SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT, PHARMACEUTICAL FORM AND STRENGTH

Sinerdol 150 mg hard capsules
Sinerdol 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sinerdol 150 mg hard capsules
Each hard capsule contains 150 mg of rifampicin.
Excipients with known effect: 25 mg of lactose monohydrate, Amaranth (E123), methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).
For a full list of excipients, see section 6.1.

Sinerdol 300 mg hard capsules
Each hard capsule contains 300 mg of rifampicin.
Excipients with known effect: 50 mg of lactose monohydrate, Amaranth (E123), methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard, capsules

Sinerdol 150 mg hard capsules
Size "2" hard capsules, with opaque red cap/opaque blue body, containing a reddish-brown powder.

Sinerdol 300 mg hard capsules
Size "1" hard capsules, with opaque red cap/opaque red body, containing a reddish-brown powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tuberculosis: In combination with other active anti-tuberculosis drugs in the treatment of all forms of tuberculosis. Sinerdol is also effective against most atypical strains of *Mycobacterium tuberculosis*.
Leprosy: In combination with at least one other active anti-leprosy drug in the management of multibacillary and paucibacillary to effect conversion of the infectious state to a non-infectious state.
Other infections: In the treatment of Brucellosis, Legionnaires Disease, and serious staphylococcal infections. To prevent emergence of resistant strains of the infecting organisms, Sinerdol should be used in combination with another antibiotic indicated for the infection.
Prophylaxis of meningococcal meningitis: For the sterilization of asymptomatic carriers of *N. meningitides* to eliminate meningococci from the nasopharynx.
For the treatment of asymptomatic carriers of *H. influenzae* or as chemoprophylaxis of exposed children of 4 years of age or younger.

4.2 Posology and method of administration

Posology

Tuberculosis

Adults: The recommended daily dose is 8-12 mg/kg of body weight.
Usual Daily dose: Patients weighing less than 50 kg: 450 mg. Patients weighing 50 kg or more: 600 mg.

Children

In children, oral doses of 10-20 mg/kg body weight daily are recommended, although a total daily dose should not usually exceed 600 mg.

Leprosy

600 mg doses of rifampicin should be given once per month. Alternatively, a daily regimen may be used. The recommended single daily dose is 10 mg/kg.
Usual daily dose: Patients weighing less than 50 kg: 450 mg. Patients weighing 50 kg or more: 600 mg.

In the treatment of leprosy, rifampicin should always be used in conjunction with other antileprosy drugs.

Brucellosis, Legionnaires Disease or serious staphylococcal infections

Adults: The recommended daily dose is 600-1200 mg given in 2 to 4 divided doses, together with another appropriate antibiotic to prevent the emergence of resistant strains of the infecting organisms.

Prophylaxis of meningococcal meningitis

Adults: 600 mg twice daily for 2 days.
Children (1 - 12 years): 10 mg/kg of body weight twice daily for 2 days.
Children (3 months - 1 year): 5 mg/kg of body weight twice daily for 2 days.

Prophylaxis of *Haemophilus influenza*

Adults and children: 20 mg per kilogram body weight daily in a single dose. No more than 600 mg per day should be given in children for 4 days.
Neonates: 10 mg/kg of body weight/day for 4 days.

Impaired liver function:

A daily dose of 8 mg/kg of body weight should not be exceeded in patients with impaired liver function.

Use in the elderly: In elderly patients, the renal excretion of rifampicin is decreased proportionally with physiological decrease of renal function; due to compensatory increase of liver excretion, the terminal half-life in serum is similar to that of younger patients. However, caution should be exercised in using rifampicin in such patients, especially if there is evidence of impaired liver function.

Method of administration

In children less than 6 years it is recommended rifampicin with age-appropriate formulations.
Take Sinerdol by mouth, with a drink of water. Daily dose depends on patient's bodyweight.
Rifampicin should be taken at least 30 minutes before a meal or 2 hours after a meal for an efficient and quick absorption.

4.3 Contraindications

Hypersensitivity to rifampicin or any of the excipients listed in section 6.1
Liver disease associated with jaundice,
Treatment with proteases inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir) or delavirdine (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Sinerdol should be given under close medical supervision.
Patients with impaired liver function should be given Sinerdol only in cases of necessity and under strict medical supervision. In these patients, rifampicin should be given in low doses and careful

monitoring of liver function, especially GPT and GOT, weekly during 2 first weeks of therapy (especially in case of association with isoniazid) and then every 2 weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be withdrawn immediately.
Rifampicin treatment should be initiated with caution in patients with a pre-existing liver disease, alcoholism, in elderly patients or under the age of 2 years and malnourished patients, especially in case of association with isoniazid. If there is no evidence of a pre-existing liver disease and your hepatic function is normal pre-treatment, hepatic tests will be made when the following symptom occur: fever, vomiting, jaundice or deterioration of general condition.

The patient will be evaluated at least monthly during the treatment.
Hyperbilirubinaemia can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion.
Rifampicin may affect the results of some blood tests: Coombs test, tests for folate, vitamin B12; urinalysis based on colorimetric reactions or spectrophotometry; serum uric acid, bilirubin, transaminases.
Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.
Rifampicin may determine reddish colour in your urine, saliva, tears, sputum and sweat, and patients should be forewarned of this. The red colour may stain soft contact lenses.
The intermittent administration of rifampicin (less than 2-3 times per week) has been reported to be associated with an immunological reaction.
If you use systemic hormonal contraceptives, replace them with non-hormonal contraceptives, during treatment with rifampicin (See also sections 4.5 Interaction with other medicinal products and other forms of interaction).

Sinerdol contains lactose monohydrate and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Sinerdol contains Amaranth (E123), which may cause allergic reactions.
Sinerdol contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). Therefore, it may cause allergic reactions (even delayed).

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use of rifampicin with proteases inhibitors (e.g. amprenavir, indinavir, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir) is contraindicated as the potential for hepatotoxicity is increased; therefore, rifampicin decreases their serum level and efficacy.

Rifampicin is a potent inducer of hepatic microsomal enzymes and may accelerate the metabolism and reduce the serum concentrations for other drugs such as: anticonvulsants, antiarrhythmics, antifungals, beta-blockers, calcium channel blockers, glucocorticoids, anti-diabetic sulphonamides, oral anticoagulants, digoxin, concurrent use of estrogen-progesterone contraceptives, antiestrogens (e.g. tamoxifen, toremifen), antipsychotics (e.g. haloperidol), tricyclic antidepressants (e.g. amitriptyline), anxiolytics and hypnotics (e.g. diazepam), barbiturates, antibacterials (e.g. chloramphenicol, clarithromycin, doxycycline, fluoroquinolones), antivirals (e.g. saquinavir, indinavir, zidovudine), cyclophosphamide, immunosuppressive agents (e.g. ciclosporin, tacrolimus), analgestics (e.g. methadone), theophylline, clofibrate, irinotecan, thyroid hormones, losartan, praziquantel, quinine, riluzole, selective 5-HT receptor antagonists (e.g. ondansetron), statins metabolised by CYP 3A4 (e.g. simvastatin), cytotoxics (e.g. imatinib), diuretics (e.g. eplerenone).

Rifampicin association with these medicines requires dose adjustment.

When rifampicin is given concomitantly with isoniazid, the potential for hepatotoxicity is increased; caution is required, especially in patients with liver disease, elderly patients or and malnourished patients.

Avoid alcoholic beverages during rifampicin treatment, because they may increase the risk of severe hepatic disorders.
Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs.
Concurrent use of rifampicin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.
When rifampicin is given concomitantly with halothane, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided.
Concomitant administration of antacids may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.
If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

Rifampicin may interfere with standard microbiological assays for serum folate and vitamin B12.
Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder.
Rifampicin causes a temporary abnormal bromosulphthalein excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

4.6 Fertility, pregnancy and lactation

Pregnancy
At very high doses in animals rifampicin has been shown to have teratogenic effects in the first trimester of pregnancy. There are no well controlled studies with rifampicin in pregnant women, therefore, rifampicin should be used in pregnant women only if strictly necessary, in the absence of an alternative treatment. When rifampicin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant.

Breast-feeding
Rifampicin is excreted in breast milk; therefore, breast-feeding should be discontinued during treatment with rifampicin.

4.7 Effects on ability to drive and use machine

Sinerdol has no influence on the ability to drive or use machines.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (<1/10000), not known (frequency cannot be estimated from available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
- Not known: haemolytic anaemia, thrombocytopenia with or without purpura (occurred primarily in case of intermittent therapy), but it is reversible if the drug is discontinued. Cerebral haemorrhage has been reported when rifampicin administration has been continued.
- Rare: disseminated intravascular coagulation (DIC)
- Very rare: eosinophilia, leukopenia, agranulocytosis.

Immune system disorders
- Common: flushing and itching with or without transient rashes;
- Uncommon: urticaria;

- Rare: exfoliative dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyell syndrome and vasculitis.
- Not known: The "flu syndrome" may also appear if rifampicin is taken irregularly by the patient, accompanied by fever, shivers, myalgia, headache, dizziness appearing most commonly during the 3rd to the 6th month of therapy reported in up to 50 % of patients. It can also occur wheezing, decrease in blood pressure, shock, anaphylaxis, acute haemolytic anaemia and acute renal failure, usually due to acute tubular necrosis or to acute interstitial nephritis.

Endocrine disorders
- Rare: adrenal insufficiency

Nervous system disorders
- Rare: psychoses

Skin and subcutaneous tissue disorders
- Not known: oedema

Musculoskeletal and connective tissue disorders
- Not known: muscle weakness, myopathy

Gastrointestinal disorders
- Not known: anorexia, nausea, vomiting, abdominal discomfort and diarrhoea. Pseudomembranous colitis has been reported with the use of rifampicin.

Hepatobiliary disorders
- Not known: hepatitis and abnormal liver function tests have been reported (see section 4.4 Special warnings and precautions for use).

Reproductive system and breast disorders
- Not known: Occasional disturbances of the menstrual cycle have been reported in women receiving long-term anti-tuberculosis therapy with regimens containing rifampicin.

Investigations
- Not known: rifampicin may produce a reddish colouration of the urine, sputum, saliva, sweat tears and saliva.

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

Signs and Symptoms: Nausea, vomiting, abdominal pain, headache, pruritus, somnolence, and unconsciousness (particularly when there is severe hepatic disease). Transient increases in liver enzymes and bilirubin, as well as hepatomegaly. The "red man syndrome" may occur: brownish-red or orange colouration of the skin, tears, sweat. Hypotension and arrhythmias were reported in some severe cases. Facial or periorbital oedema may occur in paediatric patients.
The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults

have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of these reports.
Nonfatal overdoses of 100 mg/kg of body weight in paediatric patients ages 1 to 4 years old for one to two doses have been reported.
Management: intensive supportive measures should be instituted and gastric lavage should be performed; the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Concomitantly general supportive measures to maintain vital functions should be applied; forced diuresis, haemodialysis. It will take into account the possibility that other medicines associated with rifampicin have been ingested in excessive dose, which requires additional specific measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, antibiotics
ATC Code: J04AB02
Mechanism of action: Rifampicin is a semisynthetic antibiotic, with bactericidal activity. Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. It exerts its bactericidal effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly. Rifampicin has bactericidal activity against slow and intermittently growing of *Mycobacterium tuberculosis* organisms. *In vitro*, rifampicin has been shown to be active against most strains of mycobacteria, chlamydia and aerobic Gram-negative/positive microorganisms: *Mycobacterium tuberculosis, Mycobacterium leprae, Neisseria meningitides, Neisseria gonorrhoea, Staphylococcus aureus, Proteus sp., Staphylococcus epidermidis, H. influenza, E. coli, Pseudomonas aeruginosa, Legionella pneumophila, Brucella sp., Streptococcus pyogenes.*

5.2 Pharmacokinetic properties

Absorption
Rifampicin is readily completely absorbed from the gastrointestinal tract. Peak levels occur between 1 and 4 hours following the oral administration of a 600 mg dose in adult and 10 mg/kg in children, with average peak values of 9 μg/mL (6-32 μg/mL). Absorption of rifampicin is reduced or delayed when the drug is ingested with food or aminosalicylates (PAS).

Distribution
Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid; rifampicin crosses the placental barrier and is excreted in breast milk. Rifampicin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues. The apparent volume of distribution is 1.6 L/kg in adults, and 1.1 L/kg in children.

Biotransformation
Rifampicin is metabolised mainly to an active metabolite, deacetyl rifampicin. Because rifampicin can induce hepatic microsomal enzymes, rifampicin increases its own rate of metabolism.

Elimination
The half-life of rifampicin ranges from 1.5 to 5 hours depending on dosage and administration. Hepatic impairment and biliary obstruction cause a longer half-life, but renal failure does not appear to cause a change at doses not exceeding 600 mg daily.
After passing through the liver, rifampicin is eliminated in the bile and partially resorbed by intestine, an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive

deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

The pharmacokinetics in special patient groups
In the presence of severe renal failure, the drug is excreted entirely in the bile.
Plasma concentrations in elderly are comparable to those reported in adults.
In patients with renal impairment rifampicin does not accumulate for doses not exceeding 600 mg. For doses exceeding 600 mg, excretion may be delayed due to saturation of biliary excretion mechanism. Dosage adjustment is required.
In patients with hepatic impairment, plasma concentrations and T1/2 increase slightly. A dosage adjustment is necessary in patients with severe hepatic impairment.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sinerdol 150 mg hard capsules
Capsule content:
Lactose monohydrate
Magnesium stearate

Capsule cap:
Titanium dioxide (E171)
Allura Red (E129)
Amaranth (E123)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Gelatin

Capsule body:
Titanium dioxide (E171)
Brilliant blue (E133)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Gelatin

Sinerdol 300 mg hard capsules
Capsule content:
Lactose monohydrate
Magnesium stearate

Capsule cap
Titanium dioxide (E171)
Allura Red (E129)
Amaranth (E123)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Gelatin

Capsule body
Titanium dioxide (E171)
Amaranth (E123)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 25 ºC, in the original package.

6.5 Nature and contents of container

Sinerdol 150 mg hard capsules
Box with 2 PVC/Al blisters of 10 hard capsules
Cardboard box with 100 PVC/Al blisters of 10 hard capsules
Not all pack sizes may be marketed.

Sinerdol 300 mg hard capsules
Box with 1 PVC/Al blister of 10 hard capsules
Cardboard box with 100 PVC/Al blisters of 10 hard capsules
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ANTIBIOTICE SA
1 Valea Lupului, Iasi 707410, Romania

8. MARKETING AUTHORISATION NUMBER

9186/2016/01-02
9187/2016/01-02

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: August 2016

10. DATE OF REVISION OF THE TEXT

August 2016

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