Sinerdol ISO, capsules, 300 mg/150 mg
Rifampicin / isoniazid

Composition

One capsule contains 300 mg of rifampicin, 150 mg of isoniazid, and 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; *capsule cap*: Brilliant Black BN (E151), gelatin.

Pharmacotherapeutic group: antimycobacterials, combinations of drugs for treatment of tuberculosis

Therapeutic indications

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

Contraindications

- Hypersensitivity to rifampicin, isoniazid or to any of the ingredients of the medicinal product;
- Liver failure, jaundice of hepatobiliary origin;
- Porphyria
- Surgery requiring general anaesthesia;
- Concurrent administration of protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, lopinavir/ritonavir, saquinavir) or delavirdine (also refer to section *Interactions*).

Precautions

Hepatic disease
Sinerdol ISO is a combination of two active substances, each of them has been associated with a possible induction of liver dysfunction. The patients with hepatic disorders should only be treated with Sinerdol ISO, if absolutely necessary, taking all precautions and under strict medical supervision. The risk of hepatotoxicity associated with isoniazid and rifampicin requires clinical supervision and regular biological monitoring of haemogram (on the 8^{th} day, at the end of the first month, then at a lower frequency, of 2 months), and hepatic function (serum transaminase value). If signs of hepatic function damage occur (hepatitis), the treatment should be discontinued.

Peripheral neuropathy
Following treatment with Sinerdol ISO, peripheral neuropathy may occur. Regular neurological examination is necessary and caution should also be exercised when administered to alcoholic patients. Pyridoxine (vitamin B6) supplementation during treatment prevents or determines 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 transaminases.
Rifampicin may produce a reddish coloration 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 *Interactions*).
Isoniazid may cause convulsions in case of overdose or, in the presence 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, on delta-amino-levulinic-syntheses acid for instance. 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 use this medicinal product.
Since this medicine contains p-hydroxybenzoates, it may cause allergic reactions (even delayed).

Interactions

Rifampicin induces microsomal hepatic enzymes, which may lead to a decrease in the plasmatic concentrations of certain medicinal products, if concomitantly used: anticonvulsants, anti-arrhythmic drugs, beta blockers, calcium channel blockers, glucocorticoids, antidiabetics, oral anticoagulants, digoxin, estroprogestative associations, antiestrogens (tamoxifen, toremifen), antipsychotics (haloperidol), tricyclic antidepressants (amitriptyline), 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, due to the decrease of plasmatic concentrations and efficacy of protease inhibitors caused by the increase in hepatic metabolism. Moreover, concomitant administration of delavirdine is also contraindicated, because it may lead to a decrease of plasma concentration and its efficacy caused by the increase in hepatic metabolism.
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 disulfiram administration is not recommended, because it may determine coordination difficulties and affect the behaviour.
Antacids or para-amino salicylic acid will be administrated at least 8 hours after administration of rifampicin, to avoid the reduction of antibiotic absorption. Rifampicin may 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 lowers the plasmatic concentration of I-st class anti-arrhythmic drugs (disopyramide, hydroquinidine, 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 prothrombin 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, eventually, an adjustment of posology.
Rifampicin decreases the plasma concentration and the morphine efficacy and morphine active metabolite. Clinical supervision is recommended, as well as the adjustment of morphine doses during 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 bromosufophthalein (BST) test must be performed in the morning, before rifampicin administration (see section *Precautions*).

Special warnings
In severe renal insufficiency, Sinerdol ISO dosage should be adjusted.

Pregnancy and breast-feeding
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 proper 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 unlikely.
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 to be used during pregnancy unless absolutely necessary.

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

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

Dosage and method of administration
Tuberculosis treatment and prevention is according to National Tuberculosis Control Programme.
The recommended dose for adults weighing more than 50 kg is of 2 capsules once daily, administered between meals.

- usual dose of rifampicin: 8 - 12 mg per kg of body weight daily
- usual dose of isoniazid: 5 mg per kg of body weight daily

Adverse reactions
Rifampicin and isoniazid are, 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 interrupted; cases of fatal cerebral haemorrhage 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 regimens with doses of 25 mg/kg or more); respiratory problems and asthma-like reactions, decrease in 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 signs of hepatic hypersensitivity (after first month of treatment): transient elevations of serum transaminases, rarely associated with clinical signs.
Skin and subcutaneous tissues disorders:
- Uncommon: vasomotor reactions, pruritus with or without a rash;
- 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 pains, arthralgia, eosinophilia, blood dyscrasia
- Very rare: rheumatoid syndrome, algodystrophy (shoulder-hand syndrome), lupus-like syndrome.
Psychiatric disorders:
- Neuropsychiatric excitement: hyperactivity, euphoria, insomnia;
- On a predisposing land, especially in association with ethyonamide, the following disorders may occur: mania-like behaviour, acute delirium or depression.
Nervous system disorders:
- Neurotoxicity (apparently due to pyridoxine deficit): peripheral neuropathy with distal paraesthesia, 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).

Overdose
The overdose symptoms are more frequently correlated with isoniazid; its lethal dose is 200 mg/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 phosphatases values and transaminases values.
Convulsive coma may occur, progressing to anorexia and death.
Metabolic acidosis, cetonuria and hyperglycaemia may occur.
Intensive supportive measures should be instituted in specialized medical centres: gastric lavage, treatment of metabolic acidosis, cardiorespiratory resuscitation, administration of anti-convulsant drugs and large doses of pyridoxine. Haemodialysis is recommended for very severe cases.

Storage
Do not use after the expiry date printed on the package (EXP).
Store below 25 °C, in the original package.
Keep out of the reach and sight of children.

Packaging
Outer carton containing 1 Al/PVC blister of 10 capsules.
Outer carton containing 100 Al/PVC blisters of 10 capsules.

Manufacturer
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Holder of Marketing Authorisation:
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