RIFAMPICIN

RIMAPED®

200 mg/5 mL Suspension
Antituberculosis

FORMULATION
Each 5 mL (1 teaspoonful) suspension contains:
Rifampicin..... 200 mg

PRODUCT DESCRIPTION
Rifampicin (Rimaped®) 200 mg/5 mL Suspension is a brick red, viscous suspension with strawberry odor and taste

Rifampicin (Rimaped®) 200 mg/5 mL Suspension is formulated using the SureDose® Technology of PediaTech® to provide a physically and chemically stable suspension.
The physical and chemical stability assure that the suspension will deliver the same amount of rifampicin with every dose.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Rifampicin, a semisynthetic antibiotic derivative of rifamycin, suppresses bacterial ribonucleic acid (RNA) synthesis by binding to the β subunit of deoxyribonucleic acid (DNA)-dependent RNA polymerase, thus inhibiting the attachment of the enzyme to DNA, blocking RNA transcription, elongation, and subsequent translation to protein. It does not inhibit the counterpart mammalian enzyme.

Rifampicin has bactericidal action and potent sterilizing effect against both intracellular and extracellular tubercle bacilli. Cross resistance has been shown only with other rifamycin derivatives.

PHARMACOKINETICS

Rifampicin is completely absorbed from the gastrointestinal tract. Peak plasma concentrations ranged from 3.5 to 15 mcg/mL after oral administration of rifampicin 10 mg/kg to children. In fasting children (6 to 58 months), peak plasma concentrations of 10.7 to 11.5 mcg/mL occurred within 1 hour after oral administration of rifampicin 10 mg/kg (as an extemporaneously prepared oral suspension in simple syrup or as a dry powder mixed in applesauce). Food may slightly reduce the peak plasma concentrations of rifampicin by approximately 30%.

Rifampicin is widely distributed in body tissues and fluids. Its diffusion into the cerebrospinal fluid (CSF) is increased when the meninges are inflamed.

Rifampicin is metabolized in the liver through deacetylation. It undergoes enterohepatic circulation and is largely reabsorbed, but the metabolite is not.

The plasma elimination half-life of rifampicin is approximately 2 to 5 hours.Excretion is mainly via the biliary tract; 3 to 30% of rifampicin 600 mg is excreted in the urine as unchanged drug and as active metabolite within 24 hours. Approximately 60% of rifampicin is excreted in the feces.

Special Populations:

Hepatic Impairment: The peak plasma concentrations of rifampicin are increased and the plasma elimination half-life is prolonged in patients with hepatic impairment.

Renal Impairment: The renal clearance of rifampicin is reduced in patients with renal impairment.

Bioequivalence Study

Rifampicin (Rimaped®) 200 mg/5 mL Suspension was shown to be bioequivalent to the reference product (innovator) in adults under fasting conditions. The following are important pharmacokinetic parameters of rifampicin in adult volunteers who received **Rifampicin (Rimaped®) 200 mg/5 mL Suspension** under fasting conditions:

Pharmacokinetic Parameters	Rifampicin 200 mg/5 mL Suspension	90% Confidence Interval
C_{max} (mcg/mL)	14.84 ± 2.24	85.06 - 97.84
AUC_{0-24h} (mcg-h/mL)	104.87 ± 21.94	91.42 - 100.56
AUC_{0-inf} (mcg-h/mL)	114.25 ± 23.10	93.38 - 101.66
T_{max} (h)	1.81 ± 0.69	
K_{el} (h)	0.16 ± 0.03	
$T_{1/2}$ (h)	4.53 ± 0.81	

C_{max} - peak plasma concentration of the drug;
AUC_{0-24h} - area under the plasma concentration-time curve from time zero to 24 hours;
AUC_{0-inf} - area under the plasma concentration time curve from time zero to infinity;
T_{max} - time the drug reached its maximum concentration in the blood;
K_{el} - elimination rate constant;
$T_{1/2}$ - plasma elimination half-life

INDICATIONS
- Treatment of all forms of tuberculosis in conjunction with at least one other antituberculous drug. (See table for recommended regimens in pediatric tuberculosis).
- For the treatment of asymptomatic carriers of ***Neisseria meningitidis*** to eliminate meningococci from the nasopharynx.
- As a prophylactic antimicrobial agent after exposure to meningococcal infection.

DOSAGE / ADMINISTRATION
Treatment of pulmonary and extrapulmonary tuberculosis: Once daily, must be taken on an empty stomach. To be taken in conjunction with at least one other antituberculous drug.
Usual Pediatric & Adult Doses: Orally, 10 to 15 mg/kg body weight given in a single daily dose (maximum daily dose is 600mg).

Age Group (Years)	Daily Dose
Children:	**200 mg / 5 mL**
1 to 2	2.5 to 5 mL (½ - 1 teaspoonful)
3 to 6	5 to 7.5 mL (1-1½ teaspoonsful)
7 to 12	7.5 to 12.5 mL (1½-2½ teaspoonsful)
Adult:	
13 & above	12.5 to 15 mL (2½ - 3 teaspoonsful)

Chemoprophylaxis of tuberculosis (to be given to close contacts of TB patients excreting INH – resistant organisms):
Orally, 15 mg/kg body weight given in a single daily dose (maximum 600 mg/day).

INITIAL TREATMENT OF TUBERCULOSIS
DOSAGE RECOMMENDATION FOR CHILDREN *
(adapted from the Philippine Coalition against Tuberculosis, the Philippine Infectious Disease Society of the Philippines and the Philippine Pediatric Society Joint Recommendations, 1997)

DRUGS	DOSAGE (mg/kg body weight)**			
	DAILY		2-3x/week (DOTS)***	
	≤ 12 y.o.	>12 y.o.	≤ 12 y.o.	>12 y.o.
Isoniazid (INH)	5-10 (max 300 mg)	5 (max 300 mg)	20-40 (max 900 mg)	15 (max 900 mg)
(Rifampicin) (Rif)	10-15 (max 600 mg)	10 (max 600 mg)	10-20 (max 600 mg)	10 (max 600 mg)
Pyrazinamide (PZA)	15-30 (max 2 g)	15-30 (max 2 g)	50-70 (max 4 g)	50-70 (max 4 g)
Ethambutol HCl (E)****	15-25 first 2 mos., then 15 (max 2.5g)	15-25 (max 2.5g)	30 (3x/week) 50 (2x/week) (max 2.5 g)	30 (3x/week) 50 (2x/week) (max 2.5 g)
Streptomycin sulfate (S)*****	20-30 (max 1 g)	15 (max 1 g)	25-30 (max 1.5 g; 2x/week) (max 1g; (3x/week)	25-30 (max 1.5 g; 2x/week) (max 1 g ; 3x/week)

* Currently recommended 6-month regimen for drug-susceptible tuberculosis consists of INH, Rif & PZA for 2 months, followed by 4 months of INH & Rif.
** Doses based on weight should be adjusted as the growing child's weight changes.
*** Directly-Observed Therapy – Short course
**** Not recommended for children < 6 y.o. due to potential ocular complications. Only an "add-on" drug if quadruple therapy is required.
***** Used as a 4th drug in children < 6 y.o. where E is not recommended. Used also in more severe types of TB such as TB meningitis & miliary TB.

Treatment of meningococcal carriers:
1 month of age or older: 10 mg/kg every 12 hours for 2 days.
Below 1 month of age: 5 mg/kg every 12 hours for 2 days.

Prophylaxis of meningococcal infection after exposure:
Orally, 10 mg/kg (maximum 600mg/day) every 12 hours for 4 doses.

Note: Rifampicin is not indicated for the treatment of meningococcal infection because of the possibility of rapid emergence of resistant organisms.

Patient Information
- Take medication on regular basis; avoid missing doses. Do not discontinue therapy except on advice of physician.
- Medication may cause a reddish-orange discoloration of the urine, stools, saliva, tears, sweat and sputum. This is to be expected and is not harmful. Soft contact lenses may be permanently stained.
- Notify physician promptly if any of the following symptoms are experienced: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, pain or swelling of the joints.

CONTRAINDICATIONS
- Hypersensitivity to rifampicin or to any component of the product
- Porphyria
- Jaundice or severe hepatic disease
- Acute hepatic disease
- Concomitant use with saquinavir-ritonavir combination (see **Interactions with other medicaments**)

WARNINGS AND PRECAUTIONS
Rifampicin has been associated with hepatic dysfunction. Use with caution and under strict medical supervision in patients with hepatic impairment. Carefully monitor liver function [i.e., alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] prior to therapy and then every 2 to 4 weeks during therapy. Discontinue treatment if signs of hepatocellular damage occur.
Discontinue treatment and evaluate at the first sign of hypersensitivity reaction. If the treatment must be continued, the product should only be given after symptoms have cleared and only under the supervision of a physician.

Periodic assessment of organ system functions (e.g., renal, hepatic, and hematopoietic) should be made during long-term treatment.

Diabetes Mellitus
Rifampicin should be used with caution in patients with a history of diabetes mellitus, as diabetes management may be more difficult.

Hyperbilirubinemia
Hyperbilirubinemia may occur in the first 2 or 3 weeks of treatment. Moderate increases in bilirubin and/or transaminase levels are not indications to discontinue rifampicin.

Thrombocytopenia
Thrombocytopenia has been reported with high dose rifampicin intermittent therapy and after resumption of interrupted treatment. This effect is reversible if the drug is discontinued as soon as purpura occurs. However, the continuation of rifampicin administration after the appearance of purpura may lead to cerebral hemorrhage and fatalities.

Vitamin K Dependent Coagulopathy and Severe Bleeding
Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding.
The occurrence of coagulopathy should be monitored particularly in patients with bleeding risk. Administration of supplemental vitamin K should be considered when applicable (vitamin K deficiency, hypoprothrombinemia).

Clostridium difficile-Associated Diarrhea
Clostridium difficile-associated diarrhea has been reported with the use of many antibacterial agents, including rifampicin. This should be considered in the differential diagnosis of patients who develop diarrhea during or following rifampicin treatment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Systemic hypersensitivity reactions such as DRESS may occur in patients receiving rifampicin. Signs and symptoms may include fever, rash, urticaria, angioedema, hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, elevated liver transaminases or flu-like syndrome. These reactions may be severe and DRESS may be fatal. Carefully monitor patients receiving rifampicin for signs and/or symptoms. If these symptoms occur, discontinue treatment and administer supportive measures.

Other Effects
Rifampicin may produce discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum, and tears. Soft contact lenses may be permanently stained.

Effects on Ability to Drive and Use Machines
Rifampicin may cause drowsiness, dizziness, mental confusion, and visual disturbances. Patients should exercise caution when driving vehicles or operating machinery.

INTERACTIONS WITH OTHER MEDICAMENTS
Drugs that decrease the effects of rifampicin: Drugs that reduce gastric motility (e.g., anticholinergics, opioids), aminosalicylic acid preparations and clofazimine.
Rifampicin decreases the effects of the following drugs due to induced hepatic metabolism:
- Angiotensin-2-receptor blockers: losartan
- Anti-arrhythmic agents: disopyramide, mexiletine, quinidine, propafenone, tocainide
- Antibacterial agents: chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones (ciprofloxacin), sulfapyridine
- Anticonvulsants: phenytoin
- Antifungal agents: ketoconazole, fluconazole, itraconazole
- Antihyperlipidemic agents: simvastatin, clofibrate
- Antiparasitics: atovaquone, praziquantel
- Antipsychotic agents: clozapine, haloperidol, aripiprazole
- Antiretroviral agents: indinavir, efavirenz, nelfinavir, lopinavir, delavirdine, zidovudine, amprenavir, atazanavir, fosamprenavir, nevirapine
- Barbiturates
- Benzodiazepines: diazepam, midazolam, triazolam
- Beta-adrenoceptor blockers: propanolol, bisoprolol
- Calcium-channel blockers: diltiazem, nifedipine, verapamil
- Cardiac glycosides: digitoxin, digoxin
- Corticosteroids: prednisolone
- Diuretics: eplerenone
- Estrogens
- Immunosuppressive agents: ciclosporin, tacrolimus, irinotecan
- Narcotic analgesics: methadone
- Ondansetron
- Oral anticoagulants: coumarins
- Oral antidiabetic agents: sulfonylureas, chlorpropamide, rosiglitazone, tolbutamide
- Progestins
- Quinine
- Riluzole
- Theophylline
- Thyroid hormone: levothyroxine
- Tricyclic antidepressants: amitriptyline, nortriptyline

Saquinavir-ritonavir combination: May increase the risk of hepatotoxicity. Therefore, rifampicin is contraindicated in patients who are taking saquinavir-ritonavir combination.
Halothane or isoniazid: May increase the risk of hepatotoxicity. If alterations in liver function tests occur, consider discontinuation of treatment.
Antacids: May reduce rifampicin absorption. Rifampicin should be given at least 1 hour before the antacid.
Oral or other systemic hormonal contraceptives: Rifampicin may decrease the effectiveness of hormonal contraceptives and may cause high incidence of menstrual disorders (e.g., spotting, breakthrough bleeding). Therefore, an alternative form of contraception should be considered.
Clarithromycin and/or ciprofloxacin: A drug-induced lupus-like syndrome consisting of malaise, myalgia, arthritis, and peripheral edema have been observed in patients receiving rifampicin concomitantly with clarithromycin and/or ciprofloxacin.
Enalapril: Rifampicin may decrease the concentration of enalaprilat, the active metabolite of enalapril.
Antiretroviral Drugs (i.e., human immunodeficiency virus (HIV) protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs): Coadministration with rifampicin may lead to ineffectiveness of either drug or increased risk of toxicity.
Anticoagulants: Rifampicin increases the requirements for anticoagulants of the coumarin type. Prothrombin time must be performed frequently or as often as necessary in patients receiving rifampicin and anticoagulants concomitantly to maintain the required dose of the anticoagulant.
Vitamin D: Rifampicin decreases plasma concentrations of 25-hydroxy vitamin D (the major circulating vitamin D metabolite) and 1α,25-dihydroxy vitamin D. There have been reports of decreased plasma concentrations of vitamin D metabolites accompanied by decreased plasma calcium and phosphate concentrations and increased parathyroid hormone concentrations.
Antibiotics: Coadministration of rifampicin with other antibiotics causing vitamin K dependent coagulopathy (e.g., cefazolin or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders.
Laboratory Interactions: Rifampicin interferes with standard microbiological assays for serum folate and vitamin B_{12}. Therefore, consider alternate assay methods in patients taking rifampicin.

Abnormalities in liver function tests (e.g., elevation in serum bilirubin, alkaline phosphatase, and serum transaminases) and decrease in biliary excretion of contrast media used for gallbladder visualization have been observed. These tests should be performed before taking rifampicin in the morning.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: **Pregnancy Category C.** There are no adequate and well-controlled studies in pregnant women. Rifampicin crosses the placental barrier and appears in cord blood. An increase in congenital malformations, particularly spina bifida and cleft palate, has been reported in the offspring of rodents given rifampicin at oral doses of 150 to 250 mg/kg/day during pregnancy.
Rifampicin can cause postnatal hemorrhages in the mother and infant, for which treatment with Vitamin K may be indicated. Rifampicin should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Lactation: Rifampicin is distributed in human milk. Therefore, a decision should be made whether to discontinue breastfeeding or the use of this medicine taking into account the benefit of the drug to the breastfeeding woman and the possible risk to the child.

Elderly: This medicine should be used with caution in elderly patients since these patients are more likely to have decreased liver and/or renal function.

Hepatic Impairment: This medicine should be used with caution and under strict medical supervision in patients with hepatic impairment.

Renal Impairment: This medicine should be used with caution in patients with renal impairment.

UNDESIRABLE EFFECTS
Blood and lymphatic system disorders: Agranulocytosis, decreased hemoglobin concentrations, disseminated intravascular coagulation, eosinophilia, hemolysis, hemolytic anemia, hyperbilirubinemia, leukopenia, thrombocytopenia, vitamin K dependent coagulation disorders
Immune system disorders: Anaphylaxis
Endocrine disorders: Adrenal insufficiency
Metabolism and nutrition disorders: Anorexia, peripheral edema
Psychiatric disorders: Behavioral changes, drowsiness, inability to concentrate, mental confusion, psychosis
Nervous system disorders: Ataxia, cerebral hemorrhage, dizziness, generalized numbness, headache
Eye disorders: Exudative conjunctivitis, tear discoloration, visual disturbances
Vascular disorders: Flushing, hypotension, shock, vasculitis
Respiratory, thoracic, and mediastinal disorders: Dyspnea, sputum discoloration, wheezing
Gastrointestinal disorders: Abdominal cramps, diarrhea, epigastric distress, flatulence, heartburn, nausea, pancreatic insufficiency, pseudomembranous colitis, sore mouth and tongue, tooth discoloration, vomiting
Hepatobiliary disorders: Asymptomatic jaundice, hepatitis or shock-like syndrome with liver involvement and abnormal liver function test results
Skin and subcutaneous tissue disorders: Acneiform eruptions, acute generalized exanthematous pustulosis (AGEP), allergic dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, exfoliative dermatitis, pemphigoid, pruritus, purpura, rash, Stevens-Johnson syndrome (SJS), sweat discoloration, toxic epidermal necrolysis (TEN), urticaria
Musculoskeletal and connective tissue disorders: Myopathy, muscular weakness, pain in muscles, joints and extremities
Renal and urinary disorders: Acute renal failure, acute tubular necrosis, chromaturia, hematuria, hemoglobinuria, interstitial nephritis, light chain proteinuria, renal insufficiency
Pregnancy, puerperium and perinatal conditions: Fetal-maternal hemorrhage, postpartum hemorrhage
Reproductive system and breast disorders: Menstrual disturbances
Congenital, familial and genetic disorders: Porphyria
General disorders and administration site conditions: Facial edema, fatigue, flu-like syndrome (i.e., fever, chills, headache, dizziness, bone pain, shortness of breath, and malaise)
Investigations: Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, liver enzymes, and uric acid concentrations

OVERDOSE AND TREATMENT
Symptoms of rifampicin overdose include extensions of the common undesirable effects (e.g., nausea, vomiting, abdominal pain, pruritus, headache, lethargy, increased liver enzymes and/or bilirubin, and brownish-red or orange discoloration of skin, urine, sweat, saliva, tears, and feces). Liver enlargement (possibly with tenderness), jaundice, rapid increases in total and direct serum bilirubin and liver enzymes, and loss of consciousness may develop after massive rifampicin overdose. Patients with known hepatic disease may experience marked hepatotoxicity. There have been reports of hypotension, sinus tachycardia, ventricular arrhythmias, seizures, and cardiac arrest in some cases of fatalities resulting from rifampicin overdose. Rifampicin is unlikely to cause undesirable effects on the body's hematopoietic system, electrolyte concentration, or acid-base balance.

Nonfatal and fatal acute overdoses in adults have been reported with rifampicin 9 to 12 g and 14 to 60 g/day, respectively. Nonfatal overdoses in pediatric patients (1 to 4 years old) have been reported with rifampicin 100 mg/kg/day.

In cases of overdose, symptomatic and supportive treatment should be given. Emesis and gastric lavage may be appropriate if undertaken within a few hours of ingestion. After removing the gastric contents, activated charcoal slurry may be instilled into the stomach to help adsorb any remaining drug in the gastrointestinal tract.

An antiemetic may be given to control severe nausea and vomiting. Active diuresis with measured intake and output may promote rifampicin excretion. Bile drainage or hemodialysis may be initiated in patients with serious hepatic impairment lasting more than 24 to 48 hours. Improvement of impaired hepatic function and reversal of liver enlargement in patients with previously normal hepatic function may occur within 72 hours.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

Do not refrigerate.

SHAKE WELL BEFORE USING.

AVAILABILITY
Rifampicin (Rimaped®) 200 mg/5 mL Suspension – in amber bottle of 120 mL

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

DATE OF FIRST AUTHORIZATION (DR-XY28362): October 2010
DATE OF REVISION OF PATIENT INFORMATION LEAFLET (PIL): October 2018 (CCDS 18-021)

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) UNILAB-1 for Metro Manila or toll-free (+1-800)-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus
Barangay Mamplasan, Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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