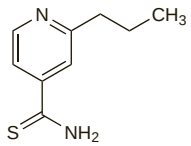
Profile
Propicillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p.314). Propicillin potassium is given orally for the treatment of susceptible mild to moderate infections in a usual dose of 700 mg three times daily.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Baycillin.

Protionamide *(BAN, rINN)*
Prothionamide; Protionamid; Protionamida; Protionamidi; Protionamidum; RP-9778; TH-1321. 2-Propylpyridine-4-carbothioamide.

Протионамид
$C_9H_{12}N_2S$ = 180.3.
CAS — 14222-60-7.
ATC — J04AD01.
ATC Vet — QJ04AD01.



Pharmacopoeias. In *Chin.*, *Int.*, and *Jpn.*

Adverse Effects, Precautions, and Antimicrobial Action
As for Ethionamide, p.275.

Pharmacokinetics
Protionamide is readily absorbed from the gastrointestinal tract and produces peak plasma concentrations about 2 hours after an oral dose. It is widely distributed throughout body tissues and fluids, including the CSF. Protionamide is metabolised to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

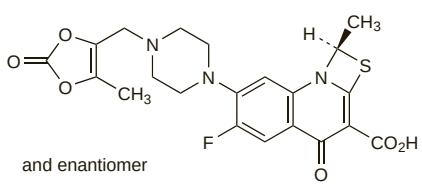
Uses and Administration
Protionamide is a thioamide derivative considered to be interchangeable with ethionamide (p.276) and is used as a second-line drug in the treatment of multidrug-resistant tuberculosis (p.196). It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p.176) but less toxic alternatives are now preferred. Complete cross-resistance occurs between the two drugs. Protionamide has been given orally in doses similar to those used for ethionamide. It has also been given as rectal suppositories; protionamide hydrochloride has been given intravenously. Like ethionamide, it has generally been replaced by less toxic antimycobacterials.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: ektebin; Peteha; ***Hong Kong:*** Peteha; ***India:*** Prothicid; ***Turk.:*** Promid; Tionamid.

Multi-ingredient: ***Austria:*** Isoprodian; ***Ger.:*** Isoprodian†; Peteha†; ***Rus.:*** Protiocomb (Протиокомб).

Prulifloxacin *(rINN)*
NM-441; Prulifloxacine; Prulifloxacino; Prulifloxacinum. (±)-7-{4-[(*Z*)-2,3-Dihydroxy-2-butenyl]-1-piperazinyl}-6-fluoro-1-methyl-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid cyclic carbonate.

Прулифлоксацин
$C_{21}H_{20}FN_3O_6S$ = 461.5.
CAS — 123447-62-1.
ATC — J01MA17.
ATC Vet — QJ01MA17.



and enantiomer

Profile
Prulifloxacin is the prodrug of ulifloxacin, a fluoroquinolone antibacterial. It is given for the treatment of susceptible infections in a usual oral dose of 600 mg daily.

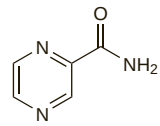
◊ Reviews.

1. Keam SJ, Perry CM. Prulifloxacin. *Drugs* 2004; **64:** 2221–34.
2. Prats G, *et al.* Prulifloxacin: a new antibacterial fluoroquinolone. *Expert Rev Anti Infect Ther* 2006; **4:** 27–41.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Unidrox; ***Gr.:*** Glimbax; Prixina; ***Ital.:*** Chinoplus; Keraflox; Unidrox; ***Port.:*** Keraflox; Oliflox.

Pyrazinamide *(BAN, rINN)*
Pirazinamid; Pirazinamida; Pirazinamidas; Pirazynamid; Pyratsiinamidi; Pyrazinamid; Pyrazinamidum; Pyrazinoic Acid Amide. Pyrazine-2-carboxamide.

Пиразинамид
$C_5H_5N_3O$ = 123.1.
CAS — 98-96-4.
ATC — J04AK01.
ATC Vet — QJ04AK01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet*.
Ph. Eur. 6.2 (Pyrazinamide). A white or almost white, crystalline powder. Sparingly soluble in water, slightly soluble in alcohol and in dichloromethane.
USP 31 (Pyrazinamide). A white to practically white, odourless or practically odourless, crystalline powder. Soluble 1 in 67 of water, 1 in 175 of dehydrated alcohol, 1 in 135 of chloroform, 1 in 1000 of ether, and 1 in 72 of methyl alcohol; slightly soluble in alcohol.

Adverse Effects and Treatment
Hepatotoxicity is the most serious adverse effect of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended doses, when given with isoniazid and rifampicin, the incidence of hepatitis has been reported to be less than 3%. Patients may have a transient increase in liver enzyme values; more seriously hepatomegaly, splenomegaly, and jaundice may develop and on rare occasions death has occurred.

Hyperuricaemia commonly occurs and may lead to attacks of gout.

Other adverse effects are anorexia, nausea, vomiting, aggravation of peptic ulcer, arthralgia, malaise, fever, sideroblastic anaemia, thrombocytopenia, and dysuria. Photosensitivity, pellagra, and skin rashes have been reported on rare occasions.

Effects on the cardiovascular system. Acute hypertension was associated with pyrazinamide in a previously normotensive woman.[1]

1. Goldberg J, *et al.* Acute hypertension as an adverse effect of pyrazinamide *JAMA* 1997; **277:** 1356.

Effects on the liver. The risk of hepatitis with antituberculous regimens containing pyrazinamide may be lower than suggested by early studies, in which large doses were used, often for long periods. The incidence of hepatitis in studies[1] of short-course regimens containing pyrazinamide has ranged from 0.2% in Africa, to 0.6% in Hong Kong, to 2.8% in Singapore. These and later studies[2-4] have shown that hepatotoxicity is not increased when pyrazinamide is added to the initial phase of short-term chemotherapy containing rifampicin and isoniazid. Nevertheless, a report[5] of 4 cases of fulminant hepatic failure in patients given triple therapy with the potentially hepatotoxic drugs rifampicin, isoniazid, and pyrazinamide (1 patient also received ethambutol) highlighted the importance of strict liver function monitoring and this was reinforced by others. The Joint Tuberculosis Committee of the British Thoracic Society has produced recommendations[6] for initial measurement of liver function in all patients and regular monitoring in patients with pre-existing liver disease, as well as the response to deteriorating liver function; prompt re-introduction of appropriate antituberculosis therapy is recommended once normal liver function is restored. Similar guidelines have been produced for the USA.[7,8] For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p.288.

The incidence of severe hepatotoxicity was found to be lower in patients receiving isoniazid, rifampicin, and pyrazinamide for initial treatment of active disease, than in those receiving rifampicin and pyrazinamide for 2 months for latent tuberculosis infection. For further information on hepatotoxicity caused by rifampicin and pyrazinamide see Effects on the Liver, under Rifampicin, p.326.

1. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 1984; **65:** 1–4.
2. Parthasarathy R, *et al.* Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1986; **67:** 99–108.
3. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
4. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
5. Mitchell I, *et al.* Anti-tuberculous therapy and acute liver failure. *Lancet* 1995; **345:** 555–6.
6. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
7. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
8. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; **174:** 935–52. Also available at: http://www.thoracic.org/sections/publications/statements/resources/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 05/10/07)

Effects on the nervous system. Convulsions that developed in a 2-year-old child receiving antituberculous therapy appeared to be due to pyrazinamide, given in a dose of 250 mg daily.[1]

1. Herlevsen P, *et al.* Convulsions after treatment with pyrazinamide. *Tubercle* 1987; **68:** 145–6.

Hyperuricaemia. Hyperuricaemia during therapy with pyrazinamide may be due to inhibition of uric acid excretion by pyrazinoic acid, the main metabolite of pyrazinamide.[1]

In a large multicentre study,[2] the incidence of elevated serum concentrations of uric acid for patients receiving rifampicin, isoniazid, and pyrazinamide was 52.2% at 8 weeks while the incidence for patients receiving rifampicin and isoniazid was 5.4%. Arthralgia was reported in 6 of 617 patients receiving rifampicin, isoniazid, and pyrazinamide, but in none of 445 patients receiving rifampicin and isoniazid.

Slight increases in plasma concentrations of uric acid occurred in 9 of 43 children after one month's treatment with rifampicin, isoniazid, ethambutol, and pyrazinamide. Arthralgias and gout did not occur. Uric acid concentrations were normal on completion of treatment with pyrazinamide.[3] Some studies[4] have suggested a relationship between elevated serum uric acid levels and arthralgia, but this has not been confirmed.[5]

1. Ellard GA, Haslam RM. Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. *Tubercle* 1976; **57:** 97–103.
2. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; **112:** 397–406.
3. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; **64:** 177–8.
4. Hong Kong Tuberculosis Treatment Services/British MRC. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. *Tubercle* 1976; **57:** 81–95.
5. Jenner PJ, *et al.* Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. *Tubercle* 1981; **62:** 175–9.

Pellagra. Pellagra, probably due to pyrazinamide, developed in a 26-year-old woman receiving antituberculous therapy.[1] Symptoms regressed, despite continued therapy, on giving nicotinamide.

1. Jørgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983; **22:** 44–5.

Precautions
Pyrazinamide should be used with caution in patients with liver disorders and is contra-indicated in established chronic or severe liver disease. In patients with liver disorders, liver function should be assessed before and regularly during treatment. The British Thoracic Society has recommended that pyrazinamide treatment should be suspended if serum aminotransferase concentrations are elevated to 5 times the normal upper limit or if the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. WHO recommends that pyrazinamide not be reintroduced if the hepatitis produced a clinical jaundice.

Pyrazinamide should not be given to patients with acute gout or hyperuricaemia and should be used with

caution in patients with a history of gout. Caution should also be observed in patients with renal impairment. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Porphyria. Pyrazinamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Although detailed teratogenicity data are not available, WHO,[1] the IUATLD,[2] the British Thoracic Society,[3] and the CDC[4] do not contra-indicate pyrazinamide in pregnant patients.

1. WHO. *Treatment of tuberculosis: guidelines for national programmes*. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 03/10/07)
2. Caminero Luna JA. *A tuberculosis guide for specialist physicians*. Paris: International Union Against Tuberculosis and Lung Disease (IUATLD), 2004. Available at: http://www.tbrieder.org/publications/specialists_en.pdf (accessed 03/10/07)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]

Interactions

Antigout drugs. The complex interactions occurring when pyrazinamide and *probenecid* are given to patients with gout have been studied.[1] Urinary excretion of urate depends on the relative size and timing of doses of the two drugs. Probenecid is known to block the excretion of pyrazinamide. A pharmacokinetic study[2] in 6 healthy subjects found that *allopurinol*, a xanthine oxidase inhibitor, increases concentrations of pyrazinoic acid (the main metabolite of pyrazinamide) thereby worsening pyrazinamide-induced hyperuricaemia. Allopurinol would therefore also appear to be unsuitable for treating pyrazinamide-induced hyperuricaemia.

1. Yü TF, *et al.* The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. *Am J Med* 1977; **63:** 723–8.
2. Lacroix C, *et al.* Interaction between allopurinol and pyrazinamide. *Eur Respir J* 1988; **1:** 807–11.

Zidovudine. Low or undetectable concentrations of pyrazinamide occurred in 4 patients also taking zidovudine.[1] In the same study, 6 of 7 patients with HIV infection taking pyrazinamide without zidovudine had normal serum pyrazinamide concentrations.

1. Peloquin CA, *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; **30:** 919–25.

Antimicrobial Action

Pyrazinamide has a bactericidal effect on *Mycobacterium tuberculosis* but appears to have no activity against other mycobacteria or micro-organisms *in vitro*. It is almost completely inactive at a neutral pH, but is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages. The initial inflammatory response to chemotherapy increases the number of organisms in the acidic environment. As inflammation subsides and pH increases, the sterilising activity of pyrazinamide decreases. This pH-dependent activity explains the clinical effectiveness of pyrazinamide as part of the initial 8-week phase in short-course treatment regimens.

Resistance to pyrazinamide rapidly develops when it is used alone.

Action. Although the antimicrobial activity of pyrazinamide has been recognised since the 1950s, the mode of action is still unclear. One proposal is that pyrazinoic acid is the active moiety. Pyrazinamidase produced by the tubercle bacilli is known to convert pyrazinamide to pyrazinoic acid. A further proposal[1] is that the pyrazinoic acid formed within the macrophage would be trapped, thereby lowering intracellular pH to levels toxic to tubercle bacilli.

1. Salfinger M, *et al.* Pyrazinamide and pyrazinoic acid activity against tubercle bacilli in cultured human macrophages and in the BACTEC system. *J Infect Dis* 1990; **162:** 201–7.

Activity with other antimicrobials. Pyrazinamide exhibited synergistic activity against *Mycobacterium tuberculosis* with clarithromycin.[1]

1. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; **41:** 2035–6.

Pharmacokinetics

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 hours after an oral dose and have been reported to be about 33 micrograms/mL after 1.5 g, and 59 micrograms/mL after 3 g. Pyrazinamide is widely distributed in body fluids and tissues and diffuses into the CSF. The half-life has been reported to be about 9 to 10 hours. It is metabolised primarily in the liver by hydrolysis to the major active metabolite pyrazinoic acid, which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidneys mainly by glomerular filtration. About 70% of a dose appears in the urine within 24 hours mainly as metabolites and about 4% as unchanged drug. Pyrazinamide is removed by dialysis. Pyrazinamide is distributed into breast milk.

◊ A short distribution phase and an elimination phase of 9.6 hours in healthy subjects after a single oral dose of pyrazinamide 27 mg/kg has been reported;[1] the half-life for the major metabolite pyrazinoic acid was 11.8 hours.

In the major metabolic pathway, pyrazinamide was deaminated to pyrazinoic acid which was hydroxylated to hydroxypyrazinoic acid; in the minor pathway, pyrazinamide was hydroxylated to hydroxypyrazinamide which was then deaminated to hydroxypyrazinoic acid. The limiting step was deamination; oxidation by xanthine oxidase occurred very quickly.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *Eur J Clin Pharmacol* 1989; **36:** 395–400.

Bioavailability. The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[1] However, another report[2] showed slightly reduced peak serum concentrations when pyrazinamide was given with a high-fat meal, and the authors suggested that pyrazinamide should preferably be given on an empty stomach.

1. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; **76:** 109–13.
2. Peloquin CA, *et al.* Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* 1998; **18:** 1205–11.

Breast feeding. The peak concentration of pyrazinamide in breast milk of a 29-year-old woman was 1.5 micrograms/mL 3 hours after a 1-g dose.[1] The peak plasma concentration was 42 micrograms/mL after 2 hours.

1. Holdiness MR. Antituberculosis drugs and breast-feeding. *Arch Intern Med* 1984; **144:** 1888.

Distribution. Pyrazinamide was given to 28 patients with suspected tuberculous meningitis in doses of 34 to 41 mg/kg. The mean concentration of pyrazinamide in the CSF after 2 hours was 38.6 micrograms/mL and represented about 75% of that in serum; concentrations at 5 and 8 hours were 44.5 and 31.0 micrograms/mL respectively and were about 10% higher than those in serum.[1] The use of corticosteroids appeared to have no influence on penetration of pyrazinamide into the CSF of patients with tuberculous meningitis.[2]

1. Ellard GA, *et al.* Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *BMJ* 1987; **294:** 284–5.
2. Woo J, *et al.* Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; **42:** 235–42.

Hepatic impairment. A study[1] of the pharmacokinetics of pyrazinamide was carried out in 10 patients with cirrhosis of the liver. After a dose of 19.3 mg/kg, the elimination phase was about 15 hours for pyrazinamide and 24 hours for the major metabolite pyrazinoic acid.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. *Arzneimittelforschung* 1990; **40:** 76–9.

HIV-infected patients. Malabsorption of pyrazinamide 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.

Uses and Administration

Pyrazinamide is used as part of multidrug regimens for the treatment of tuberculosis (p.196), primarily in the initial 8-week phase of short-course treatment. Pyrazinamide is usually given daily or 2 or 3 times weekly. In the UK, usual recommended oral doses for adults under 50 kg are 1.5 g daily, or 2 g three times weekly, or 3 g twice weekly. The usual dose for those 50 kg or greater is 2 g daily, or 2.5 g three times weekly, or 3.5 g twice weekly. The recommended doses in the USA are 20 to 25 mg/kg daily (maximum 2 g) or 1.5 to 3 g three times weekly or 2 to 4 g twice weekly. WHO recommends 25 mg/kg daily or 35 mg/kg three times weekly.

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

Pyrazinamide has also been used in the chemoprophylaxis of tuberculosis (see below).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy; thereby decreasing the risk of acquired drug resistance. Combination products containing pyrazinamide with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and ethambutol are available in some countries.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests a dose of pyrazinamide of 20 to 40 mg/kg daily or 50 mg/kg (to a maximum of 2 g) twice weekly by mouth, for the initial treatment phase. For children 1 month and older the *BNFC* suggests a dose of 35 mg/kg (to a maximum of 1.5 g in those under 50 kg and 2 g in those over 50 kg) once daily or 50 mg/kg (to a maximum of 2 g in those under 50 kg and 2.5 g in those over 50 kg) three times a week. WHO recommends 25 mg/kg once daily or 35 mg/kg three times a week.

Administration in hepatic impairment. See Precautions, above.

Administration in renal impairment. Pyrazinamide is mainly metabolised in the liver, but its metabolites are excreted in the urine, therefore the CDC[1] suggests that the dose may need to be reduced in patients with renal impairment. The Joint Tuberculosis Committee of the British Thoracic Society[2] and WHO[3] consider that standard dosage may be used in such patients. Dialysis affects the clearance of pyrazinamide and CDC recommends reducing the dose to 25 to 35 mg/kg three times a week after dialysis.

In a study[4] of 6 patients on haemodialysis, the average amount of pyrazinamide and its metabolites removed during a dialysis session was 926 mg after an oral dose of 1700 mg. It was recommended that the usual pyrazinamide dose be given to patients on dialysis as the risk of accumulation was negligible, and that the dose on dialysis days be given after the procedure.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53:** 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. WHO. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 03/10/07)
4. Lacroix C, *et al.* Haemodialysis of pyrazinamide in uraemic patients. *Eur J Clin Pharmacol* 1989; **37:** 309–11.

Tuberculosis chemoprophylaxis. In the USA, the American Thoracic Society and the CDC recommended a dose of pyrazinamide 15 to 20 mg/kg daily (maximum 2 g daily) with rifampicin 600 mg daily as an alternative to isoniazid monotherapy for the treatment of latent tuberculosis infection.[1] (In those unable to take rifampicin, it was substituted with rifabutin 300 mg daily.) However, owing to reports of serious and fatal liver damage (see Effects on the Liver, under Adverse Effects, above) the CDC and the American Thoracic Society now recommend that the combination of pyrazinamide with rifampicin should not be offered to persons with latent tuberculosis.[2].

1. American Thoracic Society and CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; **161** (suppl): S221–S247.
2. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52:** 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)

Preparations

BP 2008: Pyrazinamide Tablets;
USP 31: Pyrazinamide Tablets; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Zinamide; ***Austria:*** Pyrafat; ***Belg.:*** Tebrazid; ***Braz.:*** Pirazinon; ***Canad.:*** Tebrazid; ***Cz.:*** Tisamid†; ***Fin.:*** Tisamid; ***Fr.:*** Pirilene; ***Ger.:*** Pyrafat; PZA; ***Hong Kong:*** Pyrafat; ***India:*** Actizid†; P-Zide; Pyzina; PZA-Ciba; Rifacom E-Z; ***Indon.:*** Corsazinamid; Neotibi; Pezeta-Ciba; Prazina; Sanazet; Siramid; TB ZET; ***Irl.:*** Zinamide†; ***Ital.:*** Piraldina; ***Malaysia:*** PZA; ***Mex.:*** Nizamyl; ***NZ:*** Zinamide; ***Philipp.:*** Pyramin; Pyrasol; PZA-Ciba; Zapedia; Zcure; Zinaplex; ***Port.:*** Pirasida†; Pramide; ***S.Afr.:*** Pyrazide†; ***Singapore:*** PZA; ***Thai.:*** Myrin-P; Pyramide; Pyratab†; PZA; ***Turk.:*** Pirazinid.

Multi-ingredient: ***Austria:*** Rifater; ***Canad.:*** Rifater; ***Denm.:*** Rimstar; ***Fin.:*** Rimstar; ***Fr.:*** Rifater; ***Ger.:*** Rifater; tebesium Trio; ***Gr.:*** Rifater; ***Hong Kong:*** Rifater; ***India:*** Akt-4; Coxina-4; Cx-5; Gocox-3; R-Cinex Z; RHZ;

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.

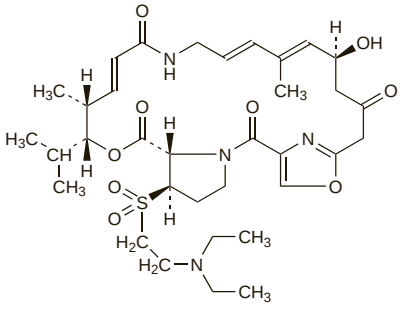
Dalfopristin Mesilate *(BANM, rINNM)*

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)

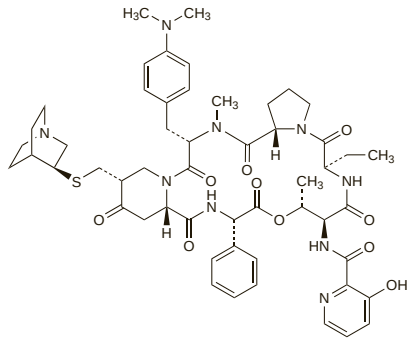
Quinupristin Mesilate *(BANM, rINNM)*

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