SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid Atb 300 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of isoniazid.

For full list of excipients, see paragraph 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to yellowish white round, flat, glossy tablets, with median line on one side

4. CLINICAL

4.1 Therapeutic indications

Treatment of active tuberculosis, pulmonary or extrapulmonary.
Treatment of symptomatic tuberculosis on primo-infection;
Exceptional, treatment of atypical infections with mycobacterial susceptible (sensitivity determined by minimum inhibitory concentration). This treatment is based on a combination of active antibiotics.
Prophylaxis of tuberculosis.

4.2 Posology and method of administration

Treatment and prophylaxis of tuberculosis are carried out according to National Tuberculosis Control Programme.

Adults: The recommended dose is 5-10 mg isoniazid / kg daily and 10-15 mg for intermittent therapy regimens.
Maximum dosage (mg) of Isoniazid Atb is 300 mg in treatment regimen 7/7 and 900 mg in treatment regimen 3/7.
Children: The recommended dose is 5-10 mg isoniazid / kg daily at the beginning of treatment, not exceed 300 mg / day.
Elderly: low doses are not necessary.
In case of liver failure it will reduce the dose.
In case of severe renal insufficiency, it is recommended not exceed 300 mg of isoniazid daily. It will take into account the creatinine clearance.

<table>
<thead>
<tr>
<th>Creatinine clearance mL / min</th>
<th>Doses</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>10-50</td>
<td>300 mg</td>
<td>every 24 hours</td>
</tr>
<tr>
<td>&lt;10</td>
<td>200 mg</td>
<td>every 24 hours</td>
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In severe renal failure, dialysis patients, isoniazid will be given at the end of haemodialysis session. (See also paragraph 4.4 Special warnings and precautions for use).

Treatment with Isoniazid Atb should be followed throughout the period recommended by your doctor. The treatment should not be discontinued prematurely due to the risk of occurrence of the resistance and disease recurrence.

Isoniazid should be administered orally, in a single dose in the morning, 30 minutes before meal. Generally, new cases of pulmonary or extra-pulmonary tuberculosis involve an initial phase that lasts two months and includes daily administration of isoniazid with rifampicin, ethambutol and pyrazinamide. Initial phase is followed by the continuation phase of 4 months when isoniazid is administered concurrently with rifampicin, 3 days per week. Isoniazid Atb is used in chemoprophylaxis. In prevention, Isoniazid Atb is administered in monotherapy daily (7/7), 10 mg / kg / day or 200 mg/m2 body surface area in children, 5 mg/kg daily in adults (maximum 300 mg daily) at least 6 months.

4.3 Contraindications

- Hypersensitivity to isoniazid or any of the excipients
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Because of hepatotoxic effects of isoniazid (especially during the first three months of treatment, and especially in combination with rifampicin and pyrazinamide) it is recommended regular monitoring of liver functions (cytolysis tests), weekly during the first month, and then monthly during treatment. A moderate increase of values (< 3 times normal value) does not require discontinuation of the treatment. In case of increased hepatic transaminases values (5 times higher than normal values), the treatment should be discontinued until the normalizing of the result of biological samples, then resume treatment for TB. Treatment should be individualized for each patient. Treatment with isoniazid should be carefully monitored by medical staff. Because the risk of peripheral neuropathy it is recommended regular neurological examination and careful management, particularly in patients with alcoholism. Concomitant use of stavudine increases the risk of peripheral neuropathy.

Isoniazid is metabolized primarily by acetylation. The rate of acetylation is genetically determined. “Slow acetylators” can cause peripheral neuropathy. However, low doses are not necessary in the most of the cases. 

Use in renal and hepatic impairment: no dosage reduction of isoniazid is necessary when given to patients with mild renal failure. Patients with severe renal failure (glomerular filtration rate of less than 10 ml/minute) and slow acetylator status might require a dose reduction of about 100 mg to maintain plasma levels at less than 1 mcg/ml. The possible risks of administration of isoniazid to patients with pre-existing non-tuberculous hepatic disease should be balanced against the benefits expected from treating tuberculosis.

Care is also required in chronic alcoholism and when prescribing isoniazid for patients with pre-existing hepatitis. Convulsions and psychotic reactions have occurred, especially in patients with a previous history of these conditions. These manifestations usually subside rapidly when the drug is withdrawn. Isoniazid should therefore be given with caution to patients with convulsive disorders and should be avoided in those with manic or hypomanic psychoses.

4.5 Interaction with other medicinal products and other forms of interaction

Combination of isoniazid with pyrazinamide causes an increase of isoniazid hepatotoxicity. It is necessary clinical and biological monitoring of hepatic function. The treatment should be discontinued.
in case of occurrence of hepatitis. The same effect can occur in case of enzymatic inductors (e.g. rifampicin, barbiturates) (see paragraph 4.8 Undesirable effects).

It is not recommended the concomitant administration of isoniazid and carbamazepine (increase in serum level of carbamazepine accompanied by overdosage signs as inhibition of hepatic metabolism of carbamazepine) or disulfiram (behavioural and coordination disorders). Isoniazid may enhance the effect of phenytoin and inhibits primidone metabolism.

Salts and aluminum hydroxide may reduce gastrointestinal absorption of isoniazid. Administer isoniazid at least 2 hours before any aluminium containing compounds.

Halogenated volatile anaesthetics enhance the hepatotoxic effect of isoniazid due to a large quantity of toxic metabolites of isoniazid. In case of a scheduled surgery isoniazid treatment is discontinued with caution a week before and is continued only after 15 days.

Glucocorticoids decrease isoniazid serum level (by increasing the isoniazid hepatic metabolism and decreasing the glucocorticoids metabolism).

Isoniazid may decrease ketoconazole serum levels. The time interval between the administrations of the two antibiotics must be at least 12 hours, if possible. Concurrent use should be well monitored and dosage increases should be made if necessary.

Concomitant administration of isoniazid with stavudine may increase the risk of peripheral neuropathy by accumulating of the side effects.

In some patients, concomitant administration of isoniazid with ethionamide may cause maniac outbursts, acute delirium or depression (see paragraph 4.8 Undesirable effects).

Ingestion of alcohol during isoniazid treatment may be associated with a higher incidence of isoniazid hepatitis.

4.6 Fertility, pregnancy and lactation

While isoniazid is generally regarded to be safe in pregnancy, there is a possibility of an increased risk of foetal malformations occurring when isoniazid is given in early pregnancy. If pregnancy cannot be excluded possible risks should be balanced against therapeutic benefits. Pyridoxine (vitamin B6) will be administered in pregnant woman in order to avoid neurological side effects in neonate.

Isoniazid is excreted in breast milk at concentrations equivalent to those found in maternal plasma, ie. 6-12 mcg/ml. This could result in an infant ingesting up to 2 mg/kg/day. Breast-feeding is not recommended during the treatment with isoniazid to prevent possible neurological side effects in infant.

4.7 Effects on ability to drive and use machines

No specific statement, but unlikely to affect the ability to drive or use machinery. However, in case of the neurological reactions occurrence, caution should be taken.

4.8 Undesirable effects

The frequency of adverse reactions of isoniazid is not defined. Side-effects have been reported mainly in association with high doses or in slow acetylators who develop higher blood levels of the drug. The most common side effects are at the nervous system and liver.

Blood and lymphatic system disorders: it may occur agranulocytosis, anaemia (aplastic, haemolytic, sideroblastic anemia), thrombocytopenia, eosinophilia.

Metabolism and nutrition disorders: hyperglycaemia, metabolic acidosis, pyridoxine deficiency.

Psychiatric disorders: On a predisposing land, especially during ethionamide association, it may occur bouts of mania, depression and acute delirium. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

Nervous system disorders: Neurotoxicity occurs due to pyridoxine deficiency and may be manifested by: peripheral neuropathy (distal paraesthesia, especially in malnourished, alcoholics or slow
acetylators), neuritis, muscle weakness, hyper-reflexia, neuropsychiatric disorders (hyperactivity, euphoria, and insomnia), seizures. Peripheral neuropathy is generally related to dose, a daily dose of 10 mg / day is within 10-20%; it could be prevented by administration of pyridoxine. 

Eye disorders: blurred vision, decreased visual acuity, optic neuritis and atrophy. 
Cardiac disorders: palpitations, tachycardia. 
Vascular disorders: hypertension, vasculitis. 
Gastrointestinal disorders: anorexia, nausea, vomiting, epigastric pain, constipation and abdominal pain. 
Hepatic-biliary disorders: it was observed relatively frequent the growth of transaminase (moderate growth in 10-20% of cases) and rare cases of acute hepatitis (with or without jaundice), sometimes even severe. Liver toxicity is increased after combination with rifampicin (a mechanism of enzyme induction) or pyrazinamide. Other inducers may have the same effect (barbiturates) (see also paragraph 4.5 Interaction with other medicinal products and other forms of interaction). There were reports of hyperbilirubinemia, bilirubinuria, jaundice. 
Skin and subcutaneous tissue disorders: erythema multiforme, rash (morbilliforme, maculopapular, pruritic or exfoliative), rarely, lupic syndrome, pellagra, purpura. 
Musculoskeletal and connective tissue disorders: myalgia, arthralgia, lymphadenopathy, rheumatic syndrome, algodystrophy (shoulder-hand syndrome), lupic syndrome. 
Renal and urinary disorders: dysuria. 
Reproductive system and breast disorders: gynecomastia. 

General disorders and administration site conditions: fever, anorexia.

4.9 Overdose

Maximum lethal dose is 200 mg / kg.

Symptoms:
Absorption of massive doses leads to: nausea, vomiting, dizziness, blurred vision, hallucinations, during the ½ -3 hours. It can be installed coma, which can be fatal.
In case of overdose can occur metabolic acidosis, ketonuria and hyperglycaemia. 
Treatment:
Overdose requiring hospitalization in a specialized centre: correction of acidosis, cardio-respiratory resuscitation, and administration of antiepileptic drugs and high doses of pyridoxine. Metabolic acidosis may require perfusions with sodium bicarbonate. In severe cases, patients are undergoing haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-mycobacterial, medicines to treat tuberculosis, hydrazide. 
ATC code: J04AC01. 
Isoniazid is the hydrazide of isonicotinic acid having a structure similar to pyridoxine (vitamin B6), having a selective and intense mycobactericidal activity against intra-and extra-cellular bacilli when they are undergoing cell division. 
Isoniazid works by inhibiting the synthesis of long chain fatty acids (mycholic acids) precursors of isonicotinic acid, essential component of mycobacterium wall. Isoniazid is a prodrug and is activated by KatG-mycobacterium peroxidase. Due to high frequency of occurrence of resistance to isoniazid single therapy it is indicated to be administered in polychemotherapy schemes. 
Isoniazid does not show a significant antimicrobial action against microorganisms, other than mycobacteria. 
Prevalence of acquired bacterial resistance can vary by geographic area and for particular species.
Susceptible species: *Mycobacterium africanum, Mycobacterium bovis, Mycobacterium bovis BCG, Mycobacterium tuberculosis*.
Moderately sensitive species: *Mycobacterium kansasii*.
Resistant species: atypical mycobacteria except *Mycobacterium kansasii*.

**Resistance**
Natural resistance and acquired resistance to isoniazid have been demonstrated *in vitro* and *in vivo* in strains of *M. tuberculosis*. *In vitro*, resistance to isoniazid develops in a stepwise manner. Mechanism of resistance may be related to failure of the drug to penetrate or be taken up by the resistant bacteria. Resistant strains of initially susceptible bacteria develop rapidly if isoniazid is used alone in the treatment of tuberculosis. However, resistance development does not represent a major problem in case of treatment prophylaxis.

### 5.2 Pharmacokinetic properties

**Absorption**
Following oral administration, peak plasma concentration is attained within 1-2 hours. After 3 hours, effective plasma concentration is 1-2 μg/mL.

**Distribution**
Isoniazid is distributed throughout tissues, organs, saliva, sputum, faeces, intestines, the cerebrospinal fluid, peritoneal and pleural fluids.
Isoniazid is not substantially bound to plasma proteins; it is distributed into milk in concentrations approximately equal to maternal plasma concentrations corresponding to an ingestion of 5 mg isoniazid (half of the therapeutic dose of the neonate).

**Elimination**
Isoniazid is mainly metabolised by acetylation in acetylisoniazid. The rate of acetylation is genetically determined (there are slow and fast acetylators). The plasma half-life of isoniazid ranges from 1-6 hours. Determination of the speed of isoniazid acetylation allows the administration of the lowest active dose: 3 mg/kg for slow acetylors and 6 mg/kg for fast acetylors.
Isoniazid is 4-30% protein bound.
Acetylisoniazid is hydrolysed and partially transformed into an instable metabolite. This metabolite is a major determinant of isoniazid-induced hepatotoxicity.

**Excretion**
Isoniazid is eliminated as unchanged drug in proportion of 10-30% in urine (fast or slow acetylation), and as metabolite in the bile.

**Special group of patients**
The plasma half-life of isoniazid can be prolonged in patients with liver failure or severe renal failure.

### 5.3 Preclinical safety data
Isoniazid has been shown to cause lung tumours in a number of species of mice. However isoniazid has no carcinogenic or tumorigenic potential in humans.
Studies conducted on rats and rabbits showed that isoniazid cause embryo death. Isoniazid has non-teratogenic potential in mice, rats or rabbits.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycolate
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 ºC, in the original package.

6.5 Nature and contents of container

Outer carton with 3 PVC/Al blisters of 10 tablets.
Cardboard box with 150 PVC/Al blisters of 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product should be disposed of according to local requirements.

7. MARKETING AUTHORISATION HOLDER

Antibiotice SA
1 Valea Lupului, 707410 Iasi, Romania, EU

8. MARKETING AUTHORISATION NUMBER(S)

1136/2012/01-02

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewal date: November, 2008

10. DATE OF REVISION OF THE TEXT

May, 2012