Rifampicin USP (RIF)

Generic and additional names: 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca [1,11,13] trienimino)naphtha[2,1-b]furan-1,11(2H)-dione 21-acetate; rifampicin; rifaldazine; rifamycin AMP; R/AMP

CAS name: 3-[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin

CAS registry number: 13292-46-1

Molecular formula: $C_{43}H_{58}N_4O_{12}$

Molecular weight: 822.94

Structure:

![2D Structure](image1)

![3D Structure](image2)

Intellectual property rights: Generic. Parent compound originally identified as a natural product from Amycolatopsis at Lapetit, Milan, Italy. Lapetit collaborated with Ciba-Geigy in the early development of this compound.

Brand names: Rifampin, Rifampicin, Rifamycin. Abrifam (Abbott); Eremfat (Fatol); Rifa (Gr’unenthal); Rifadin(e), Rifaldin (Aventis); Rifapiam (Piam); Rifaprodin (Almirall); Rifoldin (Aventis); Rimactan(e) (Novartis)

Derivatives: Rifapentine, Rifalazil, Rifabutin

Description: A semisynthetic antibiotic produced from *Streptomyces mediterranei* having a broad antibacterial spectrum, including activity against several forms of
**Mycobacterium.** It is bactericidal, and acts on both intracellular and extracellular organisms.

**Properties:**

**State:** Solid

**Melting point:** 183°C

**Solubility:** Freely soluble in chloroform and DMSO; soluble in ethyl acetate, methanol, tetrahydrofuran; slightly soluble in acetone, water, carbon tetrachloride

*Water solubility: 1.4 mg/mL*

**Polarity:** Log P 3.719

**Acidity/basicity:** pKa 1.7 for the 4-hydroxy and pKa 7.9 for the 3-piperazine nitrogen.

**Spectrum of activity:** RIF is bactericidal with a very broad spectrum of activity against most Gram-positive and some Gram-negative organisms (including *Pseudomonas aeruginosa* and *M. tuberculosis*).

**In-vitro potency against MTB:** MIC values in the range of 0.1-0.39 mg/ml against *M. tuberculosis* H37Rv.

**Optimal human dosage:** Dose 10 mg/kg, in a single daily administration, not to exceed 600 mg/day, oral or i.v

**Pharmacology**

**Mechanism of action:** RIF acts via the inhibition of DNA-dependent RNA polymerase, leading to a suppression of RNA synthesis and cell death.

**Indication:** For the treatment of Tuberculosis and Tuberculosis-related mycobacterial infections.

**Pharmacodynamics:** RIF is an antibiotic that inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. It is bactericidal and has a very broad spectrum of activity against most gram-positive and gram-negative organisms (including *Pseudomonas aeruginosa*) and specifically *Mycobacterium*
tuberculosis. Because of rapid emergence of resistant bacteria, use is restricted to treatment of mycobacterial infections and a few other indications.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Species</th>
<th>Half-life (h)</th>
<th>AUC (mg·h/l)</th>
<th>Cmax (µg/ml)</th>
<th>PK methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>7.61 ± 1.32</td>
<td>139.7 ± 10.7</td>
<td>10.58 ± 0.28</td>
<td>Single oral dose of 10 mg/kg</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>4.3 ± 0.7</td>
<td>8.4 ± 1.1</td>
<td>1.2 ± 0.3</td>
<td>Single oral dose of 12 mg/kg</td>
</tr>
<tr>
<td>Human</td>
<td>2.46</td>
<td>117.93</td>
<td>14.91</td>
<td>Single oral dose of 10-15 mg/kg</td>
</tr>
</tbody>
</table>

**Absorption:** RIF is well absorbed from gastrointestinal tract when taken orally.

**Distribution:** RIF diffuses well to most body tissues and fluids, including the cerebrospinal fluid (CSF); concentrations in the liver, gallbladder, bile, and urine are higher than those found in the blood; therapeutic concentrations are achieved in the saliva, reaching 20% of serum concentrations; RIF crosses the placenta, with fetal serum concentrations at birth found to be approximately 33% of the maternal serum concentration; it penetrates into aqueous humour; it is distributed into breast milk.

**Metabolism:** Metabolism is mainly hepatic with 13-24% of the drug excreted unchanged in the urine. The drug is present in plasma as parent and deacetyl-RIF. RIF PK/PD is characterized by auto-upregulation of hepatic and gut metabolism with time such that the pharmacokinetics of RIF changes with repeated administration; steady state is usually reached by the sixth daily dose of 600 mg/kg.

**Route of elimination** Less than 30% of the dose is excreted in the urine as RIF or metabolites.

**Half-life:** 3.35 (+/- 0.66) hours

**Protein binding:** 89%
**Safety and Tolerability**

*Animal drug-drug interactions:* Antagonism occurs between INH, RIF and PZA in mice.

*Animal toxicity*

*Acute toxicity:* LD50 value in rats & mice are as follows:

<table>
<thead>
<tr>
<th>Species</th>
<th>Oral (mg/kg)</th>
<th>I.V (mg/kg)</th>
<th>I.P (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>885</td>
<td>260</td>
<td>640</td>
</tr>
<tr>
<td>Rats</td>
<td>1720</td>
<td>330</td>
<td>550</td>
</tr>
</tbody>
</table>

*Chronic toxicity:* Chronic exposure may cause nausea, vomiting and unconsciousness.

*Hepatotoxicity:* Liver abnormalities were seen in all species tested (rats 5 times, monkeys 8 times and mice 6 times recommended daily human dose). RIF administered in encapsulated form once or twice a week was as effective as free drug and showed less liver toxicity as measured by ALT, alkaline phosphatase and bilirubin levels. INH and RIF dosed simultaneously in rabbits caused an elevation in phospholipids and a reduction in phosphatidylcholine, cardiolipin and inorganic phosphates, possibly via a choline deficiency, which may lead to the observed liver toxicity.

*Reproductive toxicology:* Testicular atrophy was seen in baboons at 4 times recommended daily human dose. Teratogenicity was seen in rats at 15-25 recommended daily human doses.

*Mutagenecity:* The available studies on mutagenicity indicate absence of a mutagenic effect. An increase of hepatomas seen in female mice has been reported in one strain of mice, following one year’s administration of RIF at a dosage of 2-10% of the maximum human dosage.

*Animal safety pharmacology:* RIF has been reported to have an immunosuppressive effect in some animal experiments.
Human drug-drug interactions: RIF induces certain cytochrome P450s, mainly 3A4 isozyme. The RIF dose of 600 mg/day was established partly to limit the CYP3A induction potential. The drug affects the metabolism of the following drugs: acetaminophen, astemizole, carbamazepine, corticosteroids, cyclosporin, dapsone, ketoconazole, methadone, phenobarbital, phenytoin, quinidine, terfenadine, theophylline, verapamil and warfarin. Generally, although RIF induces CYP3A and lowers the plasma concentrations of some other drugs, its own PK is largely unaffected by this induction. The drug can also induce CYP1A2, CYP2C and CYP2D6.

Human potential toxicity: Hepatotoxicity is generally rare with RIF alone but preexisting conditions can be exacerbated. For RIF (10 mg/kg), clinically apparent hepatotoxicity has been reported to occur in 2-5% of cases and altered liver function tests in 10-15%.

Human adverse reactions

Hepatitis and serious hypersensitivity reactions including thrombocytopenia, hemolytic anaemia, renal failure have been reported. Asymptomatic elevations of serum transaminase enzymes, increase in serum bile acids and bilirubin concentrations can occur. Marked elevation of serum alkaline, phosphatase and bilirubin suggests RIF toxicity.

Cardiovascular: Hypotension and shock.

Respiratory: Shortness of breath.

CNS: Rare cases of organic brain syndrome have been reported (i.e. confusion, lethargy, ataxia, dizziness and blurring of vision). Peripheral neuropathy, affecting the limbs, muscles and joints in the form of numbness and pain, has been reported.

Gastrointestinal: Nausea, vomiting, diarrhoea. RIF causes orange-red staining of all body fluids.