(p.1165). It is also used to reduce the risk of cardiovascular events in patients with stable ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164).

Perindopril is converted in the body into its active metabolite perindoprilat. ACE inhibition is reported to occur within 1 hour of a dose, to be at a maximum at about 4 to 8 hours, and to be maintained for 24 hours. Perindopril is given orally as the erbumine salt and should be taken before food. In some countries perindopril is also available as the arginine salt; 5 mg of perindopril arginine is equivalent to about 4 mg of perindopril erbumine.

In the treatment of **hypertension** perindopril is given in an initial dose of 4 mg of the erbumine or 5 mg of the arginine salt once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and in such patients the initial dose may be halved to 2 or 2.5 mg respectively once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly. The same lower initial dose may also be used in the elderly. The dose of perindopril may be increased according to response to a maximum of 8 mg of the erbumine or 10 mg of the arginine salt daily. In the USA a maximum dose of 16 mg of perindopril erbumine daily is allowed in uncomplicated hypertension.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be initiated with a low dose under close medical supervision. Perindopril is given in an initial dose of 2 mg of the erbumine or 2.5 mg of the arginine salt in the morning. The usual maintenance dose is 4 mg or 5 mg respectively daily.

In the management of patients with **ischaemic heart disease** perindopril is given in an initial dose of 4 mg (erbumine) or 5 mg (arginine) once daily for 2 weeks, then titrated up to a maintenance dose of 8 or 10 mg respectively once daily if tolerated. Elderly patients should be started on 2 or 2.5 mg once daily for the first week.

Dosage should be reduced in patients with impaired renal function (see below).

◊ References.

1. Todd PA, Fitton A. Perindopril: a review of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991; **42:** 90–114.
2. Doyle AE, ed. Angiotensin-converting enzyme (ACE) inhibition: benefits beyond blood pressure control. *Am J Med* 1992; **92** (suppl 4B): 1S–107S.
3. Hurst M, Jarvis B. Perindopril: an updated review of its use in hypertension. *Drugs* 2001; **61** 867–96.
4. Simpson D, *et al*. Perindopril: in congestive heart failure. *Drugs* 2002; **62:** 1367–77.
5. Curran MP, *et al*. Perindopril: a review of its use in patients with or at risk of developing coronary artery disease. *Drugs* 2006; **66:** 235–55.
6. Telejko E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Curr Med Res Opin* 2007; **23:** 953–60.

Administration in renal impairment. The dose of perindopril should be reduced in patients with renal impairment. UK licensed product information recommends the following doses:

- creatinine clearance (CC) between 30 and 60 mL/minute: 2 mg of the erbumine or 2.5 mg of the arginine salt daily
- CC between 15 and 30 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on alternate days
- CC less than 15 mL/minute: 2 mg (erbumine) or 2.5 mg (arginine) on dialysis days.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Coverene; ***Austral.:*** Coversyl; Perindo; ***Austria:*** Coversum; ***Belg.:*** Coversyl; ***Braz.:*** Coversyl; ***Canad.:*** Coversyl; ***Chile:*** Coversyl; ***Cz.:*** Apo-Perindo; Cordesyl; Covedaspen; Covemarin; Covemedal; Covepet; Coverdosyn; Coverdyne; Coverex; Coversidin; Coversyspes; Covethanar; Prenessa; Prestarium; Prestarium Neo; Prexanil; Pricoron; ***Denm.:*** Coversyl; ***Fin.:*** Coversyl; ***Fr.:*** Coversyl; ***Ger.:*** Coversum; ***Gr.:*** Coversyl; ***Hong Kong:*** Acertil; ***Hung.:*** Armix; Coverex; Perindan; Prenessa; ***India:*** Coversyl; Perigard; ***Indon.:*** Prexum; ***Irl.:*** Coversyl; ***Ital.:*** Coversyl; Procaptan; ***Jpn:*** Coversyl; ***Malaysia:*** Covapril; Coversyl; Perinace; ***Mex.:*** Coversyl; ***Neth.:*** Coverex; Coversyl; ***NZ:*** Coversyl; ***Philipp.:*** Coversyl; ***Pol.:*** Coverex; Irpax; Prenessa; Prestarium; ***Port.:*** Coversyl; Ostion; Prexum; ***Rus.:*** Prestarium (Престариум); ***S.Afr.:*** Coversyl; Prexum; ***Singapore:*** Coversyl; ***Spain:*** Coversyl; ***Switz.:*** Coversum; ***Thai.:*** Coversyl; ***Turk.:*** Coversyl; ***UK:*** Coversyl; ***USA:*** Aceon; ***Venez.:*** Coversyl.

Multi-ingredient: ***Arg.:*** Bipreterax; Preterax; ***Austral.:*** Coversyl Plus; ***Austria:*** Predonium; Preterax; ***Belg.:*** Bi Preterax; Coversyl Plus; Preterax; ***Braz.:*** Coversyl Plus; ***Canad.:*** Coversyl Plus; Preterax; ***Cz.:*** Noliprel; Prenewel; Prestarium Combi; Prestarium Neo Combi; ***Denm.:*** Coversyl Comp; ***Fin.:*** Coversyl Comp; ***Fr.:*** Bipreterax; Preterax; ***Ger.:*** Coversum Combi; Preterax; ***Gr.:*** Preterax; ***Hong Kong:*** Predonium; ***Hung.:*** Armix Komb; Armix Prekomb; Co-Prenessa; Coverex Komb; Coverex Prekomb; Noliprel†; Noriplex†; ***India:*** Coversyl Plus; Perigard D; Perigard DF; ***Irl.:*** Bipreterax; Coversyl Plus; Preterax; ***Ital.:*** Prelectal; Preterax; ***Malaysia:*** Coversyl Plus; ***Mex.:*** Preterax; ***Neth.:*** Coversyl Plus; Predonium; Preterax; ***NZ:*** Coversyl Plus; Predonium; ***Philipp.:*** Bi-Preterax; Preterax; ***Pol.:*** Noliprel; Prestarium Plus; ***Port.:*** Bi Predonium; Bi Preterax; Predonium; Preterax; ***Rus.:*** Noliprel (Нолипрел); ***S.Afr.:*** Bipreterax; Coversyl Plus; Preterax; Prexum Plus; ***Singapore:*** Coversyl Plus; Preterax; ***Spain:*** Bipredonium†; Bipreterax; Preterax; ***Switz.:*** Coversum Combi; Preterax; ***Turk.:*** Coversyl Plus; Preterax; ***UK:*** Coversyl Plus; ***Venez.:*** Bipreterax; Preterax.

Phenindione *(BAN, rINN)*

Fenindion; Fenindiona; Fenindione; Fenindioni; Phénindione; Phenindionum; Phenylindanedione; Phenylinium. 2-Phenylindan-1,3-dione.

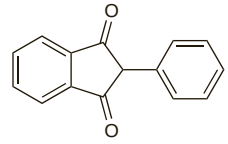
Фениндион

$C_{15}H_{10}O_2$ = 222.2.

CAS — 83-12-5.

ATC — B01AA02.

ATC Vet — QB01AA02.



Pharmacopoeias. In *Br.* and *Fr.*

BP 2008 (Phenindione). Soft, odourless or almost odourless, white or creamy-white crystals. Very slightly soluble in water; slightly soluble in alcohol and in ether; freely soluble in chloroform. Solutions are yellow to red.

Adverse Effects and Treatment

As for Warfarin Sodium, p.1425. However, phenindione and the other indanediones are generally more toxic than warfarin with hypersensitivity reactions involving many organs and sometimes resulting in death. Some of the reactions include skin rashes and exfoliative dermatitis, pyrexia, diarrhoea, vomiting, sore throat, liver and kidney damage, myocarditis, agranulocytosis, leucopenia, eosinophilia, and a leukaemoid syndrome.

Phenindione may discolour the urine pink or orange and this is independent of any haematuria. Taste disturbances have been reported.

Effects on the gastrointestinal tract. There have been cases of paralytic ileus, one fatal, associated with phenindione.[1,2]

1. Menon IS. Phenindione and paralytic ileus. *Lancet* 1966; **i:** 1421–2.
2. Nash AG. Phenindione and paralytic ileus. *Lancet* 1966; **ii:** 51–2.

Precautions

As for Warfarin Sodium, p.1426.

Phenindione is not recommended in pregnancy.

Breast feeding. Phenindione is distributed into breast milk, with reported concentrations[1] of 1 to 5 micrograms/mL after a single dose of 50 or 75 mg. A woman receiving phenindione 50 mg each morning and 50 and 25 mg on alternate nights breast-fed her infant son,[2] who required a herniotomy at 5 weeks. After surgery he had an enormous scrotal haematoma and oozing from the wound, and was found to have extended prothrombin and partial thromboplastin times. The American Academy of Pediatrics therefore considers[3] that phenindione should be given with caution to breast-feeding mothers.

1. Goguel M, *et al*. Thérapeutique anticoagulante et allaitement: etude du passage de la phényl-2-dioxo, 1,3 indane dans le lait maternel. *Rev Fr Gynecol Obstet* 1970; **65:** 409–12.
2. Eckstein HB, Jack B. Breast-feeding and anticoagulant therapy. *Lancet* 1970; **i:** 672–3.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Interactions

The interactions associated with oral anticoagulants are described in detail under warfarin (p.1427). Specific references to interactions involving phenindione can be found there under the headings for the following drug groups: analgesics; antibacterials; antifungals; antiplatelets; anxiolytic sedatives; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

Pharmacokinetics

Phenindione is absorbed from the gastrointestinal tract. It crosses the placenta and is distributed into breast milk. Metabolites of phenindione excreted in the urine are responsible for any discoloration that may occur.

Uses and Administration

Phenindione is an oral indanedione anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187), but because of its higher incidence of severe adverse effects it is now rarely employed.

The usual initial dose of phenindione is 200 mg on the first day, 100 mg on the second day, and then maintenance doses of 50 to 150 mg daily according to coagulation tests.

Preparations

BP 2008: Phenindione Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Dindevan; ***Fr.:*** Pindione†; ***India:*** Dindevan.

Phenoxybenzamine Hydrochloride

(BANM, rINNM)

Fenoksybenzaminy chlorowodorek; Hidrocloruro de fenoxibenzamina; Phénoxybenzamine, Chlorhydrate de; Phenoxybenzamini Hydrochloridum; SKF-688A. Benzyl(2-chloroethyl)(1-methyl-2-phenoxyethyl)amine hydrochloride.

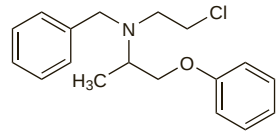
Феноксибензамина Гидрохлорид

$C_{18}H_{22}ClNO,HCl$ = 340.3.

CAS — 59-96-1 (phenoxybenzamine); 63-92-3 (phenoxybenzamine hydrochloride).

ATC — C04AX02.

ATC Vet — QC04AX02.



(phenoxybenzamine)

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2008 (Phenoxybenzamine Hydrochloride). A white or almost white, odourless or almost odourless, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform.

Adverse Effects and Treatment

The adverse effects of phenoxybenzamine are mainly due to its alpha-adrenoceptor blocking activity. They include orthostatic hypotension and dizziness, reflex tachycardia, nasal congestion, and miosis. Inhibition of ejaculation may occur. These effects may be minimised by using a low initial dose, and may diminish with continued use, but the hypotensive effect can be exaggerated by exercise, heat, a large meal, or alcohol ingestion. Other side-effects include dry mouth, decreased sweating, drowsiness, fatigue, and confusion. Gastrointestinal effects are usually slight. When phenoxybenzamine is given intravenously, idiosyncratic profound hypotension can occur within a few minutes of starting the infusion. Convulsions have been reported after rapid intravenous infusion of phenoxybenzamine.

Severe hypotension may occur in overdose and treatment includes support of the circulation by postural measures and parenteral fluid volume replacement. Sympathomimetics are considered to be of little value, and adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia. Sources differ as to the value of noradrenaline in overcoming alpha-receptor blockade.

Phenoxybenzamine has been shown to be mutagenic in *in vitro* tests and carcinogenic in *rodents*.

Precautions

Phenoxybenzamine should be given with care to patients with heart failure, ischaemic heart disease, cerebrovascular disease, or renal impairment, and should be avoided if a fall in blood pressure would be dangerous. Phenoxybenzamine may aggravate the symptoms of respiratory infections.