SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid Atb 100 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of isoniazid.

Excipient with known effect: 33.93 mg of lactose monohydrate

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to yellowish white round, flat, glossy tablets.

4. CLINICAL

4.1 Therapeutic indications

- Treatment of active pulmonary or extra-pulmonary tuberculosis in combination with other tuberculostatics;
- Treatment of symptomatic tuberculosis on primo-infection;
- By way of exception in the treatment of atypical infections with mycobacterial susceptibility (sensitivity determined by minimum inhibitory concentration). This treatment is based on a combination of active antibiotics;
- Tuberculosis prophylaxis.

4.2 Posology and method of administration

Posology

Treatment regimen of tuberculosis is standardized (according to National TB Prevention, Surveillance and Control-2015).

Adults: 5 - 10 mg/kg daily for continuous treatment and 10-15 mg/kg daily for intermittent therapy regimens.
Maximum dosage of isoniazid is 300 mg in treatment regimen 7/7 and 900 mg in treatment regimen 3/7.

Children: 5 - 10 mg/kg daily, not exceed 300 mg/day.
Children weighing more than 25 kg should be treated according to the recommended adult treatment.

Due to pharmaceutical form isoniazid should not be administered in children under 6 years old only after crushing and dissolution of the tablet in a glass of water; to increase compliance, in water can be added a sweetener.

Elderly: low doses are not necessary.

In case of chronic liver failure it will reduce the dose to 100-200 mg/day.
In case of severe renal insufficiency, it is recommended not exceed 300 mg of isoniazid daily. It will take into account the creatinine clearance.

Creatinine clearance mL / min	Doses	Frequency
10-50	300 mg	every 24 hours
<10	200 mg	every 24 hours

In severe renal failure, dialysis patients, isoniazid will be given at the end of haemodialysis session. (See also paragraph 4.4).

Method of Administration

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 Atb 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 is also used in chemoprophylaxis. In prevention, isoniazid is administered in monotherapy daily (7/7), 10 mg/kg/day or 200 mg/m^2 body surface area in children, 5 mg /kg/day in adults (maximum daily dose of 300 mg) for at least 6 months.

4.3 Contraindications

- You are allergic to isoniazid or any of the other ingredients of the medicine (see Section 6.1);

- You have severe hepatic failure.

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 upper limit of the normal value-ULN) does not require discontinuation of the treatment. In case of increased hepatic transaminases values (5 times ULN), 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.
Severe and sometimes fatal hepatitis may occur even after many months of treatment. The risk of hepatitis is increased in patients over 35 years of age and: chronic alcohol consumption, pre-existing liver disease, IV drug users and black or Hispanic women. Tell your doctor to monitor the common prodromal symptoms of hepatitis such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued.

Patients with diabetes mellitus should be carefully monitored because isoniazid may modify the level of serum glucose.

Because the risk of peripheral neuropathy it is recommended regular neurological examination and careful management, particularly in patients with alcoholism, malnourished patients, diabetics or with renal failure.
Isoniazid is metabolised by acetylation, which is subject to genetic variation. The 'slow acetylators' may be more susceptible to drug-induced peripheral neuropathy. However, dose adjustment is not normally required.

Care should be exercised in the treatment of elderly or malnourished patients, breastfed children, children with deficient diet in protein, patients with conditions which predispose them to neuropathy who may also require vitamin B6 supplementation with the isoniazid therapy.

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 (GFR) <10 mL/minute) and slow acetylator status might require a dose reduction of 100 mg to maintain plasma levels of 1mcg/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 in patients with pre-existing hepatitis. Convulsions and psychotic reactions were reported, 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 those with maniacal and hypomaniacal psychoses.

Patients with hypersensitivity to ethionamide, pyrazinamide, niacin (nicotinic acid) or other related medications may also be hypersensitive to isoniazid.

Isoniazid Atb contains lactose. The patients with rare hereditary disorders of galactose intolerance, lactase deficiency (Lapp) or glucose-galactose malabsorption should not take this medicinal product.

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), acetaminophen, paracetamol.

It is not recommended the concomitant administration of isoniazid with carbamazepine and valproate (increase in their serum level accompanied by overdosage signs as inhibition of their hepatic metabolism) or disulfiram (behavioural and coordination disorders).
Isoniazid may enhance the effect of phenytoin and inhibits primidone metabolism.
Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations. Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly.
Concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.
Aluminium salts and aluminum hydroxide may reduce gastrointestinal absorption of isoniazid. If possible, 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. Eventually, concurrent use should be well monitored and dosage will be adjusted.
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). Concomitant administration of ethionamide and isoniazid increased isoniazid serum level for both fast and slow acetylators. In case of extreme necessity pyridoxine will be administered and side effects of isoniazid will be monitored (peripheral neuritis, hepatoxicity, encephalopathy).

Concurrent administration of isoniazid and anticoagulants (warfarin) may inhibit the enzymatic metabolism of the anticoagulants, leading to increased plasma concentrations with an increased risk of bleeding. Therefore, INR should be closely monitored.

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

Concurrent ingestion with isoniazid may lead to inhibition of mono-oxidase by isoniazid, interfering with food containing tyramine (cheese, red wine etc). Also, diamine oxidase may also be inhibited, causing exaggerated response (e.g., headache, hyperhidrosis, palpitations, flushing, hypotension) to foods containing histamine (e.g, tuna, other tropical fish).
Tyramine- and histamine-containing foods should be avoided in patients receiving isoniazid.

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no controlled clinical studies regarding the use of isoniazid during pregnancy.
During pregnancy first-line anti-tuberculosis medicines are administered (including isoniazid, and except streptomycin) in women with TB. The pregnant woman should take 10-20 mg of pyridoxine daily. Anti-tuberculosis treatment is not an indication for therapeutic abortion.
Lactation
Isoniazid is excreted into the breast milk. No adverse effects in the baby have been reported. The risk/benefit ratio should be assessed before initiating isoniazid treatment during breastfeeding.

4.7 Effects on ability to drive and use machines

Isoniazid has moderate influence on the ability to drive and use machines
Isoniazid may cause neurological reactions occurrence, therefore caution should be taken.

4.8 Undesirable effects

The frequency of adverse reactions is defined using the following convention:
Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1000 and <1/100)
Rare (≥1/10,000 and <1/1000)
Very rare (<1/10,000)
Not known: frequency cannot be estimated from the available data

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:
- Not known: it may occur agranulocytosis, anaemia (aplastic, haemolytic, sideroblastic anemia), thrombocytopenia, leukopenia.

Metabolism and nutrition disorders:
- Not known: hyperglycaemia, metabolic acidosis, pyridoxine deficiency, pellagra (lack of niacin);

Psychiatric disorders:
- Uncommon: mental disturbances, toxic psychosis
- Not known: confusion, disorientation, hallucinations.

Nervous system disorders:
- Very common: peripheral neuropathy usually proceeded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces this risk (see section 4.4)
- Uncommon: convulsions, chronic encephalopathy
- Not known: dizziness, headache, tremors, vertigo, hyper-reflexes

Eye disorders:
- Not known: blurred vision, decreased visual acuity, optic neuritis and atrophy.

Cardiac disorders:
- Not known: palpitations, tachycardia;

Vascular disorders:
- Not known: hypertension, **vasculitis**;

Gastrointestinal disorders:
- Not known: anorexia, nausea, vomiting, epigastric pain, constipation, flatulence, dry mouth, gastric irritation, **pancreatitis**.

Hepatic-biliary disorders:
- Not known: it was observed a transient increase of transaminases (moderate growth in 10-20% of cases)
- Uncommon: **acute hepatitis** (with or without jaundice), sometimes severe cases.

Skin and subcutaneous tissue disorders:
- Rare: **toxic epidermal necrolysis, eosinophilia and systemic symptoms**
- Not known: erythema multiforme, rash (morbiliforme, maculopapular, pruritic or exfoliative), purpura;

Musculoskeletal and connective tissue disorders:
- **Not known**: myalgia, arthralgia, lymphadenopathy, rheumatic syndrome, algodystrophy (shoulder-hand syndrome), lupus syndrome;

Renal and urinary disorders:
- Not known: urinary retention, nephrotoxicity including interstitial nephritis.

Reproductive system and breast disorders:

-Not known: gynecomastia;

General disorders and administration site conditions:
- Not known: fever.

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 national reporting system whose details are published on website of National Agency for Medicines and Medical Devices http://www.anm.ro

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 convulsive coma with anoxia, which can be fatal.
In case of overdose metabolic acidosis, ketonuria and hyperglycaemia can occur.

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), 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 time 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 vivo*, 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 prophylaxis treatment.

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 1to 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

Lactose monohydrate
Powdered 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

Folding carton with 2 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Antibiotice SA
1 Valea Lupului, Iaşi 707410, Romania

8. MARKETING AUTHORISATION NUMBER(S)

4553/2012/01-02

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Renewal date: April 2012

10. DATE OF REVISION OF THE TEXT

December 2016