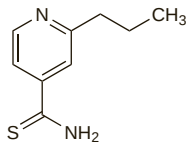
Profile
Propicillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p.314). Propicillin potassium is given orally for the treatment of susceptible mild to moderate infections in a usual dose of 700 mg three times daily.

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.

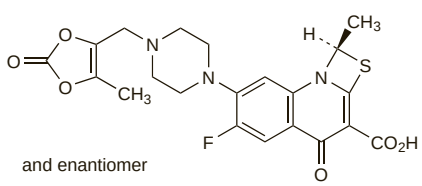
Uses and Administration
Protionamide is a thioamide derivative considered to be interchangeable with ethionamide (p.276) and is used as a second-line drug in the treatment of multidrug-resistant tuberculosis (p.196). It has also been used, as a substitute for clofazimine, in regimens for the treatment 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 Like ethionamide, it has generally been replaced by less toxic antimycobacterials.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.

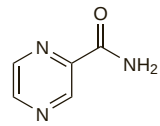
◊ Reviews.

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