Rifadin®
Intravenous 600mg Powder and Solvent for Concentrate for Solution for Infusion
Rifampicin

Is this leaflet hard to see or read?
Phone 01 403 5600 for help.
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Rifadin is and what it is used for

Rifadin Intravenous 600mg Powder and Solvent for Concentrate for Solution for Infusion is one of a group of medicines called antibiotics. It is used to treat tuberculosis (also known as TB) and other similar types of infection.

2. Before you take Rifadin

Do not take Rifadin if:
- You are allergic (hypersensitive) to rifampicin or any of the other ingredients.
- You have yellowing of the skin and eyes (jaundice).
- You are taking saquinavir or ritonavir for HIV infection (see 'Taking other medicines' section below).
- You are taking medicine called lurasidone for schizophrenia and bipolar disorders (see 'Taking other medicines' section below.

Do not use if any of the above apply to you. If you are not sure, talk to your doctor, nurse or pharmacist before having Rifadin.

Warnings and precautions

Inform your doctor immediately while taking this medicine

• If your symptoms of tuberculosis return or get worse (see 4. Possible side effects)
• if you develop new or sudden worsening of shortness of breath, possibly with a dry cough or fever not

responding to antibiotic treatment. These could be symptoms of lung inflammation (interstitial lung disease/pneumonitis) and can lead to serious breathing problems due to collection of fluid in the lungs and interfere with normal breathing which can lead to life threatening conditions

Take special care with Rifadin

Tell your doctor or pharmacist if:
- if you have a history of lung inflammation (interstitial lung disease/pneumonitis)
- You have liver or kidney problems.
- You have a rare blood problem called 'porphyria'.
- If you have a problem with bleeding or tendency to bruise easily.
- If you are taking other antibiotics at the same time.
- Rifadin may produce a discolouration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears. If you wear contact lenses- please note that Rifadin may permanently stain soft contact lenses.
- If you have severe skin reaction such as severe extensive skin damage (separation of the epidermis and superficial mucous membranes) (toxic epidermal necrolysis, TEN,), Skin blistering, red/purple rash, fever headache, cough and joint pain (Stevens-Johnson syndrome, SJS) or large areas of red, swollen skin with small pus-filled elevations (acute generalized Exanthematous pustulosis, AGEP) may occur. Treatment must be immediately discontinued if any symptoms or signs of AGEP, SJS or TEN are present.
- The person having this medicine is a child.
- You are aged 65 years or older.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before having Rifadin.

Blood Tests
Your doctor will need to check your blood before you are given this medicine.
This will help your doctor know if any changes happen to your blood after having this medicine.
You may also need to have regular blood tests to check how your liver is working.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
This includes medicines you buy without a prescription, including herbal medicines.
This is because Rifadin can affect the way some other medicines work. Also some medicines can affect the way Rifadin work.

In particular, tell your doctor if you are taking:
• Saquinavir or ritonavir used for HIV infection.
• Other antibiotic medicines such as cefazolin (concomittant use should be avoided as it may lead to severe blood disorders, which may result in fatal outcome (especially in high doses).

The following medicines can make Rifadin work less well:
• Antacids used for indigestion. Have Rifadin at least 1 hour before taking antacids.
• Other medicines used for TB such as P-aminosalicyclic acid (PAS). PAS and Rifadin should be taken at least 8 hours apart.

Tell your doctor or pharmacist if you are taking any of the following medicines:
Heart and blood medicines
• Medicines for high blood pressure.
• Medicines for heart problems or to control your heartbeat.
• Some medicines used to thin the blood such as warfarin, clopidogrel.
• Medicines used to lower cholesterol.

Mental health, epilepsy and motor neurone medicines
• Medicines for thought disorders known as 'antipsychotics' such as haloperidol.
• Medicines to calm or reduce anxiety (hypnotics, anxiolytics).
• Medicines to help you sleep (barbiturates).
• Medicines used for epilepsy such as phenytoin.
• Some medicines used for depression such as amitriptyline and nortriptyline.
• Riluzole - used for motor neurone disease.
• Lurasidone for schizophrenia and bipolar disorders, as rifampicin may reduce the blood levels of lurasidone.

Medicines for infections and the immune system
• Some medicines used for viral infections such as indinavir, efavirenz, ritonavir, saquinavir, zidovudine.
• Medicines used for the treatment of fungal infections such as caspofungin, fluconazole, itraconazole, ketoconazole.
• Medicines used for bacterial infections (antibiotics).
• Medicines used for lowering your immune system such as ciclosporin and tacrolimus.
• Praziquantel - used for tapeworm infections.
• Atovaquone - used for pneumonia.
• Dapsone: If you are taking dapsone (an antibiotic) with rifampicin, it may cause haematological toxicity including a decrease in bone marrow and blood cells, and methemoglobinemia (decrease in oxygen in your blood caused by changes in red blood cells)

Hormone and cancer medicines
• Some hormone medicines (estrogen, systemic hormones, progestogens) used for contraception.
• Some hormone medicines (anti-estrogens) used for breast cancer or endometriosis such as tamoxifen, toremifene and gestrinone.
• Levothyroxine (thyroid hormone) used for thyroid problems.
• Irinotecan - used for cancer.

Pain, inflammation and gout medicines
• Paracetamol: If you are taking paracetamol and rifampicin, it can increase the risk of liver damage
• Medicines used for pain.
• Corticosteroids used for inflammation such as hydrocortisone, betamethasone and prednisolone.
• Methadone - used for heroin withdrawal.

Other medicines
• Medicines used for diabetes.
• Medicines used to relax muscles before surgery (anaesthetics) such as halothane.
• Some medicines used for feeling sick or being sick such as ondansetron.
• Quinine - used for malaria.
• Theophylline - used for wheezing or difficulty in breathing.

Tell your doctor or pharmacist if you are pregnant and planning or required to undergo pregnancy termination using mifepristone.

Taking Rifadin with food and drink
Not applicable.

Pregnancy and breast-feeding
You should not be administered Rifadin if you are pregnant or breast-feeding a baby. Rifadin could harm your baby.

If you are using oral contraception ("the Pill") it is important that you use an alternative barrier method of contraception or the "coil" whilst taking Rifadin and to continue using this form of contraception for two weeks after finishing your course of treatment. This is because Rifadin may make "the Pill" less effective. If you have any questions or are unsure about this talk to your doctor or pharmacist.

Driving and using machines
You may feel dizzy or faint, have problems with vision or have other side effects that could affect your ability to drive while having this medicine. If this happens, do not drive or use any tools or machines.

3. How to take Rifadin

Rifadin will usually be given to you by administration into a vein. The dose of Rifadin is determined by the type and severity of the infection.

Tuberculosis
The usual adult daily dose is a single administration of 600mg (1 vial) over 2 to 3 hours. The usual daily dose for a child over 3 months is 15 (10-20) mg/kg body weight, however this should not exceed 600mg.

Impaired Liver Function
Your doctor will probably reduce your dose if you have impaired liver function, usually to no more than 8mg/kg a day.
In elderly patients, your doctor may monitor your dose more closely, especially if you show signs of liver dysfunction.
When you start to feel better, your doctor may decide to change your medicine
to the capsule or syrup form of Rifadin. Follow your doctors instructions on how much Rifadin to take and for how long.

If you are given more Rifadin than you should
Your doctor will carefully calculate how much Rifadin you should get.
Therefore it is unlikely your doctor or nurse will give you too much of this
medicine. But, if you think that you have been given too much or too little Rifadin, tell your doctor or nurse.

If you miss a dose of Rifadin
Your doctor or nurse will have instructions on when to give you this medicine.
It is unlikely that you will not be given the medicine as it has been prescribed. However, if you think you may have missed a dose, then talk to your doctor or nurse.

If you stop taking Rifadin
You should only stop taking Rifadin if your doctor tells you to. It is essential to take the medicine and not to stop and start as this could cause unwanted side effects.

4. Possible side effects

Like all medicines, Rifadin can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
• Paradoxical drug reaction: Symptoms of tuberculosis can return, or new symptoms can occur after initial improvement during treatment. Paradoxical reactions have been reported as early as 2 weeks and as late as 18 months after beginning anti-tuberculosis treatment. Paradoxical reactions are typically associated with fever, swollen lymph nodes (lymphadenitis), breathlessness, and cough. Patients with paradoxical drug reaction can also experience headaches, loss of appetite, and weight loss.

Tell a nurse or doctor straight away if you notice any of the following side effects:
- You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, wheezing, swelling of your lips, face, throat or tongue.
- You have a fever and yellowing of the skin or whites of the eyes, feel tired, weak or generally unwell, loss of appetite (anorexia), feeling sick (nausea), being sick (vomiting). These may be early signs of liver problems.
- You get blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may have a serious skin problem.
- You have severe bleeding (haemorrhage).
- You bruise more easily than usual. Or you may have a painful rash of dark red spots under the skin which do not go away when you press on them (purpura). This could be because of a serious blood problem.
- You have chills, tiredness, unusually pale skin colour, shortness of breath, fast heartbeat or dark coloured urine. This could be signs of a serious type of anaemia.
- You have blood in your urine or an increase or decrease in amount of urine you produce. You may also get swelling, especially of the legs, ankles or feet. This may be caused by serious kidney problems.
- You have a sudden severe headache. This could be a sign of bleeding in the brain.
- You get confused, sleepy, cold clammy skin, shallow or difficult breathing, a racing heartbeat or your skin is paler than normal.
  These could be signs of shock.
- You get more infections more easily than normal. Signs include fever, sore throat or mouth ulcers. This could be because you have a low number of white blood cells.
- You have bleeding from your nose, ear, gums, throat, skin or stomach.
  Signs may include a feeling of tenderness and swelling in your stomach, purple spots on your skin and black or tar-like stools.
- Severe watery diarrhoea that will not stop and you are feeling weak and have a fever. This may be something called 'Pseudomembranous colitis'.

If you experience the following side effects contact your doctor immediately:
- A drug reaction that causes rash, fever inflammation of internal organs, hematologic abnormalities and systemic illness (DRESS syndrome). Large areas of red, swollen skin with small pus-filled elevations (acute generalized exanthematous pustulosis, AGEP).
- Severe bleeding.
- Itching, weakness, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin or dark urine. These symptoms might be related to a severe liver injury.

Not known: frequency cannot be estimated from the available data
- Inflammation of the lungs (interstitial lung disease/pneumonitis): Tell your doctor immediately if you develop new or sudden worsening of shortness of breath, possibly with a cough or fever

Tell your doctor as soon as possible if you have any of the following side effects:
- Water retention (oedema) which may cause swollen face, stomach, arms or legs.
- Muscle weakness or pain or loss of muscle reflexes.
- Dizziness, feel lightheaded and faint especially when you stand or sit up quickly (due to low blood pressure).
- Swollen fingers, toes or ankles.
- Hair loss.
- Being unable to concentrate, feeling nervous, irritable or depressed.
- Feeling very tired and weak or difficulty sleeping (insomnia).
- Short-term memory loss, anxiety, being less alert or responsive.
- Wasting of muscles or other body tissues.
- Weight loss, night sweats and fever. These could be signs of a blood condition called eosinophilia.

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:
- Skin flushing or itching.

• Irregular periods.
• Diarrhoea or stomach discomfort.
• Pain, redness or swelling at the site of injection.

You notice a discolouration (yellow, brown, orange or red colour) in your teeth (which may be permanent), urine, sweat, phlegm (sputum), saliva or tears. The colour may permanently stain soft contact lenses.

If you notice any other side effects not listed in this leaflet talk to your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly in Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; e-mail: medsafety@hpra.ie.
In Malta: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

By reporting side effects you can help provide more information on the safety of this medicine

5. How to store Rifadin

Do not use Rifadin after the expiry date which is stated on the vial, ampoule and carton after EXP. The expiry date refers to the last day of that month.
Your doctor or nurse will ensure that Rifadin is properly stored. Do not store above 25°C. Keep out of the reach and sight of children. Reconstituted solution: the solution should be used immediately. Discoloured solution should not be used.
Medicines should not be disposed of via wastewater or household waste.
Ask your pharmacist how to dispose of medicines no longer required.
These measures will help to protect the environment.

6. Further information

What Rifadin contains
The active substance is rifampicin. Each 20ml vial contains 600mg rifampicin powder for concentrate for solution for infusion. The powder also contains sodium sulfoxylate formaldehyde and sodium hydroxide. The total sodium content is less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium- free”. The rifampicin powder is dissolved with a 10ml vial of solvent, containing water for injections, to make a concentrate. This concentrate is then diluted to make a solution that will be administered by infusion.

What Rifadin looks like and contents of the pack
Powder and solvent for concentrate for solution for infusion. Red sterile lyophilised powder for reconstitution with accompanying ampoule of sterile solvent for dilution for use as an intravenous infusion. The reconstituted solution is red in colour. Discoloured solution should not be used.

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Rifadin® Intravenous 600mg Powder and Solvent for Concentrate for Solution for Infusion

Technical Information
The following information is extracted from the SPC. Technical information for the preparation and administration of Rifadin Intravenous 600mg Powder and Solvent for Concentrate for Solution for Infusion.

4.2. Posology and Method of Administration

Treatment with Rifadin for Infusion should preferably include the concomitant use of other appropriate antibiotics to prevent the emergence of resistant strains of the causative organism. Rifadin for infusion is for intravenous infusion only and must not be administered by intramuscular or subcutaneous route (see 4.4 Special Warnings and Precautions for Use).

Adults: a single daily administration of 600mg (8 to 12 mg/kg b.w.) given in an intravenous infusion drip over 2 to 3 hours has been found to be effective and well tolerated for adult patients.

Serum concentrations following the dosage regimen are similar to those obtained after 600mg by mouth.

Lower doses are recommended for frail and elderly patients. A daily dose of 8mg/kg bodyweight should not be exceeded in patients with impaired liver function.

When patients are able to accept oral medication, they should be transferred to Rifadin Capsules or Syrup (for further information on these products see their separate data sheets).

In non-tuberculosis infection other than those due to Mycobacteria, divided daily dosing regimens should be used; for example, 450mg twice a day or 300mg three times a day for patients 50kg or above.

Children over 3 months: Paediatric usage has not yet been established. However, the following regimen is suggested.

In tuberculosis: a single daily dose of 15 (10-20) mg/kg bodyweight is recommended, although the total daily dose should not exceed 600mg.

In non-tuberculosis infections: other than those due to Mycobacteria, up to 20mg/kg bodyweight daily should be given in divided doses.

4.3. Contra-indications

Rifadin is contra-indicated in the presence of jaundice, and in patients who are hypersensitive to the rifamycins or any of the excipients.

Rifadin use is contra-indicated when given concurrently with the combination of saquinavir/ritonavir (See Section 4.5).
Concomitant administration with lurasidone (See section 4.5)

4.4. Special Warnings and Precautions for Use

Rifadin for Infusion is for intravenous infusion only and must not be administered by intramuscular or subcutaneous route. Avoid extravasation during injection; local irritation and inflammation due to extravascular infiltration of the infusion have been observed. If these occur, the infusion should be discontinued and restarted at another site.

Patients with impaired liver function should only be given Rifadin 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 glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should be carried out prior to therapy and then every two to four weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be discontinued.

Cases of mild to severe cholestasis have been reported with rifampicin therapy. Patients should be instructed to contact their physician immediately if they experience symptoms such as itching, weakness, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin or dark urine. If cholestasis is confirmed, Rifadin should be discontinued

In some cases of hyperbilirubinaemia resulting from competition between Rifadin and bilirubin for excretory pathways of the liver at the cell level can occur in early days of treatment. 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.

Certain hypersensitivity phenomena affecting platelets and vascular tissue may occur as well as renal failure. Adequate surveillance should be maintained to permit early detection of these effects, particularly if there has been an interruption of treatment. Appearance of such effects should be an indication to discontinue use.

Because of the possibility of immunological reactions including anaphylaxis occurring (see 'Undesirable Effects' with intermittent therapy (less than 2 to 3 times a week) patients should be closely monitored. Patients should cautioned against interruption of dosage regimens since these reactions may occur.

Interstitial lung disease (ILD)/Pneumonitis:
There have been reports of ILD or pneumonitis in patients receiving Rifadin for treatment of tuberculosis (see section 4.8). ILD/pneumonitis is a potentially fatal disorder. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea accompanied by dry cough) and fever should be performed to confirm the diagnosis of ILD/pneumonitis. If ILD/pneumonitis is diagnosed, Rifadin should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

DRESS
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 (See Section 4.8). 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.

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

Severe bullous reactions
Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported with rifampicin. If symptoms or signs of AGEP, SJS or TEN are present, rifampicin treatment must immediately be discontinued.

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

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary.

Rifadin 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 Rifadin administration as a result of induction of delta amino levulinic acid synthetase.

Rifadin may produce a discolouration (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.

Rifadin is a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease or increase concomitant drug exposure, safety and efficacy (see Section 4.5). Therefore patients should be advised not to take any other medication without medical advice.

Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding (see Section 4.8). 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).

Paradoxical drug reaction

After initial improvement of tuberculosis under therapy with TM, the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions or the development of new lesions have been detected. Such reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. In case a paradoxical reaction is suspected, symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary. Furthermore, continuation of the planned tuberculosis combination therapy is recommended.

Patients should be advised to seek medical advice immediately if their symptoms worsen. The symptoms that occur are usually specific to the affected tissues. Possible general symptoms include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8).

Rifadin contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium- free’.

4.5. Interactions with other Medicaments and other forms of Interaction

4.5.1 Pharmacodynamic Interactions:

Concomitant use of paracetamol with rifampicin may increase the risk of hepatotoxicity.

When Rifadin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifadin with saquinavir/ritonavir is contra-indicated (See Section 4.3).

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

If p-aminosalicyclic 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.

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternate assay methods should be considered. Transient elevation of BSP and serum bilirubin have been reported. Therefore, these tests should be performed before the daily administration of Rifampicin.

Induction of Drug Metabolizing Enzymes and Transporters

Rifadin is a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by Rifadin 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 Rifadin simultaneously. Therefore, Rifadin may accelerate the metabolism and decrease the activity of certain co-administered drugs or increase the activity of a coadministered pro-drug (where metabolic activation is required), 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 Rifadin.

Table 1 Effect of Rifampicin Coadministration on Drugs or Drug Classes

Drug or Drug Class	**Effect**	**Comment**
antiretroviral drugs (e.g zidovudine, saquinavir, indinavir, efavirenz)	↓antiretroviral exposure	Rifampicin 600mg daily reduced zidovudine exposure (AUC) by 47% via induction of zidovudine glucuronidation and amination metabolism pathways . Rifampicin 600mg daily reduced saquinavir exposure (AUC) by 70% in healthy volunteers and by 47% in HIV-infected patients most likely via induction of CYP3A4 and possibly P-gp pathways . Rifampicin 600mg daily reduced efavirenz exposure (AUC) by 60% primarily via induction of efavirenz CYP2B6-mediated 8-hydroxylation pathway (See Section 4.3: Contraindications)
hepatitis-C antiviral drugs (e.g, daclatasvir, simeprevir, sofosbuvir, telaprevir)4	↓exposure to hepatitis-C antiviral drug exposure	The hepatitis C antivirals are cleared by various drug metabolizing enzymes and transporters which are susceptible to induction by multiple dose rifampicin. Rifampicin 600 mg daily reduced the exposure (AUC) of daclatasvir by 79% , simeprevir by 48% , sofosbuvir by 77% and telaprevir by 92% compared to control subjects. Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.

Drug or Drug Class	Effect	Comments
systemic hormonal contraceptives including estrogens and progestins	↓Contraceptive exposure	Rifampicin treatment reduces the systemic exposure of oral contraceptives Patients using systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy and to continue using this form of contraception for two weeks after completing the course of treatment
Enalapril	↓enalapril active metabolite exposure	Dosage adjustments should be made if indicated by the patient's clinical condition.
Anticonvulsants (e.g phenytoin)	↓ phenytoin exposure	Phenytoin is metabolized mainly by CYP2C9/2C19. Rifampicin 450 mg daily doubled the clearance of phenytoin and reduced the half-life by about 50%.
Antiarrhythmics (e.g disopyramide, mexiletine, quinidine, propafenone, tocainide)	↓ antiarrhythmic drug exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of mexiltine by 41%, quinidine by about 80%, propafenone by 87%, and tocainide by 25%.
antiestrogens (e.g tamoxifen, toremifen)	↓tamoxifen and toremifen exposure	Tamoxifen and toremifen are predominantly substrates of CYP3A4. Rifampicin 600 mg daily reduced the systemic exposure (AUC) of tamoxifen by 86% and of toremifen by 87%.
antipsychotics (e.g haloperidol)	↓haloperidol exposure	Coadministration of rifampicin to schizophrenic patients receiving haloperidol decreased haloperidol trough concentrations up to 70%.
Lurasidone	↓lurasidone exposure	Rifampicin 600mg was shown to markedly reduce exposure of lurasidone compared to the use of lurasidone alone. Lurasidone should not be given concomitantly with rifampicin (See section 4.3).
oral anticoagulants (e.g warfarin)	↓warfarin exposure	S-Warfarin is a clinical index substrate for CYP2C9. Rifampicin 600 mg daily reduced the exposure (AUC) of S-warfarin by 74%.
Clopidogrel	↑active Metabolite exposure	Rifadin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.

antifungals (e.g fluconazole, itraconazole, ketoconazole)		Rifampicin 600 mg daily reduced fluconazole exposure (AUC) by approximately 23%, itraconazole by 88% and ketoconazole by about 80%.
Caspofungin	↓ antifungal exposure	After two weeks of repeated administration of rifampicin, trough levels of caspofungin were 30 % lower than in adult subjects who received caspofungin alone.

Drug or Drug Class	Effect	Comments
barbiturates	↓ barbiturate exposure	Rifampicin has been shown to increase hexobarbital metabolic clearance by 2- to 3-fold in healthy volunteers and patients, and to significantly decrease hexobarbital half-life
beta blockers	↓beta blocker exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of metoprolol by 33% and increased the clearance of propranolol by 169%
benzodiazepines (e.g diazepam)	↓diazepam exposure	Rifampicin 600 and 1200 mg daily increased the clearance of diazepam by 60% and 98%, respectively.
benzodiazepine related drugs (e.g zolpiclone, zolpidem),	↓zopiclone and zolpidem exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of zolpiclone by 82% and of zolpidem by 27% .
calcium channel blockers (e.g diltiazem, nifedipine, verapamil),	↓calcium channel blocker exposure	Calcium channel blockers are primarily substrates of CYP3A4. Rifampicin 1200 mg administered as a single oral dose 8 h before administering a single oral dose of nifedipine 10 mg reduced nifedipine exposure (AUC) by 64%. Rifampicin 600 mg daily reduced the exposure (AUC) of verapamil by 93%.
chloramphenicol	↓ chloramphenicol exposure	In two children treated concomitantly with intravenous chloramphenicol and rifampicin, peak chloramphenicol serum concentrations were reduced by 85.5% in one patient and by 63.8% in the other
clarithromycin	↓clarithromycin exposure	Rifampicin 600 mg daily markedly reduced plasma concentrations of clarithromycin and increased clarithromycin metabolite concentrations.

Drug or Drug Class	Effect	Comments
corticosteroids	↓ corticosteroid exposure	Numerous cases appear in the literature describing a decrease in glucocorticoid effect when rifampicin is prescribed concurrently. The literature contains reports of acute adrenal crisis or adrenal insufficiency induced by the combination of rifampicin-isoniazid-ethambutol or rifampicin-isonizid in patients with Addison's disease. In patients receiving concomitant rifampicin, prednisolone AUC was reduced by 48% to 66% and clearance was increased by 45% to 91%.
cardiac glycosides	↓ cardiac glycoside exposure	Digoxin is a clinical index substrate for P-gp activity. Rifampicin 600 mg daily reduced the bioavailability of oral digoxin by 30% and increased intestinal P-gp content 3.5-fold, which correlated with the AUC after oral digoxin. Several reports have been published regarding the interaction of digitoxin and rifampicin. Decreased serum digitoxin levels were observed during antituberculosis therapy with rifampicin-isoniazid- ethambutol or with rifampicin alone; serum digitoxin levels decreased by 53% and 54% respectively.
clofibrate	↓clofibrate exposure	Rifampicin 600 mg daily significantly reduced steady- state plasma concentrations of clofibrate's main circulating metabolite, chlorophenoxyisobutyric acid (CPIB), from 50 µg/mL to 33 µg/mL. Although CPIB plasma half-life of individual subjects was decreased during rifampicin treatment, the change was not significant.
dapsone	↓dapsone exposure ↑ exposure to hydroxylamine metabolite, responsible for adverse effects that include methemoglobinemia, haemolytic anaemia, agranulocytosis, and haemolysis.	Dosage adjustment may be required for dapsone and necessitate monitoring of haematological adverse events.
doxycycline	↓ doxycycline exposure	In a group of hospitalized patients rifampicin (10 mg/kg daily) reduced the exposure (AUC) of doxycycline by about 50%.

Drug or Drug Class	Effect	Comments
fluoroquinolones	↓ fluoroquinolone exposure	Rifampicin 900 mg daily modestly reduced the AUC of perfloxacin by about 35%. Rifampicin 450 mg to 600 mg daily has been shown to reduce the exposure (AUC) of moxifloxacin by about 30%.
oral hypoglycemic agents (sulfonylureas)	↓sulfonylurea exposure	Sulfonylureas are primarily substrates of CYP2C9. Rifampicin 600 mg daily reduced the exposure (AUC) of glyburide by 39% and of glipizide by 22%, and reduced the half-life of both drugs. It is probable that the blood glucose–lowering effect of glyburide is reduced during concomitant treatment with rifampicin.
immunosuppressive agents (e.g, cyclosporine, tacrolimus)	↓ cyclosporine, tacrolimus exposure	Cyclosporine and tacrolimus are substrates of CYP3A4 and P-gp. In 6 healthy volunteers oral bioavailability of cyclosporine was reduced from 33% to 9% with coadministration of rifampicin 600 mg daily . In 4 kidney transplant patients coadministration of rifampicin 600 mg daily reduced the exposure of cyclosporine (AUC) by approximately 60%. In 6 healthy volunteers oral bioavailability of tacrolimus was reduced by 51% with coadministration of rifampicin 600 mg daily via induction of CYP3A4 and P-gp.
Irinotecan	↓ irinotecan active metabolite exposure	Irinotecan is extensively metabolized by various enzyme systems, including carboxyl esterases, UGT, and CYP3A4. Rifampicin 450mg/day was administered to a patient as part of an antibiotic regimen including isoniazid (300 mg/day) and streptomycin (0.5 g/day im). Although there was no change in irinotecan exposure (AUC), irinotecan active metabolite exposure (AUC) decreased by 20% and its glucuronide metabolite decreased by 58.8%, possibly via induction of CYP 3A4.

Drug or Drug Class	Effect	Comments
levothyroxine	↓ levothyroxine exposure	Rifampicin 600 mg daily was administered to a patient previously treated with levothyroxine. Approximately 2 weeks after initiation of rifampicin, thyroid stimulating hormone (TSH) concentration increased by 202% compared to the pretreatment concentration. TSH concentration returned to normal 9 days after discontinuance of rifampicin.
Losartan	↓ losartan and active metabolite exposure	Losartan is metabolized by CYP2C9 and CYP3A4 to an active metabolite, E3174, which has greater antihypertensive activity than the parent compound. Rifampicin 600 mg daily reduced the exposure (AUC) of losartan by 35% and E3174 by 40%. Losartan oral clearance was increased by 44%. The half-life values of both compounds were decreased by 50%.
narcotic analgesics	↓narcotic analgesics exposure	Various studies and case reports have been reviewed between rifampicin and both opioid analgesics. Rifampicin 600 mg daily decreased the mean AUC for IV and oral oxycodone by 53% and 86%, respectively, while oral oxycodone's mean bioavailability decreased by 70%. Rifampicin 600 mg daily reduced morphine Cmax by 41% and AUC by 28%. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.
Methadone	↓ methadone exposure	Methadone is predominantly metabolized by CYP2B6 and CYP3A4. Rifampicin 600 mg daily reduced the oral bioavailability of methadone from 70% to 50%.

Drug or Drug Class	Effect	Comments
praziquantel	↓ praziquantel exposure	Praziquantel is extensively metabolized by CYP enzymes. Rifampicin 600 mg daily reduced plasma concentrations of praziquantel to below detectable levels in 7 of 10 subjects administered single dose praziquantel; of the 3 subjects with detectable concentrations, praziquantel exposure (AUC) was reduced by 85%. In the same study, rifampicin reduced multiple dose praziquantel concentrations below detectable levels in 5 of 10 subject; of the 5 subjects with detectable concentrations, praziquantel exposure was reduced by 80%.
Quinine	↓ quinine exposure	Quinine is mainly metabolized by CYP3A4. Rifampicin 600 mg daily increased quinine clearance by 6.9-fold and reduced quinine exposure (AUC) and half-life.
selective 5-HT3 receptor antagonists (eg ondansetron)	↓ondansetron exposure	Ondansetron is metabolized by multiple CYP Enzymes Rifampicin 600 mg daily reduced the exposure (AUC) of orally administered ondansetron by 65% compared with placebo and the elimination half-life (t1⁄2) by 38%. The oral bioavailability of ondansetron was reduced from 60% to 40%.
statins metabolized by CYP3A4 (e.g, simvastatin)	↓ simvastatin exposure	Simvastatin is a clinical index substrate of CYP3A4. Rifampicin 600 mg daily reduced simvastatin exposure (AUC) by 87% compared to placebo. Because the elimination half-life of simvastatin was not affected by rifampicin, induction of the CYP3A4-mediated first-pass metabolism of simvastatin in the intestine and the liver probably explains this interaction.

Drug or Drug Class	Effect	Comments
teithromycin	↓ telithromycin exposure	Telithromycin is metabolized primarily by CYP3A4. Rifampicin 600 mg daily reduced telithromycin exposure (AUC) by 86%.
theophylline	↓ theophylline exposure	Theophylline is a clinical index inhibitor of CYP1A2. Rifampicin 600 mg daily increased theophylline clearance by 40%, reduced theophylline exposure (AUC) by 27%, and reduced elimination half-life by 30%.
thiazolidinediones (e.g.rosiglitazone)	↓ rosiglitazone exposure	Rosiglitazone is primarily metabolized by CYP2C8 and to a lesser extent by CYP2C9. Rifampicin 600 mg daily increased rosiglitazone apparent oral clearance by 3-fold, reduced rosiglitazone exposure (AUC) by 65%, and reduced elimination half-life from 3.9 to 1.5 h.
tricyclic antidepressants (e.g nortriptyline)	↓ nortriptyline exposure	Higher than expected doses of nortriptyline were required to obtain a therapeutic drug level when it was associated with Rifampicin 600 mg daily given as part of a tuberculosis treatment regimen that included isoniazid 300 mg daily, pyrazinamide 500 mg 3x per day and pyridoxine 25 mg. Following the discontinuation of rifampicin, the patient became drowsy and the serum nortriptyline levels rose precipitously (3-fold) into the toxic range.
Mifepristone	↓Mifepristone exposure	Rifampicin was shown to decrease mifepristone AUC by 6.3-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone by 20-fold and 5.9-fold, respectively. Therefore, reduced efficacy can be expected when mifepristone is given concomitantly with rifampicin. If concomitant use is necessary, the dose of mifepristone should be increased.

↓ : decrease; ↑ : increase

Effect of other medicinal products on Rifadin
Concomitant antacid administration may reduce the absorption of Rifadin. Daily doses of Rifadin should be given at least 1 hour before the ingestion of antacids.

Other Drug Interactions with Rifadin
When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Concurrent use of ketoconazole and Rifadin has resulted in decreased serum concentration of both drugs.

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those stated as compatible in this section or mentioned in section 6.6. Compatibilities: Rifadin for Intravenous Infusion is compatible with the following infusion solutions: Dextrose 5% solution for injections and saline solutions. Incompatibilities: Rifadin for Intravenous Infusion is incompatible with the following: Perfudex, Sodium Bicarbonate 5%, Sodium Lactate 0.167M, Ringer Acetate with Dextrose.

6.3. Shelf Life

Unopened vial of lyophilisate:	3 years
Unopened ampoule of solvent:	5 years
Reconstituted solution:	Immediate use
Reconstituted solution further diluted in normal Saline	6 hours
Reconstituted solution further diluted in dextrose 5%	6 hours.

The product once reconstituted with solvent should be used immediately.
Product once reconstituted with solvent and further diluted with either Normal Saline or 5% Dextrose: The chemical and physical in use stability of the diluted solution in either normal saline or 5% dextrose has been demonstrated for use within 6 hours at room temperature.
From a microbiological point of view, once the reconstituted solution has been diluted in either normal saline or 5% dextrose the solution should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user and would normally be not longer than 24 hours at 2-8 °C unless reconstitution / dilution has taken place in controlled and validated asceptic conditions.

6.6. Instruction for Use/Handling
Rifadin for Infusion is prepared for use by aseptically adding the 10ml vial of solvent provided (water for injections) to the vial of 600mg rifampicin powder. Swirl the vial gently to completely dissolve the antibiotic. The resultant solution is red in colour and contains 60mg of Rifadin per ml. This reconstituted solution, should be diluted for use immediately in the one of the recommended infusion mediums (normal saline or 5% dextrose for injection).

Prior to dilution, withdraw the volume of reconstituted Rifadin solution required and dilute the dose into 500ml of infusion medium. Mix well and infuse at a rate allowing for complete infusion in up to 3 hours.

Dilutions in dextrose 5% for injection are stable up to 6 hours at room temperature and should be prepared and used within this time.
Dilutions in normal saline are stable up to 6 hours at room temperature and should be prepared and used within this time.

Precipitation of Rifadin from the infusion solution may occur beyond this time.

Other infusion solutions are not recommended.
Any unused product or waste material should be disposed of in accordance with local requirements.