SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ethambutol Atb 250 mg film-coated tablets
Ethambutol Atb 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of ethambutol hydrochloride.
Each film-coated tablet contains 400 mg of ethambutol hydrochloride.

For full list of excipients see paragraph 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet
Pink, round, biconvex film-coated tablets with 12 mm diameter.
White, round, biconvex film-coated tablets with 13 mm diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of pulmonary and extra-pulmonary tuberculosis, including tuberculous meningitis, during the initial polychemotherapy and re-treatment.

Ethambutol should be used only in conjunction with other antituberculosis agents and antibacterial chemotherapy for tuberculosis (germs develop resistance after monotherapy), both in the primary treatment and re-treatment.

Ethambutol is included in first-time re-treatment therapy.

4.2 Posology and Method of Administration

Posology

Tuberculosis treatment is planned as recommended by the national therapeutic programs. Ethambutol Atb is orally administered.

Use in adults:
The usual dose of ethambutol is of 15- 25 mg per kg of bodyweight per day (not more than 1.6 g/day), 7 times a week, or 30-50 mg per kg of bodyweight per day (not more than 2 g/day), 3 times a week.

Use in children:
Ethambutol will be administered only after close evaluation of risk/benefit ratio in patients whose side effects on visual acuity cannot be accurately determined (see section section 4.4 Special warnings and precautions for use).
The usual dose of ethambutol is of 15 - 25 mg per kg of bodyweight daily.

Renal failure
Caution is recommended in patients with renal failure (See section 4.4). It is recommended to increase the dosing interval as follows:

Crcl (mL/min)	Dose
< 30	15-20 mg every 48 hours with monitoring of ethambutol plasma level

Alternatively, doses may be reduced according to following scheme:

Crcl (mL/min)	Dose
25-50	Normal
10-20	7.5-15 mg/kg/day
< 10	5-7.5 mg/kg/day

Hepatic failure
It is not necessary to adjust doses in patients with hepatic failure.

Method of administration
Film-coated tablets will be administered orally, in a single dose, under close monitoring within treatment period.
The duration of antituberculous therapy depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility studies of *Mycobacterium tuberculosis* isolated from the patient.
If therapy is interrupted, the treatment schedule should be extended to a later completion date depending on the length of the interruption, the time during therapy or the patient's status.

4.3 Contraindications

Hypersensitivity to ethambutol or to any of the excipients (see section 6.1). Optic neuritis.

4.4 Special warnings and precautions for use

Complete ophthalmological examination should be performed prior to therapy with ethambutol - visual acuity, vision field, colour vision, optic fundus. Ophthalmological examination will be controlled in the third week of treatment, then in the second month and continues every 2 months. Therapy with

ethambutol must be discontinued if visual disturbances emerge. Optic neuritis is often reversible in few months upon discontinuation of therapy.
Ethambutol is contraindicated in case of optical neuritis and should be administered with caution in patients with pre-existing visual defects or in other risk situations such as: alcoholics, tobaccos, diabetics, or in case of concurrent treatment with toxic medication for retina.
Since ethambutol is mainly eliminated via the kidneys, dose adjustment is required in patients with impaired renal function (see section 4.2 Posology and Method of Administration). In renal impairment, there is a high risk of overdose by accumulation. Visual acuity should be monitored more closely in these patients. It is recommended avoiding ethambutol administration if renal function cannot be monitored.
Ethambutol is not recommended at young ages as children might be less likely to report ocular toxicity. The usual dose of ethambutol for children over 5 years old is 15 mg per kg of body weight per day (see section 4.2 Posology and Method of Administration).
Ethambutol is excreted via the same pathway as uric acid, thereby leading to increased serum concentration of uric acid. Concomitant therapy with isoniazid or pyridoxine may enhances this effect. Patients with pre-existing hyperuricaemia or symptoms of gout should be monitored for signs of deterioration when treated with ethambutol.

4.5 Interaction with other medicinal products and other forms of interaction

Aluminium hydroxide salts impair the digestive absorption of ethambutol (the interval between their administrations should be of at least 4 hours).
The optic toxicity of ethambutol may be enhanced by concurrent use of other drugs with toxic risk for optic nerve and retina: chlorpromazine, phenothiazine, and other thiazines, digitalis, chloramphenicol.
Concomitant use of disulfiram increases the risk of ocular toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Studies in animals have shown that ethambutol crosses the placenta. Administration during pregnancy has not been associated with the occurrence of any foetal anomalies. The effects of ethambutol on the foetus when administered concurrently with other anti-tuberculosis medications are not known.

Breastfeeding:
Ethambutol is excreted in the breast milk.

Ethambutol should be administered during pregnancy and breastfeeding only after the evaluation of foetal potential risk/maternal therapeutic benefit ratio.

4.7 Effects on ability to drive and use machines

Due to ocular adverse reactions, ethambutol can influence the ability to drive or use machine.

4.8 Undesirable Effects

Frequencies of side effects is defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare, (≤1/10,000), not known (cannot be estimated from available data).

Blood and lymphatic system disorders:
Very rare: Thrombocytopenia, leukopenia (allergic), neutropenia with eosinophilia

Immune system disorders:
Very rare: hypersensitivity, anaphylactic reactions

Metabolic and nutrition disorders:
Uncommon: Hyperuricaemia
Very rare: Gout

*Psychiatric disorders***:**
Not known: confusion, disorientation, hallucination.

Nervous system disorders
Not known: Peripheral neuropathy (paraesthesia), especially in the legs, dizziness, headache, tremor.

Eye disorders
Common: visual disturbances due to optic neuritis (retrobulbar neuritis). The frequency depends on the dose and duration of therapy. The change may be unilateral or bilateral and has been reported more frequently in patients receiving ethambutol 25 mg/kg/day for several months. Typical initial signs include impairment of colour vision (red-green blindness) and constriction of visual field (central or peripheral scotoma). These changes are often reversible upon discontinuation of therapy. For doses of 15 mg/kg/day visual disturbances are very rare. To avoid development of irreversible optic atrophy, visual acuity should be regularly monitored and ethambutol therapy must be immediately discontinued when visual disturbances occur (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Not known: pneumonitis, pulmonary infiltrates, with or without eosinophilia

Gastrointestinal disorders
Not known: nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea.

Hepatobiliary disorders:
Not known: hepatitis, jaundice, transient increases in liver enzymes, hepatic failure.

Skin and subcutaneous tissue disorders:
Rare: transient skin rash, itching, urticaria.
Very rare: photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis.

Renal and urinary disorders:
Very rare: Interstitial nephritis.

General disorders and administration site conditions
Not known: fever, malaise.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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

Symptoms: Anorexia, vomiting, gastrointestinal disturbances, fever, headache, dizziness, hallucinations and/or visual disturbances.
Treatment: Emesis and gastric lavage may be of value. There is no specific antidote and treatment is supportive. Ethambutol is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other drugs for the treatment of tuberculosis.
ATC code: J04 AK02

Mechanism of action
Ethambutol has a bacteriostatic action and acts intracellular and extracellular on the tubercle bacilli which are in the exponential multiplication phase and appears to inhibit the synthesis of one or more metabolites thus causing impairment of cell metabolism, arrest of multiplication and cell death. Literature data shown that ethambutol inhibits synthesis of RNA and DNA and may form chelates with metals essential to bacteria.

Pharmacodynamic effects
Ethambutol, a synthesis compound, is one of the major chemotherapeutic antituberculosis agents. Ethambutol has a toxic elective action on *M. tuberculosis* - MIC (minimum inhibitory concentration) is of 1-2 μg/ml for most strains. *M. kansasii* is also sensitive but to higher concentrations. Ethambutol has a bacteriostatic action and acts only on the germs which are in the exponential multiplication phase; their growing is stopped 24 hours after ethambutol incorporation in the culture. It is active against extracellular and also intracellular bacilli. It inhibits mycobacterium arabinosyl transferase implicated in arabinogalactan synthesis, essential compound of mycobacterium cell wall. In this way cellular barrier is altered and the transmembrane permeability of the lipophilic drugs (rifampicin, ofloxacin) is increased.

5.2 Pharmacokinetic Properties

Absorption
Approximately 80% of ethambutol is absorbed after oral administration. Following intake of 15 mg/kg body weight, a peak serum concentration of approximately 4 mg/l is achieved in 2-4 hours. When the drug is administered daily for a longer periods of time at this dose, serum levels are similar.
Distribution
The intracellular concentrations of erythrocytes reach peak values approximately twice those of plasma and maintain this ratio throughout the 24 hours. The mean volume of distribution has been estimated to 3.89 l/kg - 8.1 l/kg.
It is reported that, depending on the administered dose, about 10-40% of the drug is bound to plasma protein.
Elimination
The plasma concentration falls biphasically, the half-life being about 4 hours initially and 10 hours Subsequently, 50 to 70% of the dose being excreted unchanged in the urine and another 7 to 15% as inactive aldehyde and carboxylic acid metabolites.
The main metabolic pathway appears to be an initial oxidation of the alcohol to an aldehydic intermediate, followed by conversion to a dicarboxylic acid.
20-22% of the initial dose is excreted in the faeces as unchanged drug. Ethambutol elimination is delayed in subjects with reduced renal function.

5.3 Preclinical safety data

Toxicological studies on high prolonged doses produced evidence of myocardial damage and heart failure, and depigmentation of the tapetum lucidum of the eyes.
Degenerative changes in the central nervous system, apparently not dose-related, have also been noted in dogs over a prolonged period. In the rhesus monkey, neurological signs appeared after treatment with high doses given daily over a period of several months. These were correlated with specific serum levels of ethambutol and with definite neuroanatomical changes in the central nervous system.
Conflicting results are available on genotoxicity (negative Ames test, negative in human lymphocyte cell cultures, positive in mouse micronucleus). In mice, ethambutol administered together with sodium nitrite gave rise to an increased frequency of lymphomas and lung tumours. Cleft palate, exencephaly and vertebral column abnormalities have been observed with high doses in studies of reproduction toxicity in mice. Studies in rats and rabbits have shown that ethambutol in high doses causes minor abnormalities of the cervical vertebrae, limb reduction defects, hare lip and cleft palate in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Ethambutol Atb 250 mg film-coated tablets
Core:
Cellulose microcrystalline type 101 Povidone
Cellulose microcrystalline type 102
Partially pregelatinized maize starch Colloidal anhydrous silica
Magnesium stearate

Film:
Partially hydrolysed polyvinyl alcohol Titanium dioxide (E 171)
Macrogol (PEG 3350)
Talc
Iron oxide, red (E 172)

Ethambutol Atb 400 mg film-coated tablets
Core:
Cellulose microcrystalline type 101
Povidone
Cellulose microcrystalline type 102
Partially pregelatinized maize starch
Colloidal anhydrous silica
Magnesium stearate
Film: *Opadry II 85F 18422*
Partially hydrolysed polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol (PEG 3350)
Talc

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

Ethambutol 250 mg film-coated tablets
Folding carton containing 2 PVC/Al blisters of 10 film-coated tablets.
Cardboard box containing 150 PVC/Al blisters of 10 film-coated tablets.

Ethambutol 400 mg film-coated tablets

Folding carton containing 2 PVC/Al blisters of 10 film-coated tablets
Cardboard box containing 150 PVC/Al blisters of 10 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

7401/2015/01-02
7402/2015/01-02

9. DATE OF RENEWAL OF THE AUTHORISATION

Date of latest renewal: February 2015

10. DATE OF REVISION OF THE TEXT

June 2015

Detailed information on this medicinal product is available on the website of National Agency for Medicines and Medical Devices http://www.anm.ro