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.

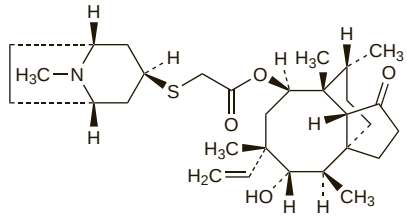
Ретапамулин

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

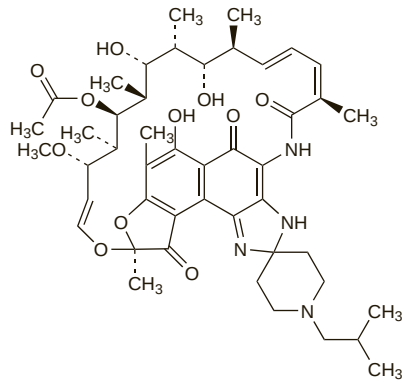
Рифабутин

$C_{46}H_{62}N_4O_{11}$ = 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]

Rash, fever, and vomiting occurred in 1 of 2 children receiving 6.5 mg/kg daily.[6]

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Torseth J, *et al.* Evaluation of the antiviral effect of rifabutin in AIDS-related complex. *J Infect Dis* 1989; **159:** 1115–18.
3. Basilisco G, *et al.* Controlled trial of rifabutin in Crohn's disease. *Curr Ther Res* 1989; **46:** 245–50.
4. Apseloff G, *et al.* Severe neutropenia caused by recommended prophylactic doses of rifabutin. *Lancet* 1996; **348:** 685.
5. Morris JT, Kelly JW. Rifabutin-induced ageusia. *Ann Intern Med* 1993; **119:** 171–2.
6. Levin RH, Bolinger AM. Treatment of nontuberculous mycobacterial infections in pediatric patients. *Clin Pharm* 1988; **7:** 545–51.

Effects on the eyes. Uveitis may occur a few weeks or months after starting rifabutin, and generally necessitates withdrawal of the drug and treatment with topical or systemic corticosteroids and cycloplegics.[1] In 1994, the UK CSM was aware of 48 reports of uveitis in patients taking rifabutin.[2] Most patients were also receiving clarithromycin for treatment of AIDS-related *Mycobacterium avium* complex (MAC) infection and many were also receiving fluconazole (see Interactions, below). A dosage reduction to 300 mg rifabutin daily is now recommended in patients also receiving macrolides or triazole antifungals[2,3] and is reported to produce a satisfactory response in MAC infections.[4] Panuveitis and retinal vasculitis has been reported[5] in 4 patients with active tuberculosis given rifabutin, and was thought to be a result of activation of the immune system by *Mycobacterium tuberculosis* and the very low weight of the patients.

Rifabutin-associated uveitis in children is less commonly reported probably because they may not notice or complain about visual changes, therefore monitoring of their vision while on treatment is advised.[6]

1. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. *Ann Pharmacother* 1995; **29:** 1149–55.
2. Committee on Safety of Medicines. Rifabutin (Mycobutin)—uveitis. *Current Problems* 1994; **20:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
3. Committee on Safety of Medicines. Revised indications and drug interactions of rifabutin. *Current Problems* 1997; **23:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023238&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
4. Shafran SD, *et al.* A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS; rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996; **335:** 377–83.
5. Skolik S, *et al.* Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. *Ocul Immunol Inflamm* 2005; **13:** 483–5.
6. Olesen HH, Krag S. Rifabutin-associated uveitis in a child. *Pediatr Infect Dis J* 2005; **24:** 1023–5.

Effects on the joints. A polyarthralgia-arthritis syndrome was reported in an initial dose finding study[1] in 9 of 10 patients receiving rifabutin, as monotherapy, at doses greater than 1 g. The syndrome did not occur in patients receiving less than 1 g daily and disappeared on drug withdrawal. Two patients with polyarthralgia-arthritis symptoms developed uveitis (see also under Effects on the Eyes, above) and aphthous stomatitis at doses of about 1.8 g daily. However, a later study[2] and case reports[3] have reported polyarthralgia-arthritis syndrome when rifabutin was given at doses of 300 to 600 mg daily as part of a multidrug regimen, including a macrolide (azithromycin or clarithromycin), for the treatment of *Mycobacterium avium* complex infection. Concentrations of rifabutin were increased as a result of inhibition of cytochrome P450 isoenzymes by the macrolide and some have suggested a maximum dose of rifabutin of 300 mg daily when used with a macrolide.[2] Higher doses of 450 to 600 mg daily may be considered for patients of large body mass or those who have failed to respond to initial treatment with a lower dose.

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.
2. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
3. Le Gars L, *et al.* Polyarthralgia-arthritis syndrome induced by low doses of rifabutin. *J Rheumatol* 1999; **26:** 1201–2.

Interactions

As for Rifampicin, p.327.

Rifabutin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme CYP3A4). It is a less potent inducer of cytochrome P450 isoenzymes than rifampicin, but similar interactions should nevertheless be anticipated. Use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of rifabutin, and possibly adverse effects.

Plasma concentrations of rifabutin are increased by clarithromycin (and possibly other macrolides) or fluconazole, resulting in increased rifabutin toxicity, in particular uveitis, (see Effects on the Eyes, above), neutropenia, and polyarthralgia-arthritis syndrome (see Effects on the Joints, above).

Some other interactions affecting the activity of rifabutin are discussed below.

Antiretroviral drugs. Rifabutin may be used as a substitute for rifampicin in the treatment of tuberculosis.[1,2] It has little effect on the serum concentrations of unboosted *HIV-protease inhibitors* (except saquinavir) and ritonavir-boosted HIV-protease inhibitors. However, HIV-protease inhibitors, particularly if boosted with ritonavir, significantly increase serum concentrations and toxicity of rifabutin. The dose of rifabutin is therefore usually substantially decreased when given with HIV-protease inhibitors (see Tuberculosis and HIV infection under Uses, below). Rifabutin should not be given with unboosted saquinavir; but saquinavir may be given with rifabutin if boosted with ritonavir.[2] Increases in the dose of indinavir are also required.[2]

Serum concentrations of rifabutin may be increased or decreased in those taking *NNRTIs*. However, rifabutin may usually be given to patients taking etravirine or nevirapine without the need for any dose modifications. Rifabutin is, however, not recommended in patients taking delavirdine or in those taking etravirine with ritonavir-boosted darunavir or ritonavir-boosted saquinavir. In patients taking efavirenz, the dose of rifabutin should be increased by at least 50% (see Tuberculosis and HIV infection under Uses, below).

No clinically significant interactions are expected with the integrase inhibitor *raltegravir* or the CCR-5 receptor antagonist *maraviroc*.[2] For further information on drug interactions with HIV-protease inhibitors see Table 1, p.917, and with NNRTIs see Table 2, p.944 in Antivirals.

Although rifabutin is reported to reduce the plasma concentrations of *zidovudine*, studies have shown that the effect is not marked (see p.915), and licensed product information for rifabutin suggests that the reduction may not be clinically relevant.

1. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 28/07/08)
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 28/07/08)

Azole antifungals. Rifabutin concentrations are increased by triazole antifungals and patients are at increased risk of rifabutin toxicity, specifically uveitis (see under Effects on the Eyes, above). Rifabutin also markedly reduces the plasma concentrations of *itraconazole*, *posaconazole*, and *voriconazole*, but does not affect the metabolism of *fluconazole*.

The area under the concentration-time curve (AUC) for rifabutin and its active 25-deacetyl metabolite were increased by 82% and 216% respectively when fluconazole was given to 12 HIV-infected patients.[1] Another study[2] in 10 patients with HIV infection, found that fluconazole increased the AUC of rifabutin by 76% and by 152% when the patients were also given clarithromycin. Raised plasma-rifabutin concentrations were reported in a patient who developed uveitis while also receiving itraconazole.[3] The mechanism of the interaction remains uncertain but could involve microsomal cytochrome P450 isoenzyme CYP3A4 (see Metabolism under Pharmacokinetics, below).

1. Trapnell CB, *et al.* Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann Intern Med* 1996; **124:** 573–6.
2. Jordan MK, *et al.* Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob Agents Chemother* 2000; **44:** 2170–2.
3. Lefort A, *et al.* Uveitis associated with rifabutin prophylaxis and itraconazole therapy. *Ann Intern Med* 1996; **125:** 939–40.

Macrolides. As discussed under Effects on the Eyes, above, most patients developing uveitis during rifabutin treatment are also receiving *clarithromycin* and it may also be implicated in the polyarthralgia-arthritis syndrome (see Effects on the Joints, above). In a study[1] of the treatment of *Mycobacterium avium* complex infection in AIDS patients, uveitis or pseudojaundice or both were noted in those receiving rifabutin, ethambutol, and clarithromycin, but not in those receiving rifabutin, ethambutol, ciprofloxacin, and clofazimine. A retrospective study[2] after an outbreak of uveitis in a similar patient population also found clarithromycin to be a risk factor, with a trend towards greater risk at higher rifabutin doses, although patient numbers were small. In 26 patients taking rifabutin with either clarithromycin or *azithromycin*,[3] the incidence and severity of adverse effects in general was similar, although the 2 patients who developed uveitis were both receiving clarithromycin.

Pharmacokinetic studies have found increased rifabutin concentrations when clarithromycin is also used. A study in healthy subjects[4] was terminated prematurely because of the high incidence of adverse effects, including neutropenia, fevers, and myalgia, particularly in subjects receiving rifabutin with azithromycin or clarithromycin. Mean serum concentrations of rifabutin and its 25-*O*-deacetyl metabolite in subjects also receiving clarithromycin were more than 4 times and 37 times those in subjects receiving rifabutin alone. Plasma concentrations were unaffected by azithromycin. Similar effects on rifabutin concentrations were found in HIV-infected subjects receiving clarithromycin[5] and reductions in clarithromycin concentrations were also noted. A study[6] to determine the tolerance and pharmacokinetic interactions of rifabutin and azithromycin in subjects with or without HIV infection found no significant drug interaction; however, the combination was poorly tolerated, mainly because of a high incidence of gastrointestinal symptoms and neutropenia.

1. Shafran SD, *et al.* Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. *N Engl J Med* 1994; **330:** 438–9.
2. Kelleher P, *et al.* Uveitis associated with rifabutin and macrolide therapy for Mycobacterium avium intracellulare infection in AIDS patients. *Genitourin Med* 1996; **72:** 419–21.
3. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21:** 594–8.
4. Apseloff G, *et al.* Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* 1998; **38:** 830–5.
5. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; **42:** 631–9.
6. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob Agents Chemother* 2001; **45:** 1572–7.

Antimicrobial Action

Rifabutin possesses a spectrum of antibacterial activity similar to that of rifampicin (p.327). However, most investigations have concentrated on its action against mycobacteria. Cross-resistance with rifampicin is common.

Antimycobacterial action. Rifabutin possesses activity against most species of mycobacteria. It may be more active *in vivo* than *in vitro* studies suggest, as a result of its favourable pharmacokinetic profile and prolonged postantibiotic effect.[1]

Rifabutin has been reported to be active in *animal* assays against *Mycobacterium leprae*,[2] including a rifampicin-resistant strain.[3] Synergistic activity against *M. leprae* has been reported[4] *in vitro* for rifabutin with sparfloxacin.

1. Kunin CM. Antimicrobial activity of rifabutin. *Clin Infect Dis* 1996; **22** (suppl 1): S3–S14.
2. Hastings RC, Jacobson RR. Activity of ansamycin against Mycobacterium leprae in mice. *Lancet* 1983; **ii:** 1079–80. Correction. *ibid.*; 1210.
3. Hastings RC, *et al.* Ansamycin activity against rifampicin-resistant Mycobacterium leprae. *Lancet* 1984; **i:** 1130.
4. Dhople AM, Ibanez MA. In-vitro activity of three new fluoroquinolones and synergy with ansamycins against Mycobacterium leprae. *J Antimicrob Chemother* 1993; **32:** 445–51.

Resistance. Rifampicin-resistant strains of *Mycobacterium tuberculosis* have been identified in 2 patients receiving rifabutin alone as prophylaxis against *M. avium* complex.[1,2] It is therefore important to exclude *M. tuberculosis* infection before beginning rifabutin prophylaxis.

Rifampicin-resistant *M. kansasii* has also been reported in a patient receiving rifabutin.[3]

Acquired resistance has been reported in HIV-infected persons receiving highly intermittent regimens (once- or twice-weekly) of rifabutin for the treatment of active tuberculosis,[4,5] and the CDC has advised that such patients receive daily treatment during the intensive phase of therapy and daily or 3 times-weekly treatment during the continuation phase.

1. Weltman AC, *et al.* Rifampicin-resistant Mycobacterium tuberculosis. *Lancet* 1995; **345:** 1513.
2. Bishai WR, *et al.* Brief report: rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *N Engl J Med* 1996; **334:** 1573–6.
3. Meynard JL, *et al.* Rifampin-resistant Mycobacterium kansasii infection in a patient with AIDS who was receiving rifabutin. *Clin Infect Dis* 1997; **24:** 1262–3.
4. CDC. Notice to readers: acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR* 2002; **51:** 214–15.
5. Burman W, *et al.*Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 2006; **173:** 350–6.

Pharmacokinetics

Rifabutin is readily but incompletely absorbed from the gastrointestinal tract and peak plasma concentrations of about 0.25 to 0.6 micrograms/mL have been reported 2 to 4 hours after an oral dose of 300 mg; doubling the dose increases the peak plasma concentration. Food may delay absorption but does not affect the extent of absorption. Rifabutin is about 70% bound to plasma proteins. Rifabutin is lipophilic and therefore is widely distributed in body tissues and fluids.

Rifabutin is rapidly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 mainly to active 25-O-deacetyl and 31-hydroxy metabolites. Rifabutin

induces its own metabolism resulting in a lower area under the curve after 4 weeks of continuous treatment than after the first few doses.

About 53% of a dose is found in the urine, mainly as metabolites and about 30% of a dose is excreted in the faeces. The mean half-life for rifabutin is reported to be about 40 hours, with a range of 16 to 69 hours.

◊ References.

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.

HIV-infected patients. Malabsorption of rifabutin and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p.328.

The pharmacokinetics of rifabutin were studied in HIV-infected patients with normal renal and hepatic function.[1] A two-compartment open pharmacokinetic model was proposed. Rifabutin was rapidly but incompletely absorbed from the gastrointestinal tract and bioavailability was poor, being 20% on day 1 of the study and 12% on day 28. Mean peak plasma concentrations occurred 2 to 3 hours after oral doses and were about 350, 500, and 900 nanograms/mL after doses of 300, 600, and 900 mg respectively. The peak and trough concentrations after 600 mg twice daily were about 900 and 200 nanograms/mL respectively. Rifabutin was about 70% bound to plasma proteins. The area under the curve showed a decrease on repeated dosage which might be explained by the induction of drug-metabolising liver enzymes. A large volume of distribution of 8 to 9 litres/kg, indicative of extensive tissue distribution, and a mean terminal half-life of 32 to 38 hours were reported.

This study[1] also showed that the peak plasma concentration of the major metabolite, 25-deacetylrifabutin, was 10% of the parent compound. Only 4% of unchanged rifabutin was excreted in the urine after oral use and between 6 to 14% after intravenous use. Total urinary excretion of rifabutin and metabolite 72 hours after intravenous use was 44%; total faecal excretion was between 30 and 49%.

Peak and trough concentrations at steady state were reported as 900 and 200 nanograms/mL respectively in a patient with tuberculosis given rifabutin 450 mg daily.[2] While these figures were the same as those previously reported with 600 mg twice daily,[1] the earlier study showed that there was considerable interpatient variability.

CSF concentrations in 5 patients with AIDS on rifabutin 450 mg daily ranged from 36 to 70% of serum concentrations.[3]

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; **33:** 1237–41.
2. Gillespie SH, *et al.* The serum rifabutin concentrations in a patient successfully treated for multi-resistant mycobacterium tuberculosis infection. *J Antimicrob Chemother* 1990; **25:** 490–1. Correction. *ibid.* 1991; **27:** 877.
3. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4:** 433–41.

Metabolism. Five metabolites of rifabutin were identified in an *in-vitro* study[1] using human hepatic and enterocyte microsomes. Cytochrome P450 isoenzyme CYP3A4 was involved in the formation of all metabolites except 25-*O*-deacetylrifabutin. Deacetylation of rifabutin was apparently mediated by microsomal cholinesterase,[1] although another study[2] showed that further metabolism of 25-*O*-deacetylrifabutin is dependent on CYP3A4. The results[1] also suggested that metabolism by intestinal CYP3A4 contributes significantly to presystemic metabolism of rifabutin (and consequently its low bioavailability) and to drug interactions with azole antifungals and with macrolides (see above).

1. Iatsimirskaia E, *et al.* Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems, and drug interactions with macrolides and antifungal agents. *Clin Pharmacol Ther* 1997; **61:** 554–62.
2. Trapnell CB, *et al.* Metabolism of rifabutin and its 25-desacetyl metabolite, LM565, by human liver microsomes and recombinant human cytochrome P-450 3A4: relevance to clinical interaction with fluconazole. *Antimicrob Agents Chemother* 1997; **41:** 924–6.

Uses and Administration

Rifabutin is a rifamycin antibacterial used as an alternative to the macrolides for the prophylaxis of *Mycobacterium avium* complex (MAC) infection in immunocompromised patients. It is also used for the treatment of other nontuberculous mycobacterial infections (including those due to MAC) (p.181) and tuberculosis (p.196). When used for treatment rifabutin, like rifampicin, should be used with other antibacterials to prevent the emergence of resistant organisms.

Rifabutin is given as a single oral daily dose. The dose for the prophylaxis of MAC infection is 300 mg daily. For the treatment of nontuberculous mycobacterial infections the dose is 450 to 600 mg daily in a multidrug regimen for up to 6 months after negative cultures are obtained. For pulmonary tuberculosis the usual dose is 300 mg daily for at least 6 months as part of a multidrug regimen; it can also be given intermittently (usually 3 times each week) as an alternative to daily use.

For details of doses in infants, children, and adolescents, see below.

Doses should be reduced to 300 mg daily in patients also receiving macrolides or azole antifungals (see under Adverse Effects, Effects on the Eyes, above). Dosage alterations may also be necessary in patients receiving HIV-protease inhibitors (see under Tuberculosis, below) and in those with severe renal impairment (see below).

◊ Reviews.

1. Brogden RN, Fitton A. Rifabutin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47:** 983–1009.

Administration in children. For the prophylaxis of MAC in HIV-infected infants and children with low CD4+ counts, the American Academy of Pediatrics (AAP) suggests an oral dose of rifabutin 5 mg/kg daily in those older than 6 years; the *BNFC* suggest the same dose may be given from 1 year of age and those 12 years of age and older may be given the usual adult dose.

For the treatment of nontuberculous mycobacterial disease in children aged 1 month to 12 years the *BNFC* suggests a dose of 5 mg/kg once daily for at least 6 months as part of a multidrug regimen; those 12 years of age and older may be given the usual adult dose.

For the treatment of tuberculosis in those 12 years of age and older the *BNFC* suggests a dose of 150 to 450 mg once daily for at least 6 months as part of a multidrug regimen.

Administration in renal impairment. Dosage of rifabutin should be reduced by 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/minute).

Cryptosporidiosis. Rifabutin may have a potential prophylactic effect against cryptosporidiosis (p.823).

Mycobacterium avium complex infections. Alterations in rifabutin dosage may be necessary in patients receiving antiretrovirals for the management of HIV infection; further details are given under Tuberculosis, below.

Peptic ulcer disease. For mention of the use of rifabutin in eradication regimens for *Helicobacter pylori* see p.1702.

References.

1. Borody TJ, *et al.* Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23:** 481–8. Correction. *ibid.*; **24:** 439.
2. Miehlke S, *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* 2006; **24:** 395–403.
3. González Carro P, *et al.* Efficacy of rifabutin-based triple therapy in Helicobacter pylori infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; **22:** 60–3.
4. Navarro-Jarabo JM, *et al.* Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. *BMC Gastroenterol* 2007; **7:** 31. Available at: http://www.biomedcentral.com/1471-230X/7/31 (accessed 12/11/07).

Toxoplasmosis. A beneficial response to rifabutin used with pyrimethamine was reported in a patient with AIDS-related *Toxoplasma gondii* encephalitis.[1] The patient was allergic to sulfonamides and clindamycin, which are commonly used (see p.826).

1. Schürmann D, *et al.* Rifabutin appears to be a promising agent for combination treatment of AIDS-related toxoplasma encephalitis. *J Infect* 1998; **36:** 352–3.

Tuberculosis and HIV infection. Rifabutin may be used in place of rifampicin in short-course therapy for tuberculosis in patients given antiretroviral drugs for HIV infection and may be preferred for patients unable to take efavirenz.[1,2] However, dose modifications are often necessary; additionally, some combinations, notably rifabutin with delavirdine, or saquinavir alone, should not be used, although rifabutin may be given with saquinavir if ritonavir is also given.

- In patients taking ritonavir-boosted HIV-protease inhibitors the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week
- In patients taking unboosted atazanavir the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week
- In those taking unboosted amprenavir, fosamprenavir, indinavir, or nelfinavir the daily dose of rifabutin should be decreased from 300 mg to 150 mg, and the dose for intermittent therapy should be 300 mg three times weekly. The dose of indinavir may need to be increased
- In patients taking efavirenz, the dose of rifabutin should be increased from 300 mg daily or intermittently to 450 to 600 mg daily or three times each week
- In patients taking nevirapine or etravirine, the usual dose of rifabutin is given (300 mg daily or 300 mg three times each week); rifabutin should not be used in patients taking etravirine plus ritonavir-boosted darunavir or saquinavir

1. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 28/07/08)
2. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 28/07/08)

Preparations

USP 31: Rifabutin Capsules.

Proprietary Preparations (details are given in Part 3) ***Austral.:*** Mycobutin; ***Austria:*** Mycobutin; ***Belg.:*** Mycobutin; ***Canad.:*** Mycobutin; ***Cz.:*** Mycobutin; ***Fin.:*** Ansatipin; ***Fr.:*** Ansatipine; ***Ger.:*** Alfacid; Mycobutin†; ***Gr.:*** Ansatipin†; Mycobutin; ***Hong Kong:*** Mycobutin; ***Israel:*** Mycobutin; ***Ital.:*** Mycobutin; ***Neth.:*** Mycobutin; ***NZ:*** Mycobutin; ***Port.:*** Mycobutin; ***Rus.:*** Mycobutin (Микобутин); ***S.Afr.:*** Mycobutin; ***Spain:*** Ansatipin; ***Swed.:*** Ansatipin; ***Switz.:*** Mycobutin; ***Turk.:*** Mycobutin; ***UK:*** Mycobutin; ***USA:*** Mycobutin.

Rifampicin *(BAN, rINN)*

Ba-41166/E; L-5103; NSC-113926; Rifaldazine; Rifampicina; Rifampicinas; Rifampicine; Rifampicinum; Rifampin *(USAN)*; Rifampisiini; Rifampisin; Rifamycin AMP; Ryfampicyna. 3-(4-Methylpiperazin-1-yliminomethyl)rifamycin SV; (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-1,2-Dihydro-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-2,7-(epoxypentadeca-[1,11,13]trienimino)naphtho[2,1-*b*]furan-21-yl acetate.

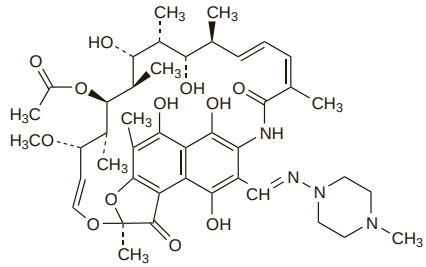
Рифампицин

$C_{43}H_{58}N_4O_{12}$ = 822.9.

CAS — 13292-46-1.

ATC — J04AB02.

ATC Vet — QJ04AB02; QJ54AB02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Rifampicin). A reddish-brown or brownish-red, crystalline powder. Slightly soluble in water, in alcohol, and in acetone; soluble in methyl alcohol. A 1% suspension has a pH of 4.5 to 6.5. Store at a temperature not exceeding 25° in an atmosphere of nitrogen in airtight containers. Protect from light.

USP 31 (Rifampin). A red-brown crystalline powder. Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methyl alcohol. A 1% suspension in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adverse Effects

Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.

Some patients may experience a cutaneous syndrome that presents 2 to 3 hours after a daily or intermittent dose as facial flushing and itching, with or without a rash, or rarely eye irritation and visual disturbances. A flu-like syndrome characterised by episodes of fever, chills, headache, dizziness, bone pain, shortness of breath, and malaise has been associated with intermittent use. It usually occurs after 3 to 6 months of intermittent treatment and has a higher incidence with doses of 25 mg/kg or more given once weekly than with currently recommended regimens. Anaphylaxis or shock has occurred rarely.

Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhoea, and epigastric distress. Taking doses on an empty stomach is recommended for maximal absorption, but dosage after a meal will minimise gastrointestinal intolerance. Pseudomembranous colitis has been reported. Rifampicin produces transient