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

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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.

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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.

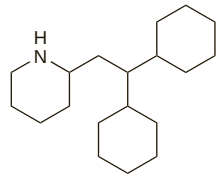
Пергексиллина Малеат

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

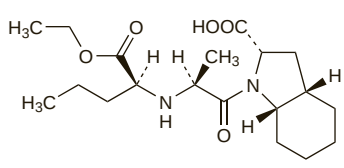
Периндоприл

$C_{19}H_{32}N_2O_5$ = 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.
5. Guérin A, *et al.* The effect of haemodialysis on the pharmacokinetics of perindoprilat after long-term perindopril. *Eur J Clin Pharmacol* 1993; **44:** 183–7.

Uses and Administration

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