(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 Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before perindopril is started and resumed later if required; if this is not possible, the initial dose may be halved similarly.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.

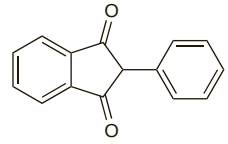
Фениндион

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

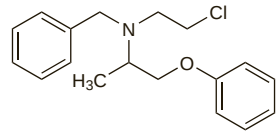
Феноксибензамина Гидрохлорид

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

When given intravenously, phenoxybenzamine hydrochloride should always be diluted and given by infusion. Intravenous fluids must always be given beforehand to ensure an adequate circulating blood volume and to prevent a precipitous fall in blood pressure. Care should be taken to avoid extravasation. Contamination of the skin should also be avoided since contact sensitisation may occur.

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

### Interactions
Since phenoxybenzamine only blocks alpha receptors, leaving the beta receptors unopposed, use with drugs such as adrenaline that also stimulate beta receptors may enhance the cardiac-accelerating and hypotensive action of phenoxybenzamine.

### Pharmacokinetics
Phenoxybenzamine is incompletely and variably absorbed from the gastrointestinal tract. After oral dosage the onset of action is gradual over several hours and persists for 3 or 4 days following a single dose. The maximum effect is attained in about 1 hour after an intravenous dose. The plasma half-life after intravenous dosage is about 24 hours. Phenoxybenzamine is metabolised in the liver and excreted in the urine and bile, but small amounts remain in the body for several days. The duration of action is thought to depend on the rate of synthesis of new alpha receptors following irreversible covalent bonding to existing alpha receptors by a reactive intermediate of phenoxybenzamine.

### Uses and Administration
Phenoxybenzamine is a powerful alpha-adrenoceptor blocker (p.1153) with a prolonged duration of action; it binds covalently to alpha receptors in smooth muscle to produce an irreversible ('non-competitive') blockade. A single large dose of phenoxybenzamine can cause alpha-adrenoceptor blockade for 3 days or longer.

Phenoxybenzamine is used in the management of phaeochromocytoma (p.1179). It has also been employed in severe shock (p.1183) and in the treatment of urinary retention (p.2180).

Phenoxybenzamine is used as the hydrochloride. It is given orally or by intravenous infusion as a dilute solution.

In **phaeochromocytoma** it is used to control the hypertension associated with excessive catecholamine release during the pre-operative period and in patients whose tumours are inoperable. A beta blocker may also be given to control tachycardia, but not before alpha blockade has completely suppressed the pressor effects of the phaeochromocytoma. The usual initial oral dose of phenoxybenzamine hydrochloride is 10 mg once or twice daily, increased gradually, according to the patient's response, to a usual dose of 1 to 2 mg/kg daily in 2 divided doses. It may be given intravenously for operative cover in patients with phaeochromocytoma in a daily dose of 1 mg/kg in 200 mL of sodium chloride 0.9% infused over at least 2 hours. A similar intravenous dose in 200 to 500 mL of sodium chloride 0.9% has been given in the management of severe **shock**.

For **urinary retention** due to neurogenic bladder an oral dose of 10 mg twice daily has been given.

### Preparations
***BP 2008:*** Phenoxybenzamine Capsules;
***USP 31:*** Phenoxybenzamine Hydrochloride Capsules.

**Proprietary Preparations** (details are given in Part 3)
***Austral.:*** Dibenyline; ***Austria:*** Dibenzyran; ***Ger.:*** Dibenzyran; ***Gr.:*** Dibenyline; ***Hong Kong:*** Dibenyline; ***India:*** Fenoxene; ***Israel:*** Dibenyline; ***Neth.:*** Dibenyline; ***NZ:*** Dibenyline; ***S.Afr.:*** Dibenyline; ***UK:*** Dibenyline; ***USA:*** Dibenzyline.

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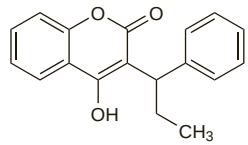
## Phenprocoumon *(BAN, USAN, rINN)*

Fenprocomón; Fenprocumon; Fenprokumon; Fenprokumoni; Phenprocoumone; Phenprocoumonum; Phenylpropylhydroxycoumarin. 4-Hydroxy-3-(1-phenylpropyl)coumarin.

Фенпрокумон

$C_{18}H_{16}O_3$ = 280.3.
*CAS — 435-97-2.*
*ATC — B01AA04.*
*ATC Vet — QB01AA04.*



### Adverse Effects, Treatment, and Precautions
As for Warfarin Sodium, p.1425.

**Effects on the liver.** A woman who had twice previously developed jaundice while taking phenprocoumon developed jaundice and parenchymal liver damage when, after some years, phenprocoumon was again given.[1] Other cases of phenprocoumon-associated liver damage have been reported.[2-4]


1. den Boer W, Loeliger EA. Phenprocoumon-induced jaundice. *Lancet* 1976; **i:** 912.
2. Slagboom G, Loeliger EA. Coumarin-associated hepatitis: report of two cases. *Arch Intern Med* 1980; **140:** 1028–9.
3. Cordes A, *et al.* Phenprocoumon-induziertes Leberversagen. *Dtsch Med Wochenschr* 2003; **128:** 1884–6.
4. Bulang T, *et al.* Akutes Leberversagen durch Phenprocoumon–drei Fallberichte. *Z Gastroenterol* 2004; **42:** 1055–8.


### Interactions
The interactions associated with oral anticoagulants are discussed in detail under warfarin (p.1427). Specific references to interactions involving phenprocoumon can be found there under the headings for the following drug groups: analgesics; antiarrhythmics; antidepressants; antidiabetics; antigout drugs; antineoplastics; gastrointestinal drugs; lipid regulating drugs; and sex hormones.

### Pharmacokinetics
Phenprocoumon is readily absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Metabolism is mediated partly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. The half-life is 5 to 6 days. It is excreted in the urine and faeces as conjugated hydroxy metabolites and parent compound. Phenprocoumon is given as a racemic mixture; the *S*-isomer is more potent. The stereoisomers have different pharmacokinetics.

◊ References.


1. Husted S, Andreasen F. Individual variation in the response to phenprocoumon. *Eur J Clin Pharmacol* 1977; **11:** 351–8.
2. Toon S, *et al.* Metabolic fate of phenprocoumon in humans. *J Pharm Sci* 1985; **74:** 1037–40.
3. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44:** 1227–46.


### Uses and Administration
Phenprocoumon is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1432). It is used in the management of thromboembolic disorders (p.1187). Initial doses are up to 9 mg on the first day followed by 6 mg on the second day. Maintenance doses are usually from 1.5 to 6 mg daily, depending on the response.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Marcoumar; ***Belg.:*** Marcoumar; ***Braz.:*** Marcoumar; ***Denm.:*** Marcoumar; ***Ger.:*** Falithrom; Marcumar; marcuphen; Phenpro; Phenprogamma; ***Neth.:*** Marcoumar; ***Switz.:*** Marcoumar.

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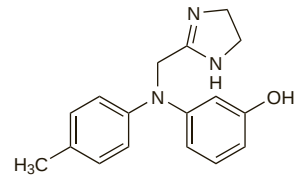
## Phentolamine Mesilate *(BANM, rINNM)*

Fentolamiinimesilaatti; Fentolamin mesylát; Fentolaminmesilat; Fentolamin-mezilát; Fentolamino mesilatas; Mesilato de fentolamina; Phentolamine, mésilate de; Phentolamine Mesylate; Phentolamine Methanesulphonate; Phentolamini mesilas. 3-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol methanesulphonate.

Фентоламина Мезилат

$C_{17}H_{19}N_3O,CH_4SO_3$ = 377.5.
*CAS — 50-60-2 (phentolamine); 73-05-2 (phentolamine hydrochloride); 65-28-1 (phentolamine mesilate).*
*ATC — C04AB01; G04BE05.*
*ATC Vet — QC04AB01; QG04BE05.*



*(phentolamine)*

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), and *US.*
**Ph. Eur. 6.2** (Phentolamine Mesilate). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.
**USP 31** (Phentolamine Mesylate). A white or off-white, odourless crystalline powder. Soluble 1 in 1 of water, 1 in 4 of alcohol, and 1 in 700 of chloroform. Its solutions in water have a pH of about 5 and slowly deteriorate. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

### Adverse Effects and Treatment
The adverse effects of phentolamine are primarily due to its alpha-adrenoceptor blocking activity and include orthostatic hypotension and tachycardia. Myocardial infarction and cerebrovascular spasm or occlusion have been reported occasionally, usually in association with marked hypotension; flushing, sweating, and feelings of apprehension may accompany hypotensive episodes. Anginal pain and arrhythmias have been reported rarely. Nausea, vomiting, and diarrhoea may also occur. Other side-effects include weakness, dizziness, flushing, and nasal congestion. Hypoglycaemia has been reported following overdosage.

Severe hypotension may occur in overdosage although phentolamine has a short duration of action. Treatment may include support of the circulation by postural measures and parenteral fluid volume replacement. Noradrenaline may be given cautiously to overcome alpha-adrenoceptor blockade. Adrenaline is contra-indicated since it also stimulates beta receptors causing increased hypotension and tachycardia.

When injected into the corpus cavernosum of the penis phentolamine has been associated with local pain; induration and fibrosis may occur with repeated use. Priapism has occurred.

### Precautions
Phentolamine should not generally be given to patients with angina pectoris or other evidence of ischaemic heart disease. Care should be taken in patients with peptic ulcer disease, which may be exacerbated.

### Interactions
Since phentolamine only blocks alpha receptors, use with drugs such as adrenaline may lead to severe hypotension and tachycardia due to unopposed beta-adrenoceptor stimulation.

### Pharmacokinetics
After intravenous dosage, the half-life of phentolamine has been reported to be 19 minutes. It is extensively metabolised and about 13% of an intravenous dose is excreted unchanged in the urine.

### Uses and Administration
Phentolamine is an alpha-adrenoceptor blocker (p.1153) which also has a direct action on vascular smooth muscle. It produces vasodilatation, an increase in cardiac output, and has a positive inotropic effect, but is reported to have little effect on the blood pressure of patients with essential hypertension. The alpha-receptor blocking action is reversible ('competitive') and non-selective, and the duration of effect is relatively short.