamide treatment should not be initiated without a baseline measurements of hepatic enzymes (transaminases, alkaline phosphatases, and total bilirubin), renal function assessment, and uricaemia (to exclude hepatic failure, renal failure, or hyperuricaemia).

In case of impaired liver function and/or hepatic risk factor (alcoholism, history of hepatitis), the pyrazinamide treatment should be given only if absolutely necessary (particularly in case of multi-drug-resistant tuberculosis), with caution, and under medical supervision. Liver function monitoring should include: transaminase level every 8 days during the 2 months of treatment, and supervision of clinical signs of liver intolerance (see Section 4.8).

If elevated transaminase test results, three times the Upper Limit of Normal, the treatment should be discontinued without delay. Early interruption is an important parameter for the normalization of liver functions.

If serum uric acid exceeds 110 mg/l (655 µmol/l), a corrective treatment should be initiated (except for xanthine oxidase inhibitors). Moderate non-gout arthralgia responds to symptomatic treatment. If arthralgia persists and appears to be gouty, pyrazinamide treatment should be discontinued.

If the kidney is normal, a monthly assessment of renal functions is recommended and considered sufficient. In patients with chronic renal insufficiency, pyrazinamide will be administered only if absolutely necessary, and only under medical supervision.

In patients with diabetes, glycaemia control is more difficult when taking pyrazinamide.

Avoid prolonged exposure to sunlight. Pyrazinamide may cause increased skin sensitivity to ultraviolet radiations.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent treatment of pyrazinamide, rifampicin and isoniazid require close clinical and biological supervision, due to the cumulative hepatotoxic side effects and to the possibility of severe adverse reaction occurrence.

Pyrazinamide has been reported to interfere with urine tests used to determine ketone levels (sodium nitroprusside method), to produce a brownish color.

Pyrazinamide may also increase uricaemia and decrease the efficacy of anti-gout medicines (such as allopurinol, colchicine, probenecid, sulphinyprazole) when used concomitantly.

Concurrent use of pyrazinamide and cyclosporine may decrease the plasma concentration of the second.

Ethanol consumption increases the risk of hepatotoxicity during the treatment with pyrazinamide.

#### **4.6 Fertility, pregnancy and lactation**

Since no studies in animals have been performed to date, the risks of pyrazinamide use during pregnancy are not known. Consequently, the drug should not be recommended during pregnancy or in case of pregnancy suspicion.

Pyrazinamide is excreted into the breast milk in small amounts, so the risk/benefit ratio should be assessed before initiating pyrazinamide treatment.

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

No effects on the ability to drive and use machines have been reported to date.

#### **4.8 Undesirable effects**

Adverse reactions are classified according to System Organ Class and frequency. Frequency categories are derived according to the following conventions: very common ( $\geq 1/10$ ), common

( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), isolated cases included.

*Blood and lymphatic system disorders*

Very rarely: haematopoiesis disorders, sideroblastic anaemia, thrombocytopenia or porphyria.

*Immune system disorders*

- Not known: transient rash

*Nervous system disorders*

Occasionally: headache, dizziness, agitation, and insomnia.

*Hepatobiliary disorders*

- Common: Liver function is frequently impaired and seems to depend on the dosage and duration of treatment. This may occur anytime during pyrazinamide treatment.
- Not known: If anorexia, nausea, vomiting, abdominal pains, severe asthenia, fever, mild jaundice occur, the hepatic functions determination should be performed. Rarely, severe cases of hepatotoxicity have been reported when pyrazinamide was associated with other drugs that are toxic for the liver.

*Skin and subcutaneous tissue disorders*

- Not known: photosensitivity phenomena.

*Musculoskeletal and connective tissue disorders*

- Common: arthralgia, myalgia and gout episodes.

*Renal and urinary disorders*

- Not known: Hyperchromic urine, dysuria and interstitial nephritis.

*Investigations*

- Very common: hyperuricaemia
- Not known: diabetic patients may experience difficulties in normalising their glycaemia

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported via the National Agency for Medicines and Medical Devices <http://www.anm.ro>.

## **4.9 Overdose**

In case of overdose, the drug should be eliminated using gastric lavage. Medical supervision is required, to detect and choose the treatment of possible hepatic, neurologic and respiratory disorders.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamics properties**

*Pharmacotherapeutic group:*, drugs for treatment of tuberculosis, other drugs for the treatment of tuberculosis. ATC Code: J04 AK01

Pyrazinamide is nicotinamide derivative. *In vivo* it is bactericidal against intracellular tuberculosis bacillus (in acid medium).

Resistant species: atypical mycobacteria and *Mycobacterium bovis*.

Susceptible species: *Mycobacterium africanum* and *Mycobacterium tuberculosis*

The primary resistance of wild-type strains may be considered null.

Risk of developing secondary resistance is higher if pyrazinamide is used only. It is very important to use pyrazinamide in combination with at least one drug for the treatment of tuberculosis. No cross-resistance to other antituberculosis drugs was observed, except morphazinamide (INN: morinamide) which is a pyrazinamide derivative.

## 5.2 Pharmacokinetic properties

### *Absorption:*

Pyrazinamide is practically completely absorbed from gastrointestinal tract; following the administration of 1.5 g of pyrazinamide,  $C_{max}$  was 33 µg/ml after 2 hours and  $C_{max} = 60$  µg/ml for a dose of 3 g of pyrazinamide.

There is no plasma protein binding of pyrazinamide.

### *Distribution*

Pyrazinamide is widely distributed to the tissues. It penetrates well intracellularly, e.g. macrophages that contain tubercle bacilli. Pyrazinamide reaches active concentrations in lungs, liver and kidneys. It reaches active concentrations in the cerebrospinal fluid.

### *Metabolism*

Pyrazinamide is metabolised in the liver in the form of pyrazinoic acid (in vitro with the same activity as pyrazinamide), which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid.

### *Elimination*

Pyrazinamide is mostly eliminated renally, as pyrazinoic acid (about 40% of the dose administered) and 5-hydroxypyrazinoic acid (about 30%). Approximately 4% of pyrazinamide dose is eliminated unchanged in 24 hours. The half-life of pyrazinamide is about 9 hours after a dose of 1.5 g and is identical after a dose of 3 g.

## 5.3 Preclinical safety data

Not available

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Cellulose microcrystalline  
Maize starch  
Colloidal anhydrous silica  
Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store below 25 °C in the original package.

### **6.5 Nature and contents of container**

Outer carton containing 2 PVC/Al blisters of 10 tablets.

Cardboard box containing 150 PVC/Al blisters of 10 tablets.

### **6.6 Special precautions for disposal and other handling**

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

### **7. MARKETING AUTHORISATION HOLDER**

Antibiotice S. A.  
1 Valea Lupului, Iasi 707410, Romania, EU

### **8. MARKETING AUTHORISATION NUMBER(S)**

5749/2013/01-02

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Re-authorisation: August 2013

### **10. DATE OF REVISION OF THE TEXT**

August 2013