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.

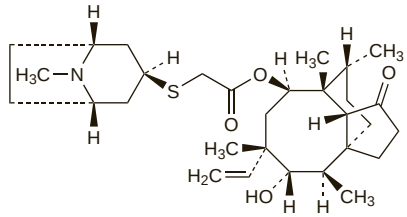
Ретапамулин

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

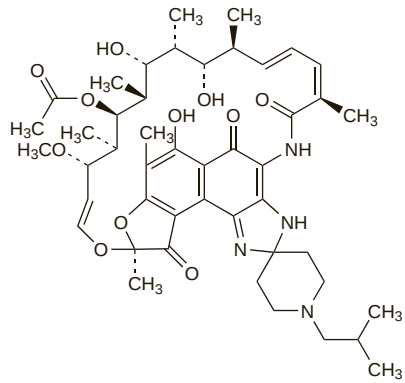
Рифабутин

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