

RIFASYNT – PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

RIFASYNT 150mg capsules.

RIFASYNT 300mg capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains either 150 mg or 300 mg of rifampicin.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see section 6.1.

Each 150mg capsule contains lactose monohydrate 23.0mg.

Each 300mg capsule contains lactose monohydrate 28.0mg.

3. PHARMACEUTICAL FORM

RIFASYNT 150 mg: Hard gelatin capsules, scarlet – scarlet size 2, for oral administration.

RIFASYNT 300 mg: Hard gelatin capsules, scarlet – scarlet size 1, for oral administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Tuberculosis: In combination with other active anti-tuberculosis drugs in the treatment of all forms of tuberculosis, including fresh, advanced, chronic and drug-resistant cases. RIFASYNT is also effective against most atypical strains of Mycobacteria.
- Prophylaxis of meningococcal meningitis: For the treatment of asymptomatic carriers of *N. Meningitides* to eliminate meningococci from the nasopharynx.
- Leprosy: In combination with at least one other active anti-leprosy drug in the management of multibacillary and paucibacillary leprosy 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, RIFASYNT should be used in combination with another antibiotic appropriate for the infection.
- Haemophilus influenzae: For the treatment of asymptomatic carriers of *H.influenzae* and as chemoprophylaxis of exposed children, 4 years of age or younger.

4.2. Posology and method of administration

Posology

Tuberculosis:

RIFASYNT should be given with other effective anti-tuberculosis drugs to prevent the possible emergence of rifampicin-resistant strains of Mycobacteria.

Adults: The recommended single daily dose in tuberculosis is 8-12mg/kg.

Usual daily dose:

Patients weighing less than 50kg: 450mg

Patients weighing 50kg or more: 600mg

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

Prophylaxis of meningococcal meningitis:

Adults: 600mg twice daily for 2 days

Paediatric population:

Children 1-12 years – 10mg/kg twice daily for 2 days

Children 3 months – 1 year: 5mg/kg twice daily for 2 days.

Leprosy:

600mg doses of rifampicin should be given once per month. Alternatively, a daily regimen may be used. The recommended single daily dose is 10mg/kg.

Usual daily dose:

Patients weighing less than 50kg: 450mg.

Patients weighing 50kg or more: 600mg.

In the treatment of leprosy, rifampicin should always be used in conjunction with at least one other antileprosy drug.

Brucellosis, Legionnaires Disease or serious staphylococcal infections

Adults: The recommended daily dose is 600-1200mg 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 Haemophilus influenzae

Adults: For members of households exposed to H. influenzae B disease when the household contains a child 4 years of age or younger, it is recommended that all members (including the child) receive rifampicin 20mg/kg once daily (maximum daily dose 600mg) for 4 days.

Index cases should be treated prior to discharge from hospital.

Neonates (1 month): 10 mg/kg daily for 4 days.

Impaired liver function

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

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 as increased blood levels have been noted in one study of rifampicin in elderly patients, caution should be exercised in using rifampicin in such patients, especially if there is evidence of impaired liver function.

Method of administration

For oral administration.

The daily dose of RIFASYNT, calculated from the patient's body weight, should preferably be taken at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption.

4.3. Contraindications

RIFASYNT is contraindicated in patients who

- have hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
- have jaundice.
- are concurrently receiving saquinavir/indinavir therapy (see section 4.5).

4.4. Special warnings and precautions for use

Rifampicin should be given under the supervision of a respiratory or other suitably qualified physician.

Cautions should be taken in case of renal impairment if dose > 600 mg/day.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with rifampicin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate).

Baseline tests are unnecessary in children unless a complicating condition is known or clinically suspected.

Patients with impaired liver function should only be given rifampicin in cases of necessity, and then with caution and under close medical supervision. In these patients, lower doses of rifampicin are recommended and careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should initially be carried out prior to therapy, weekly for two weeks, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.

Rifampicin should also be withdrawn if clinically significant changes in hepatic function occur. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily.

In patients with impaired liver function, elderly patients, malnourished patients, and possibly, children under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with RIFASYNT. If the patient has no evidence of pre-existing liver disease and normal pre-

treatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occur.

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions.

In some patients hyperbilirubinaemia can occur in the early days of treatment. This results from competition between rifampicin and bilirubin for hepatic excretion.

An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Because of the possibility of immunological reaction including anaphylaxis occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interrupting treatment.

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.

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy.

RIFASYNT capsules should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Severe cutaneous adverse reactions (SCARs) including Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with a not known frequency in association with RIFASYNT capsules treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult immediately their physician.

If signs and symptoms suggestive of these reactions appear, RIFASYNT capsules should be withdrawn immediately and an alternative treatment considered (as appropriate).

Most of these reactions occurred within 2 days to 2 months after treatment initiation; the time to onset can vary depending on the conditions.

RIFASYNT capsules may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained.

RIFASYNT capsules are a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease concomitant drug exposure and efficacy. Therefore, potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.

Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding. Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinemia).

All patients with abnormalities should have follow up examinations, including laboratory testing, if necessary.

4.5. Interactions with other medicinal products and other forms of interaction

Pharmacodynamic Interactions

When rifampicin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of RIFASYNT with saquinavir/ritonavir is contraindicated (see section 4.3 Contraindications).

When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored closely for hepatotoxicity.

The concomitant use of rifampicin with other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (especially in high doses).

Effect of RIFASYNT capsules on other medicinal products

Induction of Drug Metabolizing Enzymes and Transporters

RIFASYNT capsules are a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by RIFASYNT capsules include cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Most drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by RIFASYNT capsules simultaneously. Therefore, RIFASYNT capsules may accelerate the metabolism and reduce the activity of certain co-administered drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes (Table 1). To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment when starting or stopping concomitantly administered RIFASYNT capsules.

Examples of drugs or drug classes affected by rifampicin:

- Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide),
- Antiepileptics (e.g. phenytoin),
- Hormone antagonist (antiestrogens e.g. tamoxifen, toremifene, gestrinone),
- Antipsychotics (e.g. haloperidol, aripiprazole),
- Anticoagulants (e.g. coumarins),
- Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole),
- Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine),
- Barbiturates
- Beta-blockers (e.g. bisoprolol, propranolol),
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zolpidem, zolpichlorone),
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine),
- Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin),
- Corticosteroids
- Cardiac glycosides (digitoxin, digoxin),
- Clofibrate,
- Systemic hormonal contraceptives including estrogens and progestogens,
- Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone),
- Immunosuppressive agents (e.g. ciclosporin, sirolimus, tacrolimus)
- Irinotecan,
- Thyroid hormone (e.g. levothyroxine),
- Losartan,
- Analgesics (e.g. methadone, narcotic analgesics),
- Praziquantel,
- Quinine,
- Riluzole,
- Selective 5-HT₃ receptor antagonists (e.g. ondansetron)
- Statins metabolised by CYP 3A4 (e.g. simvastatin),
- Theophylline,
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline),
- Cytotoxics (e.g. imatinib),
- Diuretics (e.g. eplerenone)
- Enalapril: decrease enalapril active metabolite exposure. Dosage adjustments should be made if indicated by the patient's clinical condition
- Hepatitis-C antiviral drugs (eg, daclatasvir, simeprevir, sofosbuvir, telaprevir): Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.
- Morphine: Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment of rifampicin.

Rifampicin treatment reduces the systemic exposure of oral contraceptives. Patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during RIFASYNT therapy. Also diabetes may become more difficult to control.

Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs.

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.

Effect of other medicinal products on RIFASYNT capsules

Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

Other drug interactions with RIFASYNT capsules

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Interference with laboratory and diagnostic tests

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary 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. There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, Rifadin should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. When Rifadin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant for which treatment with Vitamin K1 may be indicated.

Lactation

Rifampicin is excreted in breast milk, patients receiving rifampicin should not breast feed unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Reactions occurring with either daily or intermittent dosage regimens include:

Blood and lymphatic system disorders

- Rare: Disseminated intravascular coagulation has also been rarely reported.
- Very rare: Agranulocytosis has been reported very rarely reported.
- Not known:
 - Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.
 - Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
 - Eosinophilia, leucopenia, oedema, muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin.

Gastrointestinal disorders

- Not known:
 - *Gastrointestinal reactions* consist of anorexia, nausea, vomiting, abdominal discomfort, and diarrhoea.
 - Pseudomembranous colitis has been reported with rifampicin therapy.

Hepatobiliary disorders

- Not known: Hepatitis can be caused by rifampicin and liver function tests should be monitored (see section 4.4).

Skin and subcutaneous tissue disorders

- Uncommon: Urticaria and more serious hypersensitivity cutaneous reactions have occurred but are uncommon.
- Rare: Exfoliate dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyell's syndrome and vasculitis has been reported rarely.
- Not known: Cutaneous reactions which are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically they consist of flushing and itching with or without a rash.

Metabolism and nutrition disorders

- Rare: Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Nervous system disorders

- Rare: Psychoses have been rarely reported.

Reactions usually occurring with intermittent dosage regimens and probably of immunological origin include:

Not known:

- 'Flu Syndrome' consisting of episodes of fever, chills, headache, dizziness, and bone pain appearing most commonly during the 3rd to the 6th monthly of therapy. The frequency of the syndrome varies but may occur in up to 50 % of patients given once-weekly regimens with a dose of rifampicin of 25 mg/kg or more.
- Shortness of breath and wheezing.
- Decrease in blood pressure and shock.
- Anaphylaxis.
- Acute haemolytic anaemia.
- Acute renal failure usually due to acute tubular necrosis or acute interstitial nephritis.

If serious complications arise, e.g. renal failure, thrombocytopenia or haemolytic anaemia, rifampicin should be stopped and never restarted.

Occasional disturbances of the menstrual cycle have been reported in women receiving long-term anti-tuberculosis therapy with regimens containing rifampicin.

Rifampicin may produce a reddish discolouration of the urine, sputum and tears. The patient should be forewarned of this.

Soft contact lenses may be permanently stained.

4.9. Overdose**Human Experience***Signs and Symptoms:*

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

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 the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Management:

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following

evacuation of the gastric contents, 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. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, antibiotics, ATC code: J04AB02

Rifampicin is an active bactericidal anti-tuberculosis drug which is particularly active against the rapidly growing extracellular organisms and also has bactericidal activity intracellularly. Rifampicin has activity against slow and intermittently-growing *M. Tuberculosis*.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Cross-resistance to rifampicin has only been shown with other rifamycins.

5.2. Pharmacokinetic properties

Rifampicin is readily absorbed from the gastrointestinal tract. Peak serum concentrations of the order of 10µg/ml occur about 2 to 4 hours after a dose of 10mg/kg body weight on an empty stomach.

Absorption of rifampicin is reduced when the drug is ingested with food.

The pharmacokinetics (oral and intravenous) in children are similar to adults.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600mg dose and increases to 5.1 hours after a 900mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600mg/day, it does not differ in patients with renal failure and consequently, no dosage adjustment is required.

Rifampicin is rapidly eliminated in the bile and 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. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

RIFASYNT 150 mg capsules also contain lactose monohydrate, croscarmellose sodium and magnesium stearate. The capsule shells contain gelatin, erythrosine (E127), indigo carmine (E132) and titanium dioxide (E171).

RIFASYNT 300 mg capsules also contain lactose monohydrate, croscarmellose sodium and magnesium stearate. The capsule shells contain gelatin, erythrosine (E127), indigo carmine (E132) and titanium dioxide (E171).

6.2. Incompatibilities

None known.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C, in the original package, in order to be protected from light.

6.5. Nature and contents of container

Capsules are available packed in aluminium foil – polyvinylchloride film blisters.
RIFASYNT 150mg caps: Cartons containing 100 capsules are available.
RIFASYNT 300mg caps: Cartons containing 100 capsules are available.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

For oral administration only.

7. MARKETING AUTHORISATION HOLDER:

KOMEDIC SDN BHD, 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya

8. MANUFACTURER:

MEDOCHEMIE LTD., 1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

9. MARKETING AUTHORISATION NUMBER

RIFASYNT 150mg caps: MAL19860789AZ

RIFASYNT 300mg caps: MAL19860825AZ

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

RIFASYNT 150mg caps: 08/05/2002

RIFASYNT 300mg caps: 08/05/2002

11. DATE OF REVISION OF THE TEXT

[12/2019](#)