SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sinerdol ISO, capsules, 300 mg/150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 300 mg of rifampicin and 150 mg of isoniazid.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size “0” hard gelatin capsules with black cap (code 8-0-1), opaque brown body (code 7-1-1A), containing a homogeneous reddish-brown powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of all forms of pulmonary and extra-pulmonary tuberculosis.

4.2 Posology and method of administration

Tuberculosis treatment is according to National Tuberculosis Control Programme.
The recommended dose for adults weighing more than 50 kg is 2 capsules once daily, administered preferably between meals.

- usual dose of rifampicin: 8 - 12 mg per kg of body weight per day;
- usual dose of isoniazid: 5 mg per kg of body weight per day.

4.3 Contraindications

- Hypersensitivity to rifampicin, isoniazid or to any other excipient of the medicinal product;
- liver failure, jaundice caused by hepatic impairments;
- porphyria
- surgery requiring general anaesthesia;
- concurrent administration of protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir) or delavirdine (also refer to section *4.5 Interactions with other medicinal products and other forms of interaction*).

4.4 Special warnings and precautions for use

Impaired hepatic function

Sinerdol ISO is a combination of two medicinal products, both of them being associated with a possible induction of hepatic dysfunction. Patients with impaired liver function should only be given Sinerdol ISO, if absolutely necessary, and then with caution and under close medical supervision.The risk of hepatotoxicity associated with isoniazid and rifampicin requires clinical supervision and regular biological monitoring of haemogram (on the 8th day, at the end of the first month, then at a lower frequency, every 2 months), and hepatic function (serum transaminase value). If signs of hepatic function damage occur (hepatitis), the treatment should be discontinued.

Peripheral neuropathy

Following Sinerdol ISO treatment, peripheral neuropathy may occur. Regular neurological examination is necessary, and also administration with caution in case of alcoholism. It may also require pyridoxine supplementation (vitamin B6) that prevents or determines the regression of rare cases of neuropathy caused by this medicinal product, especially in the treatment of elderly or malnourished patients.

Intermittent treatment

Hypersensitivity reactions are more frequent, even exclusive, in case of intermittent treatment, or abrupt discontinuance/re-administration of rifampicin.

Other warnings and precautions

Rifampicin may delay the biliary excretion of contrast media.

Rifampicin is in competition with bilirubin and BSP test. To avoid false positive reactions, BSP test should be carried out in the morning, before rifampicin administration.

Rifampicin may influence certain laboratory results, such as Coombs test; the microbiological methods used to determinate folic acid and vitamin B12; urine analysis based on colorimetric or spectrophotometric reactions; serum concentrations of uric acid, bilirubin, and transaminase.

Rifampicin may produce a reddish colouration of the urine, saliva, tears, sputum and sweat; the patient should be warned of this. Soft contact lenses may also stain in red.

Systemic hormonal methods of contraception must be replaced with non-hormonal means of contraception during treatment with rifampicin (see section *4.5 Interactions with other medicinal products and other forms of interaction*).

In severe renal impairment, Sinerdol ISO dosage should be adjusted.

Isoniazid may cause convulsions in case of overdose, or of favourable conditions (patients showing a slow rate of acetylation). Monitoring and administration of anticonvulsants are essential measures, when needed.

Isoniazid has an enzyme inducing effect, e.g. on delta-amino-levulinic-syntetase acid. Isolated reports have associated porphyria exacerbation with rifampicin administration.

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

Since this medicine contains p-hydroxybenzoates, it may cause allergic reactions (even delayed).

4.5 Interactions with other medicinal products and other forms of interaction

Rifampicin induces microsomal hepatic enzymes, and therefore lowers the plasmatic concentrations of certain medicinal products, if concomitantly used: anticonvulsants, anti-arrhythmic drugs, beta blockers, calcium channel blockers, glucocorticoids, antidiabetics, oral anticoagulants, digoxine, estroprogestative associations, antiestrogens (tamoxifen, toremifen), antipsychotics (haloperidol), tricyclic antidepressants (amitriptillin), benzodiazepines (diazepam), barbiturates, chloramphenicol, clarithromycin, doxycycline, fluoroquinolones, antiretroviral drugs (zidovudine), cyclophosphamide, phenytoin, cyclosporine, tacrolimus, methadone, theophylline, terbinafine.

When rifampicin is used concurrently with these drugs, the dosage should be adjusted accordingly.

Concurrent administration of protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir) is contraindicated, because of the decrease of plasmatic concentrations and efficacy of protease inhibitors by hepatic metabolism enhancement. Concomitant administration of delavirdine is also contraindicated, because it may lead to a decrease of plasmatic concentration and its efficacy by hepatic metabolism enhancement.

Concomitant use of halothane or other volatile halogenated anaesthetics must be avoided, due to increased hepatotoxic risks. In case of planned surgery, the treatment with Sinerdol ISO should be interrupted a week before the surgery; the treatment should be resumed only 15 days after the surgical intervention.

Concomitant administration with Disulfiram is not recommended, because it may determine coordination difficulties and behaviour changes.

Antacids or para-amino salicylic acid will be administrated at least 8 hours from rifampicin administration, to avoid the reduction of the antibiotic absorption. Rifampicin can interfere with the standard microbiological assays used to determine folic acid and vitamin B12.

Following the treatment with Sinerdol ISO, the plasmatic concentration of calcium channel blockers (Verapamil, Diltiazem and Nifedipine) decreases due to the increase of hepatic metabolism. Where associated therapy is required, the adjustment of calcium channel blockers doses and clinical supervision during and after the discontinuance of treatment with rifampicin are recommended.

Sinerdol ISO decreases the plasmatic concentration of Ist class anti-arrhythmic drugs (Disopyramide, Hydroquinidine, and Quinidine). Clinical and electrocardiographic monitoring and, possibly, the determination of plasma concentrations of the anti-arrhythmic drugs are recommended. If necessary, the anti-arrhythmic dosage will be adjusted during and after the discontinuance of treatment with Sinerdol ISO (arrhythmic drug overdose risk may occur).

The administration of Sinerdol ISO decreases the effect of oral anticoagulants. In such situations, the protrombin level control is indicated. The doses of anticoagulant should also be adjusted, both during the treatment with Sinerdol ISO, and 8 days after the discontinuance of treatment.

The association of Sinerdol ISO and antifungal drugs (fluconazole, itraconazole, ketoconazole) reduces the plasma concentrations and the efficacy of the two anti-infectious drugs (enzymatic induction of rifampicin and decrease of intestinal absorption due to azole antifungal group). The decrease of plasma concentration of fluconazole is more significant than that of the other antifungal drugs. The recommendations are: spacing the administration of the two medicinal products which should be taken at an interval of 12 hours apart, monitoring of the plasma concentration of antifungal azoles and possibly an adjustment of posology.

Rifampicin determines the decrease of plasma concentration and morphine efficacy and morphine active metabolite. Clinical supervision is recommended, as well as the adjustment of morphine doses during the treatment with rifampicin and immediately after its discontinuance.

Sinerdol ISO in association with pyrazinamide enhances its hepatotoxic effects. Clinical and biological supervision is recommended.

Rifampicin may delay the biliary excretion of radiological contrast media used for gallbladder opacification.

Rifampicin causes a temporary competitive inhibition of bromosulfophthalein excretion. To avoid any inaccurate pathological results, the bromosulfophthalein test (BST) must be performed in the morning, before rifampicin administration (see also section *4.4 Special warnings and precautions for use*).

4.6 Pregnancy and lactation

Pregnancy

Rifampicin

Animal studies showed that rifampicin has a teratogenic effect in rats and mice, when given in large doses. The clinical studies carried out on a limited number of pregnant women, apparently, did not determine any malformations or foetotoxic effects. However, the consequences of exposal to rifampicin during pregnancy have not been assessed by clinical studies in humans, and therefore rifampicin can be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Rifampicin administration in the last weeks of pregnancy may cause postnatal haemorrhages.

Isoniazid

Animal studies in animals did not show any teratogenic effects of isoniazid. In the absence of teratogenic effects in animals, a malformative effect in humans is improbable.

The use of isoniazid in clinical studies carried out on a limited number of pregnant women, apparently, did not determine any malformations or foetotoxic effects. However, complementary studies are necessary to assess the consequences of isoniazid effect during pregnancy.

The combination of the two active substances in Sinerdol ISO is not recommended during pregnancy unless absolutely necessary.

Lactation

Both active substances of Sinerdol ISO are excreted in breast milk, therefore infants should not be breast fed during the treatment.

4.7 Effects on ability to drive and use machines

No effect on ability to drive and use machines has been reported. However, if neurological reactions occur, caution should be exercised.

4.8 Undesirable effects

Sinerdol ISO is generally well tolerated if administrated as recommended.

Rifampicin

Blood and lymphatic system disorders:

- Rare: eosinophilia, leukopenia, agranulocytosis and oedema. Isolated cases of thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but are reversible if the treatment is discontinued. If purpura occurs, the administration of rifampicin must be discontinued; cases of fatal cerebral haemorrhages have been reported when the treatment has been continued after the appearance of purpura.

Immune system disorders:

- Such reactions usually occur with intermittent dosage regimens or after occasional interruptions of drug administration: 'Flu Syndrome' (consisting of episodes of fever, chills, headache, dizziness, and bone pain; these reactions appear most commonly during the 3rd to the 6th month of therapy. The frequency of this syndrome varies but may occur in up to 50% of patients given once weekly 25 mg/kg doses of rifampicin or more). Respiratory problems and asthma-like reactions, decrease of blood pressure and shock, acute haemolytic anaemia, acute renal failure due to reversible acute tubular necrosis. Cases of cortical necrosis have also been reported.

Endocrine disorders:

- Uncommon: disturbances of the menstrual cycle have been reported in women receiving long-term antituberculosis therapy with regimens containing rifampicin.

Gastrointestinal disorders:

- Uncommon: anorexia, nausea, abdominal discomfort, meteorism;

- Rare: vomiting, diarrhoea;

- Isolated cases of pseudomembranous colitis.

Hepatobiliary disorders:

- Rare: early manifestation of hepatic hypersensitivity (after the first month of treatment): isolated rise in transaminase serum values, very rarely associated with clinical manifestations.

Skin and subcutaneous tissues disorders:

- Uncommon: vasomotor reactions, pruritus, with or without rash or urticarial.

- Isolated cases of cutaneous hypersensitivity reactions; few cases of Lyell syndrome, exfoliative dermatitis.

Other reactions:

Rifampicin may produce a reddish coloration of the urine, sputum and lachrymal fluid. Soft contact lenses may be permanently stained.

Isoniazid
Blood and lymphatic system disorders:
- Anaemia, agranulocytosis

Immune system disorders:
- Rare: fever, rash, acne, jaundice or hepatitis, lymphadenopathy, muscle pain, arthralgia, eosinophilia, blood dyscrasia;
- Very rare: rheumatoid syndrome, algodystrophy (shoulder-hand syndrome), lupus-like syndrome.

Psychiatric disorders:
- Neuropsychiatric excitement: hyperactivity, euphoria, insomnia;
- In predisposed patients, especially in association with ethyonamide, the following reactions may occur: mania-like behaviour, acute delirium or depression.

Nervous system disorders:

- Neurotoxicity (apparently due to pyridoxine deficit): peripheral neuropathy, distal paresthesia, especially in “slow acetylators”, malnourished and alcoholic patients;

- Convulsions, optic neuritis and atrophy;

- The frequency of seizures may be increased in patients with epilepsy.

Gastrointestinal disorders:

- Nausea, vomiting, epigastric distress, anorexia

Hepatobiliary disorders:

- Relatively frequent rise in transaminase serum values, bilirubin, rare cases of acute, sometimes severe, hepatitis (with or without jaundice).

4.9 Overdose

The overdose symptoms are more frequently correlated with isoniazid; its lethal dose is 200 mg per kg of body weight. The absorption of large quantities of isoniazid causes reactions within 30 minutes to 3 hours after ingestion: nausea, vomiting, dizziness, blurring of vision, hallucinations, red colouration of the skin and urine, hepatomegaly, moderate increase of serum alkaline phosphatase values and transaminase values.

Convulsive coma may occur, progressing to anorexia and death.

Metabolic acidosis, ketonuria and hyperglycaemia may occur.

Intensive supportive measures should be instituted in specialized medical centres: gastric lavage, treatment of metabolic acidosis, cardiorespiratory resuscitation, administration of anticonvulsant drugs and large doses of pyridoxine. Haemodialysis is recommended for very severe cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, Combinations of drugs for treatment of tuberculosis
ATC code: J04AM02.

Rifampicin and isoniazid are active bactericidal antituberculosis drugs which are particularly active against the rapidly growing of extracellular organisms and have, also, intracellular bactericidal activity.

Rifampicin is active against slow- and intermittently - growing *Mycobacterium Tuberculosis*.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Isoniazid acts against actively growing tuberculosis bacilli.

Antibacterial activity spectrum:

Isoniazid
Susceptible species: Mycobacterium africanum, Mycobacterium bovis, Mycobacterium bovis BCG, Mycobacterium tuberculosis (3-12%);

Moderately susceptible species (intermediate sensitivity *in vitro*)*: Mycobacterium kansasii*

Resistant species: Atypical mycobacteria (except *Mycobacterium kansasii*).

Rifampicin
Susceptible species:

- Gram-positive aerobic micro-organisms: *Bacillus anthracis, Listeria monocytogenes, Rhodococcus equi, Staphylococcus aureus* methicillin-*sensitive, Staphylococcus* methicillin resistant, *Staphylococcus* coagulaso-negative (0-25%), streptococci of groups A, B, C, G, *Streptococcus pneumoniae, Streptococcus viridans* or unclassified streptococci;

- Gram-negative aerobic micro-organisms: *Branhamella catarrhalis, Brucella, Haemophilus influenzae, Haemophilus ducrey, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella.*

- anaerobic micro-organisms: bacteroides, *Clostridium difficile, Clostridium perfringens,* fusobacterium, peptostreptococcus, *Propionibacterium acnes.*

- other species: *Chlamydia trachomatis, Chlamydia psittaci, Coxiella burnetii, Legionella, Mycobacterium africanum, Mycobacterium bovis, Mycobacterium bovis BCG, Mycobacterium kansasii, Mycobacterium tuberculosis.*

Moderately susceptible species (intermediate sensitivity *in vitro*)*:*

- Gram-positive aerobic micro-organisms: enterococci

Resistant species:

- Gram-negative aerobic micro-organisms: enterobacteriaceae, *Pseudomonas,*

- Other bacteria: atypical mycobacteria (except *Mycobacterium kansasii*).

5.2 Pharmacokinetic properties

Rifampicin

Absorption

The digestive absorption is rapid and complete. Absorption of rifampicin is reduced when the drug is ingested with food. Peak serum concentrations of 10 μg/ml occur about 2-3 hours after a dose of 600 mg of rifampicin à jeun.

Distribution:

The apparent volume of distribution is 0.8 l/kg of body weight for adults and 1.1 l/kg of body weight for children. Rifampicin is about 80% protein bound. Intracellular penetration is adequate, reaching to the macrophages that include BK channels. The distribution is largely achieved to the lungs, liver and kidneys, being adequate at the level of other tissues, but reduced in LCR and only in case of meningitis. Rifampicin crosses the foetoplacental barrier.

Metabolism

Rifampicin is mainly metabolized into desacetylrifampicin, having similar antibacterial activity. Rifampicin has an inductive effect on its own metabolism.

Elimination

The elimination half-life is dose-dependent: about 2.5 hours after a dose of 300 mg, 3-4 hours after a dose of 600 mg and about 5 hours after a dose of 900 mg. With repeated daily administration of a few days, the bioavailability of rifampicin decreases and the half-time decreases to 1-2 hours after 66 mg repeated doses. Due to its enzyme-inductive effect at liver level, rifampicin accelerates its own metabolism and therefore its systemic clearance rises after repeated administrations. The medicinal product is mostly eliminated via the biliary route; 80% of excreted amount is a metabolite, desacetylrifampicin. Rifampicin is excreted in the urine. After administration of 150 – 900 mg, 4-18% of the dose is excreted in the urine depending on the dose and as unchanged substance. After the administration of a dose of 600 mg, its excretion in breast milk is about 2 μg/ml, and in the saliva about 0.5 μg/ml.

Patient-Related Characteristics

Elderly

Plasma concentrations in elderly patients are similar to those in young patients. If renal functions are monitored, the elimination half-life does not rise unless the doses exceed 600 mg daily. Dosage

adjustment during dialysis is not required. In case of altered hepatic functions, plasma concentrations increase as elimination half-time increases. In severe hepatic insufficiency, dosage adjustment is required.

Isoniazid:

After oral administration, isoniazid produces peak blood levels within 1 to 2 hours. Within 3 hours, an efficient plasma concentration is between 1 – 2 μg/ml.

Isoniazid is readily distributed in the body, especially into the pleural fluid, lungs, sputum, saliva, cerebrospinal fluid, peritoneal and ascitic fluids. Isoniazid crosses the foetoplacental barrier. Its concentration in breast milk is identical to plasma concentration.

Isoniazid is primarily metabolized in acetyl isoniazid by acetylation. The rate of acetylation is genetically determined (there are slow and rapid acetylators).

Acetyl isoniazid is then transformed into acetyl hydrazine, which is responsible for isoniazid hepatotoxicity. The elimination half-time may show variations, in these conditions, between 1 and 6 hours. The determination of acetylation rate allows the administration of the efficient dose to each patient: the dose is 3 mg/kg for slow acetylators and 6 mg/kg for rapid acetylators.

About 75 - 95% of ingested isoniazid doses are excreted in the urine within 24 hours, primarily as metabolites. The other elimination paths (i.e. saliva) are less important from the quantitative view point.

5.3 Preclinical safety data

Carcinogenic potential

The white mice (females) used in the study, especially the one presenting haematoma, received large doses of rifampicin for 60 weeks. They were monitored for 46 weeks, a time period that allowed the observation of an increase in haematoma frequency.

No carcinogenic effect was observed neither in mice nor in rats treated under similar experimental conditions.

It was demonstrated that rifampicin has an immunosuppressive action *in vitro*, in rabbits, mice, rats and white mice.

After the administration of isoniazid to certain species of mice, the occurrence of pulmonary tumours was reported.

Mutagenicity

No sign of mutagenicity was demonstrated after having administrated this medicine product, in bacteria, *Drosophila melanogaster* or in mice. Rifampicin does not determine chromosomal anomalies on human lymphocytes. However, the chromosomal aberrations developed in cell cultures containing blood, which have been previously treated with rifampicin. A growth of chromosomal anomalies was noticed *in vitro*, in patients treated with the medicine combination consisting of rifampicin – isoniazid – pyrazinamide.

Toxicity to reproduction

Rifampicin has embryotoxic effects on rabbits and teratogenic effects on mice and rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of the capsule: lactose monohydrate, sodium starch glycolate, talc, magnesium stearate.
Capsule body: titanium dioxide (E171), carmoisine (E122), Sunset Yellow (E110), Brilliant Blue FCF (E133), gelatin, methyl parahydroxybenzoate, n-propyl parahydroxybenzoate.
Body cap: Brilliant Black BN (E151), gelatin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Store in the original package, at temperatures below 25 °C.

6.5 Nature and contents of container

Outer carton containing 1 Al/PVC blister of 10 capsules.

Cardboard containing 100 Al/PVC blisters of 10 capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

ANTIBIOTICE S.A.

1 Valea Lulupui, Iasi 707410, Romania, EU

8. MARKETING AUTHORISATION NUMBER

41/2007/01-02

9. DATE OF FIRST AUTHORISATION OR RENEWAL OF THE AUTHORISATION

Authorisation: April 2007

10. DATE OF REVISION OF THE TEXT

May 2007