Preparations

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

Multi-ingredient: ***S.Afr.:*** Cosaldon†.

Pentosan Polysulfate Sodium *(BAN, USAN, rINN)*

Natrii pentosani polusulfas; Natrii Pentosani Polysulfas; Natriumpentosaanipolys Ulfaatti; Natriumpentosanpolysulfat; Pentosan Polysulphate Sodium; Pentosane polysulfate sodique; Pentosano polisulfato de sodio; PZ-68; Sodium Pentosan Polysulphate; Sodium Xylanpolysulphate; SP-54.

Натрия Пентозана Полисульфат

CAS — 37319-17-8; 116001-96-8.
ATC — C05BA04.
ATC Vet — QC05BA04.

Description. Pentosan polysulfate sodium is a mixture of linear polymers of β-1→4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally (approximately 1 in every 4 residues) substituted at the 2-position with 4-*O*-methyl-α-D-glucuronic acid 2,3-*O*-sulfate. The average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40 000.

Adverse Effects and Precautions

As for Heparin, p.1301. Gastrointestinal disturbances may also occur.

Uses and Administration

Pentosan polysulfate sodium is a heparinoid with anticoagulant and fibrinolytic properties; it may also have hypolipidaemic and anti-inflammatory effects. It is used in thromboembolic disorders, although its anticoagulant effect is less than that of heparin. It is also used in the management of interstitial cystitis (see below) and has been tried in a number of other conditions, including variant Creutzfeldt-Jakob disease (see below). Pentosan polysulfate sodium has been used orally, parenterally, and topically.

In the management of interstitial cystitis, pentosan polysulfate sodium is given orally in a dose of 100 mg three times daily.

Cystitis. Pentosan polysulfate sodium has been used in inflammatory conditions of the bladder, including interstitial cystitis (p.2179) and is thought to act by enhancing the protective effect of mucins at the bladder surface.[1] Studies have differed concerning its efficacy in the treatment of interstitial cystitis and an analysis[2] of placebo-controlled trials concluded that pentosan polysulfate sodium was more effective in treating pain, urgency, and frequency, but that the difference was small. Any benefit is usually apparent within 3 to 6 months and only occurs in a minority of patients.[3] Pentosan polysulfate sodium was reported[4] to have minimal long-term efficacy in a group of patients with severe or refractory interstitial cystitis.

Pentosan polysulfate sodium has also been reported[5-7] to be useful in the control of radiation-induced haemorrhagic cystitis (p.2178).

1. Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; **66:** 821–35.
2. Hwang P, *et al*. Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology* 1997; **50:** 39–43.
3. Anonymous. Pentosan for interstitial cystitis. *Med Lett Drugs Ther* 1997; **39:** 56.
4. Jepsen JV, *et al*. Long-term experience with pentosanpolysulfate in interstitial cystitis. *Urology* 1998; **51:** 381–7.
5. Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. *J Urol (Baltimore)* 1986; **136:** 813–14.
6. Hampson SJ, Woodhouse CRJ. Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; **25:** 40–2.
7. Sandhu SS, *et al*. The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int* 2004; **94:** 845–7.

Prostatitis. Pentosan polysulfate sodium is one of a number of drugs that have been tried in the management of prostatitis (p.2181). An improvement in symptoms was reported[1] in an uncontrolled study of oral pentosan polysulfate sodium in men with chronic prostatitis/chronic pelvic pain syndrome. A randomised study[2] using pentosan polysulfate sodium 300 mg three times daily found that symptoms were moderately or markedly improved at the end of the 16-week treatment period in more members of the active treatment group than in the group given placebo.

1. Nickel JC, *et al*. Pentosan polysulfate therapy for chronic nonbacterial prostatitis (chronic pelvic pain syndrome category II-IA): a prospective multicenter clinical trial. *Urology* 2000; **56:** 413–17.
2. Nickel JC, *et al*. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol (Baltimore)* 2005; **173:** 1252–5.

Variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease (vCJD) is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. Pentosan polysulfate sodium has been tried in small numbers of patients with vCJD, although there is little published research data. In 2003 the UK Department of Health[1] took advice from the CJD Therapy Advisory Group and the CSM; both groups considered that there was insufficient information on which to base prescribing regimens, and further work was needed.

1. UK Department of Health. Use of pentosan polysulphate in the treatment of, or prevention of, vCJD. Available at: http://www.dh.gov.uk/en/Publichealth/Communicablediseases/CJD/CJDgeneralinformation/DH_4031039 (accessed 19/08/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Elmiron; ***Austral.:*** Elmiron†; ***Austria:*** Polyanion; ***Canad.:*** Elmiron; ***Fr.:*** Hemoclar; ***Ger.:*** Fibrezym; ***Hong Kong:*** Elmiron; SP 54†; ***Hung.:*** SP 54; ***Ital.:*** Fibrase; ***Malaysia:*** SP 54; ***Port.:*** Fibrocide; ***S.Afr.:*** Tavan-SP 54; ***Spain:*** Thrombocid; ***USA:*** Elmiron.

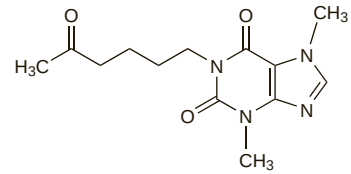
Multi-ingredient: ***Austria:*** Thrombocid; ***Cz.:*** Thrombocid; ***Ger.:*** Thrombocid; ***Hong Kong:*** Anso; Thrombocid; ***Port.:*** Thrombocid; ***Spain:*** Anso; ***Switz.:*** Thrombocid.

Pentoxifylline *(BAN, USAN, rINN)*

BL-191; Oksentifilin; Oxpentifylline; Pentoksifilin; Pentoksifilinas; Pentoksifylliini; Pentoxifilina; Pentoxifillin; Pentoxifylin; Pentoxifyllin; Pentoxifyllinum. 3,7-Dimethyl-1-(5-oxohexyl)xanthine.

Пентоксифиллин

$C_{13}H_{18}N_4O_3$ = 278.3.
CAS — 6493-05-6.
ATC — C04AD03.
ATC Vet — QC04AD03.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Pentoxifylline). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.
USP 31 (Pentoxifylline). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform and in methyl alcohol; slightly soluble in ether.

Adverse Effects

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing, angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions may also occur. Bleeding events have been reported rarely, usually in association with bleeding risk factors.

Overdosage with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.

Haemorrhage. Three major bleeding episodes including 2 fatal cerebral haemorrhages were reported in a group of patients receiving pentoxifylline 400 mg three times daily together with acenocoumarol for intermittent claudication.[1] Gastrointestinal bleeding occurred in a 67-year-old patient with a history of duodenal ulcer after a single dose of pentoxifylline for optic neuropathy.[2]

1. APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication: a controlled clinical study. *Angiology* 1989; **40:** 237–48.
2. Oren R, *et al.* Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* 1991; **25:** 315–16.

Overdosage. A 22-year-old woman who took pentoxifylline 4 to 6 g with suicidal intent experienced severe bradycardia and first- and second-degree AV block; other effects included nausea, vomiting, abdominal cramps, hypokalaemia, excitation, and insomnia.[1] She recovered after intensive supportive and symptomatic treatment.

1. Sznajder IJ, *et al*. First and second degree atrioventricular block in oxpentifylline overdose. *BMJ* 1984; **288:** 26.

Precautions

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, severe cardiac arrhythmias, and acute myocardial infarction. It should be used with caution in patients with ischaemic heart disease or hypotension. The dose of pentoxifylline may need to be reduced in patients with hepatic or renal impairment (see under Uses and Administration, below).

Porphyria. Pentoxifylline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Pentoxifylline may potentiate the effect of antihypertensives. High parenteral doses of pentoxifylline may enhance the action of insulin and oral hypoglycaemics in diabetic patients. Pentoxifylline should not be given with ketorolac as there is reported to be an increased risk of bleeding and/or prolongation of the prothrombin time. There may also be an increased risk of bleeding during use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.

Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half-life of pentoxifylline is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine, mainly as metabolites, and less than 4% is recovered in the faeces. Elimination of pentoxifylline is decreased in elderly patients and patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.

◊ References.

1. Beermann B, *et al*. Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; **37:** 25–8.
2. Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *Am J Obstet Gynecol* 1985; **151:** 1094–7.
3. Smith RV, *et al*. Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986; **75:** 47–52.
4. Rames A, *et al*. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
5. Paap CM, *et al*. Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Uses and Administration

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease (p.1178). Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine, tumour necrosis factor alpha (TNFα), and this property is under investigation in a number of diseases (see below).

In the treatment of peripheral vascular disease the usual oral dose is 400 mg three times daily in a modified-release formulation; this may be reduced to 400 mg twice daily for maintenance or if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. In severe hepatic or renal impairment, doses may need to be reduced (see below). Beneficial effects may not be evident until after 2 to 8 weeks of treatment. Pentoxifylline may also be given parenterally.

◊ General references.

1. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987; **34:** 50–97.
2. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; **30:** 603–21.

Administration in hepatic and renal impairment. The elimination half-life of pentoxifylline and its metabolites is significantly prolonged in patients with hepatic cirrhosis,[1] and some metabolites have a prolonged half-life in renal impairment.[2] The UK manufacturers state that in patients with severely impaired hepatic function the dose of pentoxifylline may need to be reduced, while accumulation may occur in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) who receive more than 400 mg once or twice daily.

References.

1. Rames A, *et al*. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47:** 354–9.
2. Paap CM, *et al*. Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30:** 724–9.

Inhibition of tumour necrosis factor alpha. Pentoxifylline inhibits production of tumour necrosis factor alpha (TNFα), a cytokine that is implicated in the pathogenesis of many diseases, and investigative work with pentoxifylline is being, or has been, carried out in many such disorders. Studies have been performed in patients with alcoholic hepatitis,[1] cardiomyopathy,[2] cerebral malaria,[3,4] diabetic nephropathy,[5] leishmaniasis,[6,7] leprosy,[8,9] membranous nephropathy,[10] radiation-induced damage,[11-13] severe sepsis or septic shock,[14] recurrent aphthous stomatitis,[15-17] and various vasculitic syndromes, including Behçet's syndrome.[18] Pentoxifylline has also been tried for improving graft survival in kidney transplantation.[19,20] For mention of a possible benefit in sarcoidosis, see p.1512. Although promising results

have been reported in some of these studies, the place of pentoxifylline in the overall management of these disorders remains to be established.

1. Akriviadis E, *et al.* Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119:** 1637–48.
2. Skudicky D, *et al.* Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. *Circulation* 2001; **103:** 1083–8.
3. Di Perri, *et al.* Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis* 1995; **171:** 1317–22.
4. Looareesuwan S, *et al.* Pentoxifylline as an ancillary treatment for severe falciparum malaria in Thailand. *Am J Trop Med Hyg* 1998; **58:** 348–53.
5. Navarro JF, *et al.* Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. *Am J Kidney Dis* 1999; **33:** 458–63.
6. Lessa HA, *et al.* Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *Am J Trop Med Hyg* 2001; **65:** 87–9.
7. Machado PRL, *et al.* Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis* 2007; **44:** 788–93.
8. Nery JAC, *et al.* The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. *Indian J Lepr* 2000; **72:** 457–67.
9. Dawlah ZM, *et al.* A phase 2 open trial of pentoxifylline for the treatment of leprosy reactions. *Int J Lepr Other Mycobact Dis* 2002; **70:** 38–43.
10. Ducloux D, *et al.* Use of pentoxifylline in membranous nephropathy. *Lancet* 2001; **357:** 1672–3.
11. Okunieff P, *et al.* Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004; **22:** 2207–13.
12. Chiao TB, Lee AJ. Role of pentoxifylline and vitamin E in attenuation of radiation-induced fibrosis. *Ann Pharmacother* 2005; **39:** 516–22.
13. Delanian S, *et al.* Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005; **23:** 8570–9.
14. Staubach K-H, *et al.* Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. *Arch Surg* 1998; **133:** 94–100.
15. Pizarro A, *et al.* Treatment of recurrent aphthous stomatitis with pentoxifylline. *Br J Dermatol* 1995; **133:** 659–60.
16. Chandrasekhar J, *et al.* Oxypentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87:** 564–7.
17. Thornhill MH, *et al.* A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; **143:** 463–70.
18. Hisamatsu T, *et al.* Combination therapy including pentoxifylline for entero-Behçet's disease. *Bull Tokyo Dent Coll* 2001; **42:** 169–76.
19. Noel C, *et al.* Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor α and adhesion molecules. *Transplantation* 2000; **69:** 1102–7.
20. Shu K-H, *et al.* Effect of pentoxifylline on graft function of renal transplant recipients complicated with chronic allograft nephropathy. *Clin Nephrol* 2007; **67:** 157–63.

Venous leg ulcers. A systematic review[1] of pentoxifylline used in the treatment of venous leg ulcers (p.1585) concluded that it was an effective adjunct to compression bandaging, and may be effective alone.

1. Jull A, *et al.* Pentoxifylline for treating venous leg ulcers. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 08/05/08).

Preparations

USP 31: Pentoxifylline Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Dospan Pento; Pentolab; Previscan; Tamixol; Trental; ***Austral.:*** Trental; ***Austria:*** Haemodyn; Pentohexal; Pentomer; Pentoxi; Pentoximed; Trental; Vasonit; ***Belg.:*** Torental; ***Braz.:*** Arteron; Chemopent†; Pentox; Pentral; Perental†; Peripan; Prodoxifilina; Trental; Vascer; ***Canad.:*** Trental; ***Chile:*** Trental; ***Cz.:*** Agapurin; Pentilin; Pentohexal†; Pentomer; Rentylin†; Trental; Vasonit; ***Denm.:*** Trental; ***Fin.:*** Artal; Pentoxin; Trental; ***Fr.:*** Hatial†; Pentoflux; Torental; ***Ger.:*** Agapurin; Azupentat†; Claudicat; durapental†; Pento; Pento-Puren; Pentohexal; Pentox; Pentoxy†; Ralofekt; Rentylin; Trental; ***Gr.:*** Taronal; ***Hong Kong:*** Pentong; Trenlin; Trental; ***Hung.:*** Angiopurin†; Chinotal; Pentoxyl-EP; Trental; ***India:*** Kinetal; Trental; ***Indon.:*** Erytral; Lentrin; Pentoxifillene; Platof; Reotal; Tarontal; Tioxad; Trenat; Trenfyl; Trental; Trentox; Trenxy; ***Irl.:*** Trental; ***Israel:*** Oxopurin; Trental; ***Ital.:*** Trental; ***Malaysia:*** Trenlin; Trental; ***Mex.:*** Artelife; Eurotofi; Fixoten; Kentadin; Pensiral; Peridane; Profiben; Sufisal; Trental; Vantoxyl; Vasofyl; Vaxolem; Xipen; ***Neth.:*** Trental; ***Norw.:*** Trental; ***NZ:*** Trental; ***Philipp.:*** C-Vex; Pentox; Trental; ***Pol.:*** Agapurin; Apo-Pentox; Dartelin; Pentilin; Pentohexal; Polfilin; Trental; ***Port.:*** Claudicat; Trental; ***Rus.:*** Flexital (Флекситал); Mellinorm (Меллинорм); Pentilin (Пентилин); Trental (Трентал 400); Vasonit (Вазонит); ***S.Afr.:*** Trental; ***Singapore:*** Agapurin†; Trenlin; Trental; ***Spain:*** Elorgan; Hemovas; Nelorpin; Retimax; ***Switz.:*** Dinostral†; Pentoxi; Trental; ***Thai.:*** Agapurin; Elastab; Flexital; Herden†; Penlol; Sipental; Trental; Trepal; ***Turk.:*** Pentox; Trental; Trentilin; Vasoplan; ***UK:*** Neotren; Trental; ***USA:*** Trental; ***Venez.:*** Agapurin; Trental.

Multi-ingredient: ***Arg.:*** Ikatral Periferico.

Perhexiline Maleate *(BANM, USAN, rINNM)*

Maleato de perhexilina; Perhexiline, Maléate de; Perhexilini Maleas; WSM-3978G. 2-(2,2-Dicyclohexylethyl)piperidine hydrogen maleate.

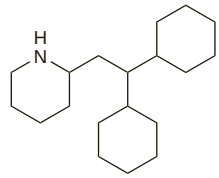
Пергексиллина Малеат

$C_{19}H_{35}N,C_4H_4O_4$ = 393.6.

CAS — 6621-47-2 (perhexiline); 6724-53-4 (perhexiline maleate).

ATC — C08EX02.

ATC Vet — QC08EX02.



(perhexiline)

Profile

Perhexiline maleate may be used in the long-term management of severe angina pectoris (p.1157) in patients who have not responded to other anti-anginal drugs. Its mode of action is complex.

The usual initial oral dose is 100 mg daily, subsequently either increased or decreased, as necessary, at intervals of 2 to 4 weeks; it is generally recommended not to give more than 300 mg daily although doses of 400 mg daily have been necessary in some patients. The maintenance of plasma-perhexiline concentrations between 0.15 and 0.60 micrograms/mL has been recommended.

Perhexiline occasionally produces severe adverse effects including peripheral neuropathy affecting all four limbs with associated papilloedema, severe and occasionally fatal hepatic toxicity, and metabolic abnormalities with marked weight loss, hypertriglyceridaemia, and profound hypoglycaemia. It is contra-indicated in patients with hepatic or renal impairment. Perhexiline should be used with caution in diabetic patients. Hepatic metabolism of perhexiline is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore caution is advised if perhexiline is used with other drugs that inhibit or are metabolised by this enzyme, and perhexiline toxicity has been reported with SSRIs such as fluoxetine or paroxetine.

Porphyria. Perhexiline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Pexsig; ***NZ:*** Pexsig.

Perindopril *(BAN, USAN, rINN)*

McN-A-2833; Perindopriili; Périndopril; Perindoprilum; S-9490. (2*S*,3a*S*,7a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonylbutyl]-L-alanyl}perhydroindole-2-carboxylic acid.

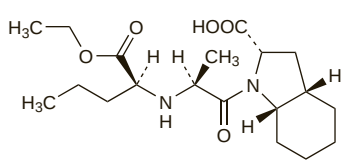
Периндоприл

$C_{19}H_{32}N_2O_5$ = 368.5.

CAS — 82834-16-0.

ATC — C09AA04.

ATC Vet — QC09AA04.



Perindopril Arginine *(BANM, rINNM)*

Perindopril arginina; Périndopril Arginine; Perindoprilum Argininum.

Периндоприл Аргинин

CAS — 612548-45-5.

ATC — C09AA04.

ATC Vet — QC09AA04.

Perindopril Erbumine *(BANM, USAN, rINNM)*

tert-Butilamino perindoprilis; Butylamini Perindoprilum; *Tert*-Butylamini Perindoprilum; Butylamin-perindopril; Erbumina de perindopril; McN-A-2833-109; Perindopriili-*tert*-butyyliamiini; Perindopril *tert*-Butylamine; Périndopril, Erbumine de; Perindopril Terbutalamin; Périndopril tert-butylamine; Perindopril-*tert*-butylamin; Perindopril-erbumin; Perindoprili Erbuminum; Perindoprilum Erbuminum; Peryndopryl z tert-butyloaminą; S-9490-3; tert-Butylamini perindoprilum.

Периндоприла Эрбумин

$C_{19}H_{32}N_2O_5,C_4H_{11}N$ = 441.6.

CAS — 107133-36-8.

ATC — C09AA04.

ATC Vet — QC09AA04.

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

Ph. Eur. 6.2 (Perindopril *tert*-Butylamine; Perindopril Erbumine BP 2008). A white or almost white, slightly hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water and in alcohol; soluble or sparingly soluble in dichloromethane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

◊ In a postmarketing surveillance study[1] of 47 351 patients receiving perindopril for hypertension, no unexpected adverse effects were reported and serious reactions were rare; 1587 (6.3%) women and 782 (3.5%) men withdrew from therapy due to adverse effects.

Although a study[2] of perindopril use in patients with stable chronic heart failure reported no significant first-dose hypotension, there has been a case report[3] of ischaemic stroke, possibly associated with hypotension, after a single dose of perindopril in a patient with post-infarction heart failure. Standard precautions as for other ACE inhibitors (p.1195) should be followed when starting perindopril therapy.

1. Speirs C, *et al.* Perindopril postmarketing surveillance: a 12 month study in 47 351 hypertensive patients. *Br J Clin Pharmacol* 1998; **46:** 63–70.
2. MacFadyen RJ, *et al.* Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991; **66:** 206–11.
3. Bagger JP. Adverse event with first-dose perindopril in congestive heart failure. *Lancet* 1997; **349:** 1671–2.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Perindopril acts as a prodrug of the diacid perindoprilat, its active form. After oral doses perindopril is rapidly absorbed with a bioavailability of about 65 to 75%. It is extensively metabolised, mainly in the liver, to perindoprilat and inactive metabolites including glucuronides. The presence of food is reported to reduce the conversion of perindopril to perindoprilat. Peak plasma concentrations of perindoprilat are achieved 3 to 4 hours after an oral dose of perindopril. Perindoprilat is about 10 to 20% bound to plasma proteins. Perindopril is excreted predominantly in the urine, as unchanged drug, as perindoprilat, and as other metabolites. The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer, the latter half-life probably representing strong binding to angiotensin-converting enzyme. The excretion of perindoprilat is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

◊ References.

1. Lecocq B, *et al.* Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. *Clin Pharmacol Ther* 1990; **47:** 397–402.
2. Verpooten GA, *et al.* Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. *Br J Clin Pharmacol* 1991; **32:** 187–92.
3. Sennesael J, *et al.* The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol* 1992; **33:** 93–9.
4. Thiollet M, *et al.* The pharmacokinetics of perindopril in patients with liver cirrhosis. *Br J Clin Pharmacol* 1992; **33:** 326–8.
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Uses and Administration

Perindopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure