RHZ-Plus; Rifacomb Plus†; Rimactazid + Z; Tricox; Wokex-4; Xeed-4; ***Indon.:*** Rimcure; Rimstar; ***Irl.:*** Rifater; ***Ital.:*** Rifater; ***Malaysia:*** Rimcure; ***Mex.:*** Arpisen; Finateramida; Rifater; ***Philipp.:*** 4D; CombiKids; CombiPack; Econokit; Econokit-MDR; Econopack; Fixcom 4; Kidz Kit 3; Myrin-P; Quadtab; Refam Pedia Kit; Rifater; Rimcure; Rimstar; SVM-Polypac-A; Triofix; Viper; ***Port.:*** Rifater; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Phthizopiram (Фтизопирам); Protiocomb (Протиокомб); Repin B (Репин В); Rifacomb Plus (Рифакомб Плюс); Rimecure 3-FDC (Римкур 3-ФДС); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Rifafour; Rifater; Rimcure; Rimstar; ***Spain:*** Rifater; Rimcure; Rimstar; ***Swed.:*** Rimcure; Rimstar; ***Switz.:*** Rifater; ***Thai.:*** Rifafour; Rifampyzid; Rifater; Rimcure 3-FDC; Rimstar; ***UK:*** Rifater; ***USA:*** Rifater; ***Venez.:*** Rimcure.

Quinupristin/Dalfopristin

Quinupristin *(BAN, USAN, rINN)*; Dalfopristin *(BAN, USAN, rINN)*; Kinupristiini/dalfopristiini; Kinupristin/dalfopristin; Quinupristina/dalfopristina; Quinupristine/dalfopristine; Quinupristinum/dalfopristinum; RP-59500.

Хинупристин/Дальфопристин

CAS — 126602-89-9 (quinupristin/dalfopristin); 176861-85-1 (quinupristin/dalfopristin).

ATC — J01FG02.

ATC Vet — QJ01FG02.

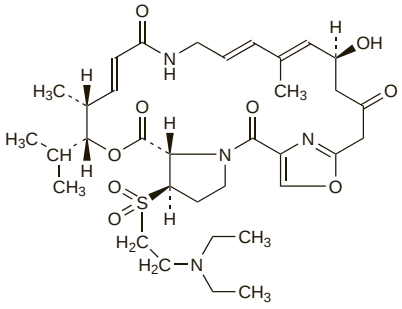
Dalfopristin Mesilate *(BANM, rINNM)*

Dalfopristin Mesylate; Dalfopristine, Mésilate de; Dalfopristini Mesilas; Mesilato de dalfopristina; RP-54476 (dalfopristin). (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-{[2-(Diethylamino)ethyl]sulfonyl}-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2.1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone methanesulphonate; (26*R*,27*S*)-26-{[2-(Diethylamino)-ethyl]sulfonyl}-26,27-dihydrovirginiamycin M_1 methanesulphonate.

Дальфопристина Мезилат

$C_{34}H_{50}N_4O_9S,CH_4O_3S$ = 787.0.

CAS — 112362-50-2 (dalfopristin).



(dalfopristin)

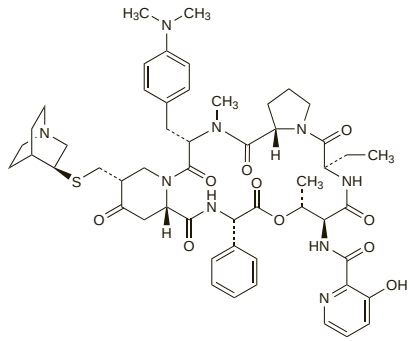
Quinupristin Mesilate *(BANM, rINNM)*

Mesilato de quinupristina; Quinupristin Mesylate; Quinupristine, Mésilate de; Quinupristini Mesilas; RP-57669 (quinupristin). *N*-{(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(Dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-{[(3*S*)-3-quinuclidinylthio]methyl}-12*H*-pyrido[2,1-*f*]pyrrolo[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl}-3-hydroxy-picolinamide methanesulphonate; 4-[4-(Dimethylamino)-*N*-methyL-L-phenylalamine]-5-(*cis*-5-{[(*S*)-1-azabicyclo[2.2.2]oct-3-ylthio]methyl}-4-oxo-L-2-piperidinecarboxylic acid)-virginiamycin S_1 methanesulphonate.

Хинупристина Мезилат

$C_{53}H_{67}N_9O_{10}S,CH_4O_3S$ = 1118.3.

CAS — 120138-50-3 (quinupristin).



(quinupristin)

Adverse Effects and Treatment

The adverse effects most frequently reported in patients receiving quinupristin/dalfopristin include nausea and vomiting, diarrhoea, skin rash, pruritus, headache, and pain. Myalgia and arthralgia have occurred and may be severe; symptoms may be improved by decreasing the dose frequency. Eosinophilia, anaemia, leucopenia, and neutropenia are also common. Individual cases of severe thrombocytopenia and pancytopenia have been reported. Pseudomembranous colitis has also been reported.

Hyperbilirubinaemia and raised liver enzyme values may occur.

Pain and inflammation at the injection site is common, and thrombophlebitis has occurred.

Quinupristin/dalfopristin is not removed by peritoneal dialysis, and removal by haemodialysis is considered unlikely.

Effects on the musculoskeletal system. References.

1. Olsen KM, *et al.* Arthralgias and myalgias related to quinupristin-dalfopristin administration. Abstract: *Clin Infect Dis* 2001; **32:** 674. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/318702 (accessed 12/08/08)
2. Carver PL, *et al.* Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. *Pharmacotherapy* 2003; **23:** 159–64.
3. Raad I, *et al.* Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. *J Antimicrob Chemother* 2004; **53:** 1105–8.
4. Gupte G, *et al.* Quinupristin-dalfopristin use in children is associated with arthralgias and myalgias. *Pediatr Infect Dis J* 2006; **25:** 281.

Precautions

Quinupristin/dalfopristin should be used with caution in patients with hepatic impairment and avoided in severe impairment, as elevated plasma concentrations of quinupristin and dalfopristin and their metabolites have been found in patients with hepatic dysfunction, and elevated concentrations of quinupristin metabolites have occurred in patients with hyperbilirubinaemia. The combination is contra-indicated in patients who have plasma-bilirubin concentrations greater than 3 times the normal upper limit.

Prolongation of the QT interval has been seen in *animals* given quinupristin/dalfopristin; therefore caution is advised in patients at risk of cardiac arrhythmias.

Interactions

Quinupristin/dalfopristin inhibits the cytochrome P450 isoenzyme CYP3A4 and it may therefore inhibit the metabolism of a number of drugs. In particular, there is a theoretical possibility of serious ventricular arrhythmias when given with drugs that prolong the QT interval, such as astemizole, cisapride, and terfenadine. Quinupristin/dalfopristin has been shown to increase plasma concentrations of ciclosporin, midazolam, nifedipine, and tacrolimus. The use of ergot alkaloids with quinupristin/dalfopristin should be avoided.

Antimicrobial Action

Quinupristin/dalfopristin is a semisynthetic streptogramin antibacterial. Quinupristin and dalfopristin each have bacteriostatic activity and in combination usually act synergistically to produce bactericidal activity. The streptogramins act on the ribosome to block protein synthesis.

Quinupristin/dalfopristin is active against a range of Gram-positive bacteria including meticillin- and multidrug-resistant strains of *Staphylococcus aureus* and *S. epidermidis*, vancomycin-resistant *Enterococcus faecium* (but not *E. faecalis*), and penicillin- and macrolide-resistant *Streptococcus pneumoniae*. It is also active against the anaerobe *Clostridium perfringens*, and Gram-negative bacteria *Legionella pneumophila*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Mycoplasma pneumoniae*, and *Neisseria meningitidis*.

◊ References.

1. Schouten MA, Hoogkamp-Korstanje JAA. Comparative in-vitro activities of quinupristin-dalfopristin against Gram-positive bloodstream isolates. *J Antimicrob Chemother* 1997; **40:** 213–19.
2. Pankuch GA, *et al.* Postantibiotic effect and postantibiotic sub-MIC effect of quinupristin-dalfopristin against Gram-positive and negative organisms. *Antimicrob Agents Chemother* 1998; **42:** 3028–31.
3. Johnson AP, *et al.* Susceptibility to quinupristin/dalfopristin and other antibiotics of vancomycin-resistant enterococci from the UK, 1997 to mid-1999. *J Antimicrob Chemother* 2000; **46:** 125–8.
4. Ling TK, *et al.* In vitro activity and post-antibiotic effect of quinupristin/dalfopristin (Synercid). *Chemotherapy* 2001; **47:** 243–9.
5. Eliopoulos GM, Wennersten CB. Antimicrobial activity of quinupristin-dalfopristin combined with other antibiotics against vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002; **46:** 1319–24.
6. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens. *Lancet Infect Dis* 2005; **5:** 209–18.

Resistance. Although uncommon, isolated reports of *E. faecium* resistant to quinupristin/dalfopristin have emerged,[1-7] and have included a link to the use of the streptogramin virginiamycin as an animal food additive.[3,4]

1. Eliopoulos GM, *et al.* Characterization of vancomycin-resistant Enterococcus faecium isolates from the United States and their susceptibility in vitro to dalfopristin-quinupristin. *Antimicrob Agents Chemother* 1998; **42:** 1088–92.
2. Bozdogan B, *et al.* Plasmid-mediated coresistance to streptogramins and vancomycin in Enterococcus faecium HM1032. *Antimicrob Agents Chemother* 1999; **43:** 2097–8.
3. Werner G, *et al.* Association between quinupristin/dalfopristin resistance in glycopeptide-resistant Enterococcus faecium and the use of additives in animal feed. *Eur J Clin Microbiol Infect Dis* 1998; **17:** 401–2.
4. Hershberger E, *et al.* Quinupristin-dalfopristin resistance in gram-positive bacteria: mechanism of resistance and epidemiology. *Clin Infect Dis* 2004; **38:** 92–8.
5. Oh WS, *et al.* High rate of resistance to quinupristin-dalfopristin in Enterococcus faecium clinical isolates from Korea. *Antimicrob Agents Chemother* 2005; **49:** 5176–8.
6. Donabedian SM, *et al.* Quinupristin-dalfopristin resistance in Enterococcus faecium isolates from humans, farm animals, and grocery store meat in the United States. *J Clin Microbiol* 2006; **44:** 3361–5.
7. Karanika M, *et al.* Reduced susceptibility to quinupristin/dalfopristin in Enterococcus faecium in Greece without prior exposure to the agent. *Int J Antimicrob Agents* 2008; **31:** 55–7.

Pharmacokinetics

After parenteral doses, quinupristin and dalfopristin are rapidly metabolised. At steady state, the half-life of quinupristin and its metabolites is about 3 hours and that of dalfopristin and its metabolites about 1 hour. Elimination half-lives of unchanged quinupristin and dalfopristin are 0.9 and 0.75 hours, respectively. Protein binding ranges from 55 to 78% for quinupristin and 11 to 26% for dalfopristin. The main route of excretion is biliary, with 75 to 77% of a dose detectable in the faeces. Urinary excretion accounts for 15% of the quinupristin and 19% of the dalfopristin dose. Negligible amounts are removed by peritoneal dialysis and probably also by haemodialysis.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet* 2004; **43:** 239–52.

Uses and Administration

Quinupristin/dalfopristin is a streptogramin antibacterial related to pristinamycin. Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin I and pristinamycin IIA respectively, and are used in the ratio 3:7. Quinupristin/dalfopristin is active against a range of Gram-positive and some Gram-negative organisms, but it is reserved for the treatment of serious

infections with multidrug-resistant Gram-positive bacteria, specifically MRSA and vancomycin-resistant *Enterococcus faecium*.

Quinupristin/dalfopristin is given as the mesilate salts by intravenous infusion, in glucose 5% over 60 minutes, in a dose of 7.5 mg/kg (equivalent to quinupristin 2.25 mg/kg and dalfopristin 5.25 mg/kg) every 8 or 12 hours for at least 7 days. To minimise venous irritation, the vein should be flushed with glucose 5% after each infusion; alternatively, the infusion may be given through a central venous catheter. The injection should not be diluted with saline solutions since it is incompatible with sodium chloride.

Doses may need to be reduced in patients with hepatic impairment (see below).

◊ References.

1. Bayston R, *et al.*, eds. Quinupristin/dalfopristin—update on the first injectable streptogramin. *J Antimicrob Chemother* 1997; **39** (suppl A): 1–151.
2. Wood MJ (ed). Quinupristin/dalfopristin–a novel approach for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 1999; **44** (suppl A): 1–46.
3. Lamb HM, *et al.* Quinupristin/dalfopristin: a review of its use in the management of serious Gram-positive infections. *Drugs* 1999; **58:** 1061–97.
4. Drew RH, *et al.* Treatment of methicillin-resistant Staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy: for the Synercid Emergency-Use Study Group. *J Antimicrob Chemother* 2000; **46:** 775–84.
5. Allington DR, Rivey MP. Quinupristin/dalfopristin: a therapeutic review. *Clin Ther* 2001; **23:** 24–44.
6. Linden PK, *et al.* Treatment of vancomycin-resistant Enterococcus faecium infections with quinupristin/dalfopristin. *Clin Infect Dis* 2001; **33:** 1816–23.
7. Goff DA, Sierawski SJ. Clinical experience of quinupristin-dalfopristin for the treatment of antimicrobial-resistant gram-positive infections. *Pharmacotherapy* 2002; 748–58.
8. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis* 2003; **36:** 473–81.
9. Brown J, Freeman BB. Combining quinupristin/dalfopristin with other agents for resistant infections. *Ann Pharmacother* 2004; **38:** 677–85.
10. Manfredi R. A re-emerging class of antimicrobial agents: streptogramins (quinupristin/dalfopristin) in the management of multiresistant gram-positive nosocomial cocci in hospital setting. *Mini Rev Med Chem* 2005; **5:** 1075–81.

Administration in hepatic impairment. Licensed product information states that in clinical studies of quinupristin/dalfopristin the incidence of adverse effects in patients with chronic liver impairment or cirrhosis was similar to that in patients with normal liver function. However, pharmacokinetic studies have shown that systemic exposure to quinupristin/dalfopristin and their metabolites may be increased in those with hepatic impairment. In some countries it has therefore been recommended that quinupristin/dalfopristin should be avoided in patients with severe hepatic impairment, and that for those with moderate impairment a dose reduction to 5 mg/kg (equivalent to quinupristin 1.5 mg/kg and dalfopristin 3.5 mg/kg) should be considered if 7.5 mg/kg is not tolerated.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Synercid†; ***Austral.:*** Synercid; ***Austria:*** Synercid; ***Braz.:*** Synercid; ***Canad.:*** Synercid; ***Cz.:*** Synercid; ***Fin.:*** Synercid†; ***Fr.:*** Synercid; ***Ger.:*** Synercid†; ***Gr.:*** Synercid; ***Hung.:*** Synercid; ***Irl.:*** Synercid; ***Israel:*** Synercid; ***Ital.:*** Synercid; ***Mex.:*** Synercid†; ***Neth.:*** Synercid; ***NZ:*** Synercid; ***Pol.:*** Synercid; ***Port.:*** Synercid; ***S.Afr.:*** Synercid†; ***Spain:*** Synercid; ***Swed.:*** Synercid†; ***Switz.:*** Synercid†; ***UK:*** Synercid; ***USA:*** Synercid.

Ramoplanin *(USAN, rINN)*

A-16686; MDL-62198; Ramoplanina; Ramoplanine; Ramoplaninum.

Рамопланин

CAS — 76168-82-6.

Profile

Ramoplanin is a glycopeptide antibiotic with a spectrum of activity *in vitro* similar to that of vancomycin (p.359) but considerably more potent. It is also active against *Bacteroides* spp. It is under investigation, notably for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for use in the prevention of systemic infection in patients colonised with vancomycin-resistant enterococci.

◊ Reviews.

1. Farver DK, *et al.* Ramoplanin: a lipoglycodepsipeptide antibiotic. *Ann Pharmacother* 2005; **39:** 863–8.

Retapamulin *(USAN, rINN)*

Retapamulina; Rétapamuline; Retapamulinum; SB-275833. (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-Ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propanocyclopenta[8]annulen-8-yl{[(1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]sulfanyl}acetate.

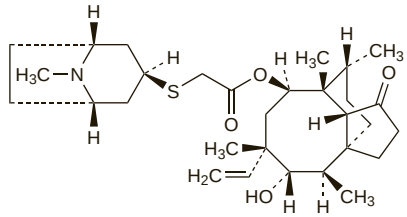
Ретапамулин

$C_{30}H_{47}NO_4S$ = 517.8.

CAS — 224452-66-8.

ATC — D06AX13.

ATC Vet — QD06AX13.



Adverse Effects and Precautions

Retapamulin is usually well tolerated; the most common reported adverse effect is application site irritation. Other local reactions such as erythema, pain, and pruritus occur rarely. Retapamulin ointment contains butylated hydroxytoluene (p.1633), which may cause local adverse effects such as contact dermatitis, or irritation to the eyes and mucous membranes. It should not be applied to abscesses.

Retapamulin has proved ineffective in infections caused by meticillin-resistant *Staphylococcus aureus*, and should not be used in their treatment.

Antimicrobial Action

Retapamulin is an antibacterial that selectively inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It is mainly bacteriostatic against meticillin-susceptible *Staphylococcus aureus*, and streptococci such as *Strep. pyogenes*. Although *in vitro* activity has been shown against meticillin-resistant *Staph. aureus* the *in vivo* efficacy of retapamulin was found to be inadequate in clinical studies.

◊ References.

1. Pankuch GA, *et al.* Activity of retapamulin against Streptococcus pyogenes and Staphylococcus aureus evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. *Antimicrob Agents Chemother* 2006; **50:** 1727–30.
2. Jones RN, *et al.* Activity of retapamulin (SB-275833), a novel pleuromutilin, against selected resistant Gram-positive cocci. *Antimicrob Agents Chemother* 2006; **50:** 2583–6.
3. Rittenhouse S, *et al.* Selection of retapamulin, a novel pleuromutilin for topical use. *Antimicrob Agents Chemother* 2006; **50:** 3882–5.
4. Champney WS, Rodgers WK. Retapamulin inhibition of translation and 50S ribosomal subunit formation in Staphylococcus aureus cells. *Antimicrob Agents Chemother* 2007; **51:** 3385–7.

Pharmacokinetics

Only very small amounts of topically applied retapamulin are absorbed into the systemic circulation. It is about 94% bound to plasma proteins and is shown to be metabolised by mono-oxygenation and N-demethylation *in vitro*.

Uses and Administration

Retapamulin is a pleuromutilin antibacterial isolated from the fungus *Clitopilus passeckerianus*. It is applied topically as a 1% ointment in the treatment of impetigo and other bacterial skin infections due to meticillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. The preparation should be applied twice daily for 5 days; treatment should be re-evaluated if there is no response within about 3 days. It is not suitable for application to mucous membranes.

For further details of skin infections and staphylococcal infections and their treatment, see p.194.

◊ References.

1. Parish LC, *et al.* Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol* 2006; **55:** 1003–1013.
2. Oranje AP, *et al.* Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. *Dermatology* 2007; **215:** 331–40.
3. Yang LPH, Keam SJ. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. *Drugs* 2008; **68:** 855–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Altargo; ***UK:*** Altargo; ***USA:*** Altabax.

Rifabutin *(BAN, USAN, rINN)*

Ansamicin; Ansamycin; Ansamycinum; Ansamysiini; LM-427; Rifabutiini; Rifabutina; Rifabutinas; Rifabutine; Rifabutinum. (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo-[2′,3′:7,8]naphth[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate.

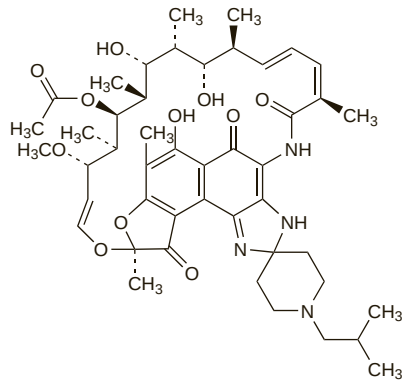
Рифабутин

$C_{46}H_{62}N_4O_{11}$ = 847.0.

CAS — 72559-06-9.

ATC — J04AB04.

ATC Vet — QJ04AB04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Rifabutin). A reddish-violet amorphous powder. Slightly soluble in water and in alcohol; soluble in methyl alcohol.

USP 31 (Rifabutin). An amorphous red-violet powder. Very slightly soluble in water; sparingly soluble in alcohol; soluble in chloroform and in methyl alcohol. Store at a temperature not exceeding 40°. Protect from light.

Stability. Study of the stability of two extemporaneous oral liquid preparations of rifabutin.[1]

1. Haslam JL, *et al.* Stability of rifabutin in two extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1999; **56:** 333–6.

Adverse Effects and Precautions

As for Rifampicin, p.325.

Rifabutin is usually well tolerated. The most common adverse effects include rash, gastrointestinal disturbances, and neutropenia. It produces a syndrome of polyarthralgia-arthritis at doses greater than 1 g daily. Uveitis has been reported, especially in patients also receiving clarithromycin or other macrolides and possibly also with fluconazole. Asymptomatic corneal opacities have been reported after long-term use.

Rifabutin should be used with caution in patients with severe hepatic or renal impairment.

◊ An orange-tan skin pigmentation has been reported to occur in most patients receiving rifabutin.[1] Urine may be discoloured.[2] A flu-like syndrome has been reported in 2 of 12 patients given 300 mg daily for Crohn's disease,[3] in 1 of 16 HIV-infected patients on continuous rifabutin,[1] and in 8 of 15 HIV-infected patients receiving increasing doses of rifabutin.[2]

Other reported adverse effects include hepatitis,[1] leucopenia[2] (including neutropenia[4]), epigastric pain,[3] rash,[3] erythema,[2] and ageusia.[5]