Sanofi-aventis U.S. LLC
100 Morris Street
Morristown, NJ, USA
07960

July 20, 2026

IMPORTANT PRESCRIBING INFORMATION

Temporary Importation of Rifadin® 600 mg infusion (rifampicin) with Foreign, Non-U.S. Labeling to Address Drug Shortage

Dear Healthcare Professional,

Due to the discontinuation of the manufacturing of Rifadin® IV (rifampin for injection), 600 mg and the current shortage in the United States (US) market, Sanofi-aventis U.S. LLC (Sanofi) is coordinating with the US Food and Drug Administration (FDA) and Drug Shortage Staff (DSS) to temporarily increase the availability of the drug by importing a formulation that is manufactured by Sanofi for the United Kingdom (UK). In order to do so, Sanofi has initiated importation of non-FDA approved Rifadin® 600 mg infusion (rifampicin) from the foreign market into the US market. Rifampicin is the same active ingredient as rifampin. Rifampin is also known as rifampicin outside of the U.S.

The imported Rifadin 600 mg infusion (rifampicin) is marketed in the UK and manufactured in Sanofi's manufacturing facility in Agnani, Italy, which is registered with the FDA. FDA has not approved Rifadin 600 mg infusion (rifampicin) in the United States.

At this time, no other entity except Sanofi and its distributors is authorized by the FDA to import and distribute Rifadin 600 mg infusion (rifampicin) in the US.

Effective as of August 2026, Sanofi will distribute the following presentation of Rifadin 600 mg infusion (rifampicin) in the US market to address the shortage:

Product Description	Strength	NDC #	Batch #	Expiration Date
Rifadin 600 mg infusion (rifampicin)	10 mL ampoule containing solvent	NDC 0068-0660-50	6J122	28 FEB 2029
	20 mL vial containing 600 mg rifampicin			
Rifadin 600 mg infusion (rifampicin)	10 mL ampoule containing solvent	NDC 0068-0660-50	6J0842	31 Jan 2029
	20 mL vial containing 600 mg rifampicin			

There are key differences between the Rifadin IV (rifampin for injection), 600 mg product previously marketed in the United States and the imported Rifadin 600 mg infusion (rifampicin). It is important to note the following:

- The imported Rifadin 600 mg infusion (rifampicin) is co-packaged with a clear glass ampoule containing 10 mL of water (solvent) used for injections.
- The dosage for the imported Rifadin 600 mg infusion (rifampicin) is a single daily administration of 600 mg given by intravenous infusion over 2 - 3 hours compared to 10 mg/kg, in a single daily administration, not to exceed 600 mg/day for Rifadin IV.
- Incompatibilities for the imported Rifadin 600 mg infusion (rifampicin) are perfudex, sodium bicarbonate 5%, sodium lactate 0.167M, and ringer acetate with glucose.

The barcode may not register accurately on the U.S. scanning systems. Institutions should manually input the product into their systems to confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

In addition, the packaging of the imported product does not include serialization information. The FDA has granted Sanofi an exemption from the product identifier requirements under Section 582(a)(9) and the manufacturer verification and tracing requirements under Section 582(b)(1)-(4) of the Federal Food, Drug, and Cosmetic Act Drug Supply Chain Security Act (DSCSA) for this imported Rifadin 600 mg infusion (rifampicin). This exemption allows for the temporary distribution of this product without the standard DSCSA serialization and verification capabilities to address the critical drug shortage in the US market.

The vial and carton labels will display the text used and approved for marketing the products in the UK. Please note that there are differences in the format and content of the labeling between the US approved product and the imported product. Please refer to the label and prescribing information comparison table at the end of this letter. Rifadin 600 mg infusion (rifampicin) is available only by prescription in the U.S. Please refer to the FDA-approved full prescribing information for complete prescribing information.

Please ensure that all healthcare providers (HCPs) and staff who may be involved with the handling and administration of Rifadin 600 mg infusion receive and read a copy of this letter.

If you have any questions about the information contained in this letter or encounter any quality-related issues, please contact 1-800-633-1610.

Please contact CustomerCare.US@sanofi.com to place an order.

Reporting Adverse Events

HCPs and patients are encouraged to report adverse events and medication errors in patients taking Rifadin 600 mg infusion (rifampicin) to Sanofi. To report an adverse event, please contact 1-800-633-1610 or visit www.sanofi.com/en/contact and select "Report Adverse Event".

HCPs may report adverse events, medication errors or quality problems experienced with the use of this product as per standard protocol through the FDA's MedWatch Adverse Event Reporting Program via online, regular mail, or by fax:

- Online: Complete and submit the report: www.fda.gov/medwatch/report.htm
- Regular mail: Form can be downloaded from www.fda.gov/MedWatch/getforms.htm
- HCPs can call 1-800-332-1088 to request a reporting form that can be returned to the address on the pre-addressed form or fax form to 1-800-FDA-0178.

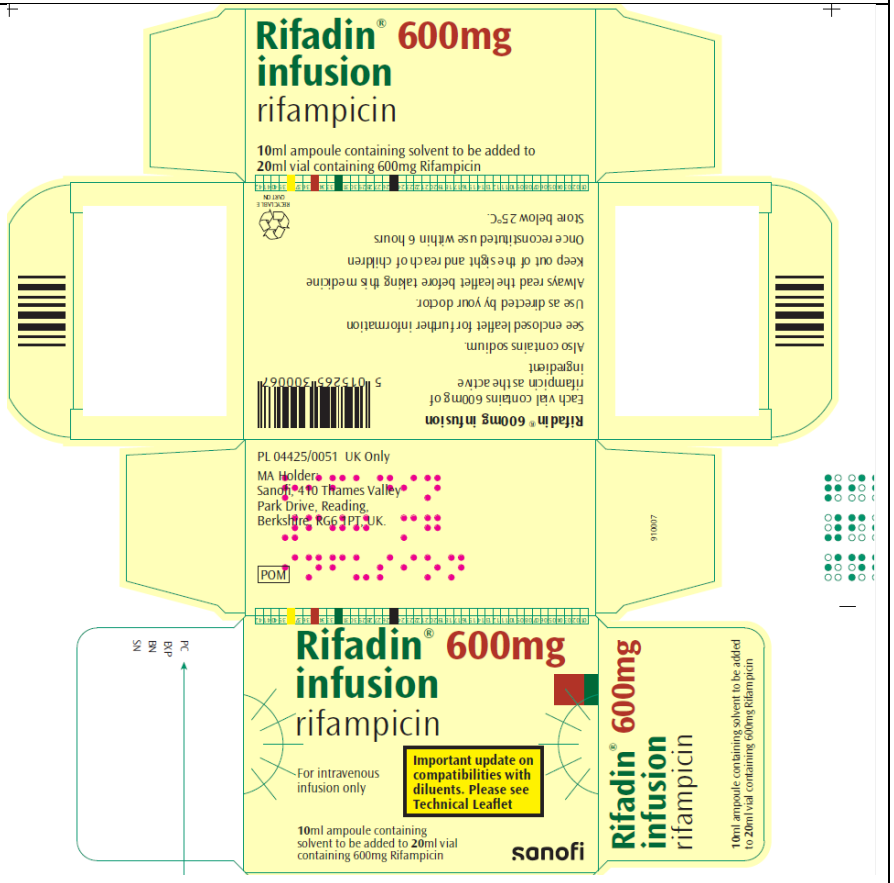
Please do not hesitate to contact Sanofi with questions or concerns about any of the information in this letter. This letter is part of Sanofi's goal to ensure that the shortage situation in the US market is mitigated.

Yours sincerely,

Agnès Riva Pezzali

Agnès RIVA-PEZZALI, PharmD
Insulins & Established Products Franchise Head
Global Regulatory Affairs | General Medicines GBU

sanofi

Product Comparison Table	**Rifadin IV (rifampin for injection) 600 mg** US FDA-Approved Product	**Rifadin 600 mg infusion (rifampicin)** Imported Product
Carton Artwork		

Product Name	**Rifadin® IV (rifampin for injection), 600 mg** US FDA-Approved Product	**Rifadin® 600 mg infusion (rifampicin)** Imported UK-Approved Product
Indications	Rifampin is indicated in the treatment of all forms of tuberculosis. A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered. Following the initial phase, treatment should be continued with rifampin and isoniazid for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive. RIFADIN IV is indicated for the initial treatment and retreatment of tuberculosis when the drug cannot be taken by mouth. **Meningococcal Carriers** Rifampin is indicated for the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. **Rifampin is not indicated for the treatment of meningococcal infection because of the possibility of the rapid emergence of resistant organisms.** (See WARNINGS.) Rifampin should not be used indiscriminately, and, therefore, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed for establishment of the carrier state and the correct treatment. So that the usefulness of rifampin in the treatment of asymptomatic meningococcal carriers is	Rifadin for Infusion is indicated for acutely ill patients who are unable to tolerate oral therapy, e.g. post-operative or comatose patients or patients in whom gastrointestinal absorption is impaired. Tuberculosis: Rifadin, used in combination with other active anti-tuberculosis drugs, is indicated in the treatment of all forms of tuberculosis, including fresh, advanced, chronic and drug-resistant cases. Rifadin is also effective against most atypical strains of Mycobacteria. Leprosy: Rifadin, used in combination with at least one other active anti-leprosy drug, is indicated in the management of multibacillary and paucibacillary leprosy to effect conversion of the infectious state to a non-infectious state. Other infections: Rifadin is indicated in the treatment of Brucellosis**,** Legionnaires Disease, and serious staphylococcal infections. To prevent emergence of resistant strains of the infecting organisms, Rifadin should be used in combination with another antibiotic appropriate for the infection.

	preserved, the drug should be used only when the risk of meningococcal disease is high. To reduce the development of drug-resistant bacteria and maintain the effectiveness of rifampin and other antibacterial drugs, rifampin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.	
Preparation for Administration and Route of Administration	Intravenous <u>Preparation of Solution for IV Infusion</u> Reconstitute the lyophilized powder by transferring 10 mL of sterile water for injection to a vial containing 600 mg of rifampin for injection. Swirl vial gently to completely dissolve the antibiotic. The reconstituted solution contains 60 mg rifampin per mL and is stable at room temperature for up to 30 hours. Prior to administration, withdraw from the reconstituted solution a volume equivalent to the amount of rifampin calculated to be administered and add to 500 mL of infusion medium. Mix well and infuse at a rate allowing for complete infusion within 3 hours. Alternatively, the amount of rifampin calculated to be administered may be added to 100 mL of infusion medium and infused in 30 minutes. Dilutions in dextrose 5% for injection (D5W) are stable at room temperature for up to 8 hours and should be prepared and used within this time. Precipitation of rifampin from the infusion solution may occur beyond this time. Dilutions in normal saline are stable at room temperature for up to 6 hours and should be prepared and used within this time. Other infusion solutions are not recommended.	Intravenous 10 mL ampoule containing solvent to be added to 20 mL vial containing 600 mg Rifampicin. <u>Shelf life after dilution or reconstitution</u>: Water for Injections (10 mL WFI): Up to 30 hours Water for injections (10 mL WFI) and then diluted in glucose 5% solution for infusion: Up to 8 hours Water for injections (10 mL WFI) and then diluted in sodium chloride 0.9% solution for infusion: Up to 6 hours
Dosage	**<u>Tuberculosis</u>** Adults: 10 mg/kg, in a single daily administration, not to exceed 600 mg/day	**Posology**

	Pediatric Patients: 10-20 mg/kg, not to exceed 600 mg/day **Meningococcal Carriers** Adults: For adults, it is recommended that 600 mg rifampin be administered twice daily for two days. Pediatric Patients: Pediatric patients 1 month of age or older: 10 mg/kg (not to exceed 600 mg per dose) every 12 hours for two days. Pediatric patients under 1 month of age: 5 mg/kg every 12 hours for two days.	Treatment with Rifadin for Infusion should include concomitant use of other appropriate anti-bacterials to prevent the emergence of resistant strains of the causative organism. **Tuberculosis** *Adults:* A single daily administration of 600 mg given by intravenous infusion over 2 - 3 hours has been found to be effective and well tolerated for adult patients. Serum concentrations following this dosage regimen are similar to those obtained after 600 mg by mouth. *Children:* The usual paediatric regimen is a single daily dose of up to 20 mg/kg bodyweight; the total daily dose should not normally exceed 600 mg. Leprosy The recommended 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 Alternatively, 600 mg doses of rifampicin may be given once per month. In the treatment of leprosy, rifampicin should always be used in conjunction with at least one other anti-leprosy drug. Brucellosis, Legionnaires Disease or serious staphylococcal infections *Adults:* The recommended daily dose is 600 – 1200 mg given in 2 - 4 divided doses, together with another antibacterial agent with similar properties to prevent the emergence of resistant strains. Impaired liver function

		A daily dose of 8mg/kg should not be exceeded in patients with impaired liver function. <u>Use in the elderly</u> 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 serum terminal half-life 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 liver function impairment. 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).
Contrain dicati-ons	RIFADIN is contraindicated in patients with a history of hypersensitivity to rifampin or any of the components, or to any of the rifamycins. Rifampin is contraindicated in patients who are also receiving ritonavir-boosted saquinavir due to an increased risk of severe hepatocellular toxicity. Rifampin is contraindicated in patients who are also receiving atazanavir, darunavir, fosamprenavir, saquinavir, tipranavir, cabotegravir, fostemsavir and lenacapavir (see prescribing information for SUNLENCA®) due to the potential of rifampin to substantially decrease plasma concentrations of these antiviral drugs, which may result in decreased antiviral efficacy and/or development of viral resistance. Rifampin is contraindicated in patients receiving praziquantel since therapeutically effective blood levels of praziquantel may not be achieved. In patients receiving rifampin who need immediate treatment with praziquantel alternative agents should be considered. However, if treatment with praziquantel is necessary,	Rifadin for Infusion is contraindicated: • in patients who are hypersensitive to rifamycins or any of the excipients (see section 6.1) • concurrent treatment with the combination of saquinavir/ritonavir (see section 4.5) • with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir (see section 4.5) Although not recommended for use in patients with jaundice, the therapeutic benefit of Rifadin for Infusion should be weighed against the possible risks.

	rifampin should be discontinued 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment. Rifampin is contraindicated in patients receiving lurasidone. Concomitant use of lurasidone with strong CYP3A4 inducers (e.g., rifampin) decreased the exposure of lurasidone compared to the use of lurasidone alone.	
Ingredients	rifampin 600 mg, sodium formaldehyde sulfoxylate 10 mg, and sodium hydroxide to adjust pH.	600 mg of rifampicin as active ingredient Sodium sulfoxylate formaldehyde Sodium hydroxide <u>Solvent</u> Water for Injections
Compatibility	<u>Incompatibilities</u> Physical incompatibility (precipitate) was observed with undiluted (5 mg/mL) and diluted (1 mg/mL in normal saline) diltiazem hydrochloride and rifampin (6 mg/mL in normal saline) during simulated Y-site administration.	*Compatibilities*: up to 6 hours with Saline Solution and up to 8 hours with Glucose 5%. *Incompatibilities*: Perfudex, Sodium Bicarbonate 5%, Sodium Lactate 0.167M, Ringer Acetate with Glucose.
Storage Conditions	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid excessive heat (temperatures above 40°C or 104°F). Protect from light.	Store below 25°C. **Shelf Life** Unopened vial of lyophilisate: 36 months Unopened ampoule of solvent: 60 months
How Supplied	RIFADIN IV (rifampin for injection USP) is available in sterile glass vials containing 600 mg rifampin (NDC 0068-0597-01).	20ml clear neutral glass vial sealed with butyl rubber stopper and aluminium/plastic "flip-off" cap (colour coded blue) containing 600mg Rifampicin and 10ml clear glass ampoule containing solvent. Pack size: combination of 1 vial of lyophilisate and 1 ampoule of solvent.
Warnings	Hepatotoxicity of hepatocellular, cholestatic, and mixed patterns has been reported in patients treated with rifampin. Severity ranged from asymptomatic elevations in liver enzymes, isolated jaundice/hyperbilirubinemia, symptomatic self-limited hepatitis to fulminant liver failure and death. Severe hepatic dysfunction	Cases of drug-induced liver injury, including fatal cases (especially when used in combination with other anti-tuberculosis drugs), have been reported in patients treated with rifampicin with an onset of a few days to a few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes, cholestatic jaundice, hepatitis,

	including fatalities were reported in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Monitor for symptoms and clinical/laboratory signs of liver injury, especially if treatment is prolonged or given with other hepatotoxic drugs. Patients with impaired liver function should be given rifampin only in cases of necessity and then under strict medical supervision. In these patients, careful monitoring of liver function should be done prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatic damage occur or worsen, discontinue rifampin. Rifampin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration. The possibility of rapid emergence of resistant meningococci restricts the use of RIFADIN to short-term treatment of the asymptomatic carrier state. **RIFADIN is not to be used for the treatment of meningococcal disease.** Systemic hypersensitivity reactions were reported with RIFADIN administration. Signs and symptoms of hypersensitivity reactions may include fever, rash, urticaria, angioedema, hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, elevated liver transaminases or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, chills, aches, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). Manifestations of hypersensitivity, such as fever, lymphadenopathy or laboratory abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. Monitor patients receiving RIFADIN for signs and/or symptoms of hypersensitivity reactions. If these signs or symptoms occur, discontinue RIFADIN and administer supportive measures. Cases of severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS)	hepatotoxicity, hepatocellular injury, and mixed liver injury. Most patients recovered on discontinuation of rifampicin treatment; nevertheless, progression to acute liver failure requiring liver transplantation can occur. The mechanism of rifampicin-induced liver injury is not clearly elucidated, but data indicate either an immuno-allergic mechanism or direct toxicity of metabolic products. Patients should be instructed to contact their physician in case symptoms suggestive of liver injury occur. In such patients rifampicin should be discontinued and liver function should be assessed. Rifampicin should not be re-introduced in patients with an episode of hepatic injury during treatment with rifampicin for which no other cause of liver injury has been determined. Because of the possibility of immunological reaction including anaphylaxis (see section 4.8) occurring with intermittent therapy (less than 2 to 3 times per week) patients should be closely monitored. Patients should be cautioned against interrupting treatment since these reactions may occur. 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. Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with Rifadin Infusion use. If laboratory or clinical findings associated with TMA occur in a patient receiving Rifadin Infusion, treatment should be discontinued and thorough evaluation for TMA performed, including platelet levels, renal function, serum lactate dehydrogenase (LDH) and a blood film for schistocytes (erythrocyte fragmentation). ADAMTS13 activity and anti-ADAMTS13-antibody determination should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Rifadin

	syndrome have been reported with rifampin. If symptoms or signs of severe cutaneous adverse reactions develop, discontinue RIFADIN immediately and institute appropriate therapy. Rifampin may cause vitamin K–dependent coagulation disorders and bleeding (see ADVERSE REACTIONS). Monitor coagulation tests during rifampin treatment (prothrombin time and other coagulation tests) in patients at risk of vitamin K deficiency (such as those with chronic liver disease, poor nutritional status, on prolonged antibacterial drugs or anticoagulants). Consider discontinuation of RIFADIN if abnormal coagulation tests and/or bleeding occur. Supplemental vitamin K administration should be considered when appropriate. Pulmonary toxicity manifested as interstitial lung disease (including, but not limited to, pneumonitis, hypersensitivity pneumonitis, eosinophilic pneumonia, pulmonary infiltrates, and organizing pneumonia) has been reported with rifampin treatment. Pulmonary toxicity could be fatal. If symptoms or signs of severe pulmonary toxicity (including respiratory failure, pulmonary fibrosis, and acute respiratory distress syndrome) develop, discontinue RIFADIN immediately and initiate appropriate treatment. Postmarketing reports suggest that concomitant administration of high doses of cefazolin and rifampin may prolong the prothrombin time, leading to severe vitamin K–dependent coagulation disorders that may be life-threatening or fatal. Avoid concomitant use of cefazolin and rifampin in patients at increased risk for bleeding. If no alternative treatment options are available, closely monitor prothrombin time and other coagulation tests, and administer vitamin K as indicated. Postmarketing cases of paradoxical drug reaction (recurrence or appearance of new symptoms, physical and radiological signs in a patient who had previously shown improvement with appropriate antimycobacterial treatment, in the absence of disease relapse, poor treatment compliance, drug resistance, side effects of treatment, or secondary infection/diagnosis) have been reported with RIFADIN	Infusion should not be resumed and patients should be treated accordingly (consider plasma exchange). 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 infusion should be discontinued if an alternative aetiology for the signs and symptoms cannot be established. <u>Paradoxical drug reaction</u> After initial improvement of tuberculosis under therapy with Rifadin infusion, 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

	(see ADVERSE REACTIONS). Paradoxical drug reactions are often transient and should not be misinterpreted as failure to respond to treatment. If worsening of symptoms or signs occurs during antimycobacterial treatment, consider paradoxical drug reaction in the differential diagnosis, monitor, or treat accordingly. Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremia syndrome, some fatal, have been reported with rifampin. Discontinue RIFADIN if clinical symptoms and laboratory findings consistent with TMA occur. The findings of unexplained thrombocytopenia and anemia should prompt further evaluation and consideration of the diagnosis of TMA.	include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8). 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 Rifadin Infusion treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Rifadin Infusion 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. Rifadin 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. Rifadin infusion 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 (see section 4.8). Rifadin infusion 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, potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.

		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, hypoprothrombinaemia). There have been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving Rifadin Infusion 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 Infusion should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary. <u>Excipients</u> *Sodium:* This medicine contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially 'sodium-free'.
Precautions	RIFADIN should be used with caution in patients with a history of diabetes mellitus, as diabetes management may be more difficult. Prescribing rifampin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills, and malaise), hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic	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.

	reactions, shortness of breath, shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated. Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases. Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D. Rifampin and isoniazid have been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone. **For intravenous infusion only. 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. **<u>Information for Patients</u>** Patients should be counseled that antibacterial drugs including rifampin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When rifampin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by rifampin or other antibacterial drugs in the future. **The patient should be told that rifampin may produce a discoloration (yellow, orange, red, brown) of the teeth,**	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 rifampicin. 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

	urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained. Rifampin is a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease or increase concomitant drug exposure and impact safety and efficacy (see DRUG INTERACTIONS). Therefore, patients should be advised not to take any other medication without medical advice. Patients should be instructed to notify their physician immediately if they experience any of the following: rash with fever or blisters, with or without peeling skin, itching, or swollen lymph nodes, loss of appetite, malaise, nausea, vomiting, abdominal pain, darkened urine, yellowish discoloration of the skin and eyes, light-colored bowel movements, fever, headache, fatigue, myalgias, cough, shortness of breath, chest pain, wheezing, and pain or swelling of the joints. Patients should be advised to seek medical advice immediately if their symptoms of mycobacterial disease, including, but not limited to, cough, fever, tiredness, shortness of breath, malaise, headache, pain, night sweats, swollen lymph nodes, loss of appetite, weight loss, weakness, skin ulcers or lesions, worsen (see ADVERSE REACTIONS). Advise patients to abstain from alcohol, hepatotoxic medications or herbal products while taking rifampin. Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.	should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition. <u>Pregnancy</u> 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 fetus is not known. Therefore, Rifadin for Infusion 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. <u>Breast-feeding</u> Rifampicin is excreted in breast milk and infants should not be breast-fed by a patient receiving rifampicin unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant.
Drug Interactions	<u>Pharmacodynamic Interactions</u> Healthy subjects who received rifampin 600 mg once daily concomitantly with saquinavir 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted saquinavir) developed severe hepatocellular	<u>Interference with laboratory and diagnostic tests</u> 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

	toxicity. Therefore, concomitant use of these medications is contraindicated. (See CONTRAINDICATIONS.) When rifampin is given concomitantly with other hepatotoxic medications such as halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampin and halothane should be avoided. Patients receiving both rifampin and isoniazid should be monitored closely for hepatotoxicity. <u>Effect of Rifampin on Other Drugs</u> *Induction of Drug Metabolizing Enzymes and Transporters* Drug metabolizing enzymes and transporters affected by rifampin 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 rifampin simultaneously. Therefore, rifampin may increase the metabolism and decrease the activity of certain coadministered 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). Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as lurasidone, sofosbuvir, daclatasvir, telaprevir, cabotegravir, fostemsavir and lenacapavir. <u>Effect of Other Drugs on Rifampin</u> Concomitant antacid administration may reduce the absorption of rifampin. Daily doses of rifampin should be given at least 1 hour before the ingestion of antacids. Concomitant use with probenecid and cotrimoxazole increases the concentration of rifampin which may increase the risk of RIFADIN	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 daily administration of Rifadin for Infusion. <u>Pharmacodynamic Interactions</u> When rifampicin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifadin with saquinvir/ritonavir is contraindicated (see section 4.3). 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). <u>Effect of Rifadin Infusion on other medicinal products</u> *Induction of Drug Metabolizing Enzymes and Transporters* Rifadin infusion is a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by Rifadin infusion 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 infusion simultaneously. Therefore, Rifadin infusion may accelerate the metabolism and decrease the activity of certain

	toxicities. Monitor for adverse reactions associated with RIFADIN during coadministration. Other Interactions Atovaquone: Concomitant use of rifampin with atovaquone decrease concentrations of atovaquone and increase concentrations of rifampin which may increase the risk of RIFADIN toxicities. Coadministration of rifampin with atovaquone is not recommended. **Drug/Laboratory Interactions** Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (e.g., Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish rifampin from opiates. Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Thus, alternate assay methods should be considered. Transient abnormalities in liver function tests (e.g., elevation in serum bilirubin, alkaline phosphatase, and serum transaminases) and reduced biliary excretion of contrast media used for visualization of the gallbladder have also been observed. Therefore, these tests should be performed before the morning dose of rifampin. **Carcinogenesis, Mutagenesis, Impairment of Fertility** A few cases of accelerated growth of lung carcinoma have been reported in humans, but a causal relationship with the drug has not been established. Hepatomas were increased in female (C3Hf/DP) mice dosed for 60 weeks with rifampin followed by an observation period of 46 weeks, at 20 to 120 mg/kg (equivalent to 0.1 to 0.5 times the maximum dosage used clinically, based on body surface area comparisons). There was no evidence of tumorigenicity in male C3Hf/DP mice or in similar studies in BALB/c mice, or in two-year studies in Wistar rats.	co-administered drugs or increase the activity of a co-administered 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. To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment when starting or stopping concomitantly administered Rifadin infusion. Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir. Significant decrease in their plasma concentrations is observed because of potent induction of CYP 3A4, P-gp, UGT1A1 by rifampicin which is likely to result in loss of their therapeutic effectiveness. Examples of drugs or drug classes affected by rifampicin: • Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide) • Antiepileptics (e.g. phenytoin) • Hormone antagonist (anti-oestrogens e.g. tamoxifen, toremifene, gestinone) • Antipsychotics (e.g. haloperidol, aripiprazole) • Anticoagulants (e.g. coumarins) • Antivirals (e.g. saquinavir, indinavir, efavirenz, cabotegravir, fostemsavir, lenacapavir, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine) • Barbiturates • Beta-blockers (e.g. bisoprolol, propanolol) • Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem) • Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine) • Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin)

	Data from published literature report that rifampin shows mutagenic potential in the Ames test and is considered to be aneugenic as well as clastogenic *in vivo* in mice after oral administration. Increased frequency of chromosomal aberrations was observed *in vitro* in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide. The clinical relevance of the nonclinical and *in vitro* findings is unclear as there is insufficient evidence of carcinogenicity, mutagenicity or impairment of fertility in humans after decades of use of rifampin. **<u>Pregnancy–Teratogenic Effects</u>** There are no adequate and well-controlled studies of RIFADIN in pregnant women. Rifampin has been reported to cross the placental barrier and appear in cord blood. While available studies cannot definitively establish the absence of risk, published data over decades of use have not established an association with RIFADIN during pregnancy and major birth defects or miscarriage. Rifampin has been shown to be teratogenic in rodents. Congenital malformations, primarily spina bifida, were increased in the offspring of pregnant rats given rifampin during organogenesis at oral doses of 150 to 250 mg/kg/day (about 1 to 2 times the maximum recommended human dose based on body surface area comparisons). Cleft palate was increased in a dose-dependent fashion in fetuses of pregnant mice treated at oral doses of 50 to 200 mg/kg (about 0.2 to 0.8 times the maximum recommended human dose based on body surface area comparisons). Imperfect osteogenesis and embryotoxicity were also reported in pregnant rabbits given rifampin at oral doses up to 200 mg/kg/day (about 3 times the maximum recommended human dose based on body surface area comparisons). The clinical relevance of the nonclinical data is uncertain. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the	• Corticosteroids • Cardiac glycosides (digitoxin, digoxin) • Clofibrate • 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) *Cabotegravir, fostemsavir, lenacapavir:* Rifampicin 600 mg daily reduced cabotegravir exposure (AUC) by 59% most likely via induction of UGTs. Rifampicin 600 mg daily reduced fostemsavir exposure (AUC) by 82% most likely via induction of CYP3A4. Rifampicin 600 mg daily reduced lenacapavir exposure (AUC) by 84% most likely via induction of CYP3A4, UGT1A1 and P-gp. *Lurasidone:* Rifampicin 600mg was shown to decrease lurasidone AUC by 81%. Therefore, markedly reduced exposure of lurasidone can be expected when lurasidone is given concomitantly with a CYP3A4 inducer such as rifampicin (see section 4.3). *Enalapril:* Decrease enalapril active metabolite exposure. Dosage adjustments should be made if indicated by the patient's clinical condition

	possibility of harm, RIFADIN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. **Pregnancy–Non-Teratogenic Effects** When administered during the last few weeks of pregnancy, rifampin can cause postnatal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated. **Nursing Mothers** Because of the potential for tumorigenicity shown for rifampin in animal studies, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Geriatric Use** Clinical studies of RIFADIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using rifampin in elderly patients. (See WARNINGS.) Refer to complete USPI for complete table of drug interactions.	*Hepatitis-C antiviral drugs (e.g, 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 with rifampicin. *Clopidogrel:* Increases 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. *Dapsone:* Rifampicin has also been shown to increase the clearance of dapsone and the production of the hydroxylamine metabolite of dapsone which could increase the risk of methaemoglobinaemia, haemolytic anaemia, agranulocytosis, and haemolysis. *Systemic hormonal contraceptives including oestrogens and progestogens:* 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 Rifadin therapy. *Mifepristone:* 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 a potent CYP inducer such as rifampicin. *Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone):* diabetes may become more difficult to control.

		Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole, caspofungin): Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs. After two weeks of repeated administration of rifampicin, trough levels of caspofungin were 30% lower than in adult subjects who received caspofungin alone. 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. <u>Effect of other medicinal products on Rifadin infusion</u> *Antacids:* 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. *Paracetamol:* Concomitant use of paracetamol with rifampicin may increase the risk of hepatotoxicity. <u>Other drug interactions with Rifadin infusion</u> When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.
Adverse Reactions	The following adverse reactions associated with the use of RIFADIN were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **<u>Gastrointestinal</u>** Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps, and diarrhea have been noted in some patients. Although *Clostridium difficile* has been shown *in vitro* to be sensitive to rifampin, pseudomembranous colitis has been reported with the use of rifampin (and other broad-spectrum antibiotics). Therefore, it	Rifadin for Infusion is generally well tolerated and accepted by patients, although hypersensitivity reactions have been described and occasionally patients have experienced fever, skin rashes and nausea/vomiting. Occasional instances of phlebitis and pain at the infusion site have been reported. Reactions occurring with either daily or intermittent dosage regimens include: **System organ** | **Frequency** | **Preferred Term**

is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Tooth discoloration (which may be permanent) may occur.

Hepatic
Hepatotoxicity including transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, alkaline phosphatase, serum transaminases, gamma-glutamyl transferase), hepatitis, shock-like syndrome with hepatic involvement and abnormal liver function tests, and cholestasis have been reported (see WARNINGS).

Hematologic
Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, have been reported (see WARNINGS).

Thrombocytopenia has occurred primarily with high dose intermittent therapy but has also been noted after resumption of interrupted treatment. It rarely occurs during well-supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

Leukopenia, hemolytic anemia, decreased hemoglobin, bleeding, and vitamin K–dependent coagulation disorders (abnormal prolongation of prothrombin time or low vitamin K–dependent coagulation factors) have been observed.

Agranulocytosis has been reported very rarely.

Central Nervous System
Headache, fever, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, muscular

class		
Infections and infestations	Not known	Pseudomembranous colitis Influenza
Blood and lymphatic system disorders	Common	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.
	Uncommon	Leukopenia
	Not known	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome Disseminated intravascular coagulation Eosinophilia Agranulocytosis Haemolytic anaemia Vitamin K dependent coagulation disorders
Immune system disorders	Not known	Anaphylactic reaction
Endocrine disorders	Not known	Adrenal insufficiency in patients with compromised adrenal function have been observed
Metabolism and nutritional disorders	Not known	Decreased appetite, hyperuricaemia
Psychiatric disorders	Not known	Psychotic disorder
Nervous system disorders	Common	Headache Dizziness
	Not known	Cerebral haemorrhage and

weakness, pains in extremities, and generalized numbness have been observed.

Psychoses have been rarely reported.

Rare reports of myopathy have also been observed.

Ocular
Visual disturbances have been observed.

Endocrine
Menstrual disturbances have been observed.

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

Renal
Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Dermatologic
Cutaneous reactions 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. More serious cutaneous reactions which may be due to hypersensitivity occur but are uncommon.

Hypersensitivity Reactions
Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms syndrome (see

		fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	Not known	Tear discolouration
Vascular disorders	Not known	Shock Flushing Vasculitis Bleeding
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea Wheezing Sputum discoloured Interstitial lung disease (including pneumonitis)
Gastrointestinal disorders	Common	Nausea Vomiting
	Uncommon	Diarrhoea
	Not known	Gastrointestinal disorder Abdominal discomfort Tooth discolouration (which may be permanent)
Hepatobiliary disorders	Not known	Drug-induced liver injury (including fatal cases especially when used in combination with other anti-tuberculosis drugs) Hepatitis Hyperbilirubinaemia (see section 4.4)
Skin and subcutaneous tissue disorders	Not known	Erythema multiforme Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS)

WARNINGS), vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed.

Anaphylaxis has been reported rarely.

Respiratory, Thoracic and Mediastinal Disorders
Pulmonary toxicity (including, but not limited to, interstitial lung disease, pneumonitis, hypersensitivity pneumonitis, eosinophilic pneumonia, pulmonary infiltrates, organizing pneumonia, respiratory failure, pulmonary fibrosis, and acute respiratory distress syndrome) has been observed (see WARNINGS).

Miscellaneous
Paradoxical drug reaction has been reported with RIFADIN (see WARNINGS). Edema of the face and extremities has been reported. Other reactions which have occurred with intermittent dosage regimens include "flu syndrome" (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The "flu syndrome" may also appear if rifampin is taken irregularly by the patient or if daily administration is resumed after a drug-free interval.

		Acute generalized exanthematous pustulosis (AGEP) (see section 4.4) Skin reaction Pruritus Rash pruritic Urticaria Dermatitis allergic Pemphigoid Sweat discoloration
Musculoskeletal and connective tissue disorders	Not known	Muscle weakness Myopathy Bone pain
Renal and urinary disorders	Not known	Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis Chromaturia
Pregnancy, puerperium and perinatal conditions	Not known	Post-partum haemorrhage Fetal-maternal haemorrhage
Reproductive system and breast disorders	Not known	Menstrual disorder
Congenital, familial and genetic disorders	Not known	Porphyria
General disorders and administration site conditions	Very common	Pyrexia Chills
	Common	Paradoxical drug reaction (Recurrence or appearance of new symptoms of tuberculosis, physical and radiological signs in a patient who had previously shown improvement with

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<tr><td></td><td></td><td>appropriate anti-tuberculosis treatment is called a paradoxical reaction, which is diagnosed after excluding poor compliance of the patient to treatment, drug resistance, side effects of antitubercular therapy, secondary bacterial/fungal infections).*</td></tr>
<tr><td></td><td>Not known</td><td>Oedema</td></tr>
<tr><td>Investigations</td><td>Common</td><td>Blood bilirubin increased
Aspartate aminotransferase increased
Alanine aminotransferase increased</td></tr>
<tr><td></td><td>Not known</td><td>Blood pressure decreased
Blood creatinine increased
Hepatic enzyme increased</td></tr>
</table></td></tr>
<tr><td>Overdosage</td><td><u>Signs and Symptoms</u>
Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage; bilirubin levels may increase and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. A direct effect upon the hematopoietic system, electrolyte levels, or acid-base balance is unlikely.</td><td><u>Human Experience</u>

<u>Signs and Symptoms</u>
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 - 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from</td></tr>
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	Facial or periorbital edema has also been reported in pediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures, and cardiac arrest were reported in some fatal cases. **Acute Toxicity** 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 gm rifampin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 gm. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported. **Treatment** Intensive support measures should be instituted and individual symptoms treated as they arise. The airway should be secured and adequate respiratory exchange established. Since nausea and vomiting are likely to be present, gastric lavage within the first 2 to 3 hours after ingestion 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. For severe cases, extracorporeal hemodialysis may be required. If this is not available, peritoneal dialysis can be used along with forced diuresis.	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 – 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.
Clinical Pharmacology	**Intravenous Administration** After intravenous administration of a 300 or 600 mg dose of rifampin infused over 30 minutes to healthy male volunteers (n=12), mean peak plasma concentrations were 9.0±3.0 and 17.5±5.0 mcg/mL, respectively. Total body clearances after the 300 and 600 mg IV doses were 0.19±0.06 and 0.14±0.03 L/hr/kg, respectively. Volumes of distribution at steady state were	**Pharmacodynamic properties** Pharmacotherapeutic group: Anti-mycobacterials, antibiotics, ATC Code: J04AB02. Rifampicin is an active bactericidial antituberculosis drug which is particularly active against the rapidly growing extracellular organisms and also has bactericidal activity intracellularly.

	0.66±0.14 and 0.64±0.11 L/kg for the 300 and 600 mg IV doses, respectively. After intravenous administration of 300 or 600 mg doses, rifampin plasma concentrations in these volunteers remained detectable for 8 and 12 hours, respectively Plasma concentrations after the 600 mg dose, which were disproportionately higher (up to 30% greater than expected) than those found after the 300 mg dose, indicated that the elimination of larger doses was not as rapid. After repeated once-a-day infusions (3-hr duration) of 600 mg in patients (n=5) for 7 days, concentrations of IV rifampin decreased from 5.81±3.38 mcg/mL 8 hours after the infusion on day 1 to 2.6±1.88 mcg/mL 8 hours after the infusion on day 7. Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore diffuses freely into tissues. Rifampin is rapidly eliminated in the bile and undergoes progressive enterohepatic circulation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. Less than 30% of the dose is excreted in the urine as rifampin or metabolites. Serum concentrations do not differ in patients with renal failure at a studied dose of 300 mg, and consequently, no dosage adjustment is required. **<u>Pediatrics</u>** <u>Intravenous Administration</u> In pediatric patients 0.25 to 12.8 years old (n=12), the mean peak serum concentration of rifampin at the end of a 30-minute infusion of approximately 300 mg/m^2 was 25.9±1.3 mcg/mL; individual peak concentrations 1 to 4 days after initiation of therapy ranged from 11.7 to 41.5 mcg/mL; individual peak concentrations 5 to 14 days after initiation of therapy were 13.6 to 37.4 mcg/mL. The	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. **Pharmacokinetic properties** After intravenous administration of a 300 or 600 mg dose of Rifadin infusion infused over 30 minutes to healthy male volunteers (n = 12), mean peak plasma concentrations were 9.0 and 17.5 µg/ml, respectively. The average plasma concentrations in these volunteers remained detectable for 8 and 12 hours, respectively. 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 600 mg dose and increases to 5.1 hours after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 – 3 hours. At a dose of up to 600 mg/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.

	individual serum half-life of rifampin changed from 1.04 to 3.81 hours early in therapy to 1.17 to 3.19 hours 5 to 14 days after therapy was initiated. In a pharmacokinetics (PK) study of 22 pediatric patients (median gestational age 27.5 weeks [range; 23-41 weeks] and median postnatal age (PNA) 7.5 days [range: 0-56 days]) receiving intravenous rifampin 10-20 mg/kg/day over 30 minutes, pediatric patients ≤7 days old had a median clearance of 0.09 L/kg/hr (range: 0.056-0.14 L/kg/hr) and a median area under the plasma drug concentration-time curve at infinity (AUC∞) of 105 mg*hr/L (range: 80172 mg*hr/L); pediatric patients >7 days PNA had a median clearance of 0.23 L/kg/hr (range: 0.14-0.32 L/kg/hr) and a median AUC∞ of 78 mg*hr/L (range: 51-170 mg*hr/L). Based on PK modeling and simulation analyses, a dose of 12 mg/kg infused over 60 minutes once daily in pediatric patients ≤7 days PNA resulted in median (90% prediction interval) for maximum plasma concentration (Cmax) of 8.4 mcg/mL (range: 5.3 - 13.3 mcg/mL) and AUC∞ of 96.4 mg*hr/L (range: 64.5 - 141.6 mg*hr/L); in pediatric patients >7 days and < 90 days PNA a dose of 14 mg/kg infused over 60 minutes once daily resulted in a median (90% prediction interval) for Cmax of 9.6 mcg/mL (range: 6.l - 15.1 mcg/mL) and AUC∞ of 73.l mg*hr/L (range: 45.6 - 131.6 mg*hr/L). All simulated AUC∞ were within the range of AUC∞ values reported in other studies in adults treated for tuberculosis. **Microbiology** <u>Mechanism of Action</u> Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible *Mycobacterium tuberculosis* organisms. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. <u>Resistance</u> Organisms resistant to rifampin are likely to be resistant to other rifamycins.	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.

	In the treatment of both tuberculosis and the meningococcal carrier state (see INDICATIONS AND USAGE), the small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. In addition, resistance to rifampin has been determined to occur as single-step mutations of the DNA-dependent RNA polymerase. Since resistance can emerge rapidly, appropriate susceptibility tests should be performed in the event of persistent positive cultures. Activity *in vitro* and *in vivo* Rifampin has bactericidal activity *in vitro* against slow and intermittently growing *M. tuberculosis* organisms. Rifampin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections (see INDICATIONS AND USAGE): Aerobic Gram-Negative Microorganisms: *Neisseria meningitidis* "Other" Microorganisms: *Mycobacterium tuberculosis* The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for rifampin against isolates of similar genus or organism group. However, the efficacy of rifampin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials. Aerobic Gram-Positive Microorganisms: *Staphylococcus aureus* (including Methicillin-Resistant *S. aureus*/MRSA) *Staphylococcus epidermidis*	

	Aerobic Gram-Negative Microorganisms: *Haemophilus influenzae* "Other" Microorganisms: *Mycobacterium leprae* β-lactamase production should have no effect on rifampin activity. <u>Susceptibility Testing</u> For specific information regarding susceptibility test criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: www.fda.gov/STIC	