inated unchanged in the urine. The effective half-life of cilazaprilat is reported to be 9 hours after once-daily dosing. The elimination of cilazaprilat is reduced in renal impairment. Both cilazapril and cilazaprilat are removed to a limited extent by haemodialysis.

◊ Reviews.

1. Kelly JG, O'Malley K. Clinical pharmacokinetics of the newer ACE inhibitors: a review. *Clin Pharmacokinet* 1990; **19:** 177–96.
2. Kloke HJ, *et al.* Pharmacokinetics and haemodynamic effects of the angiotensin converting enzyme inhibitor cilazapril in hypertensive patients with normal and impaired renal function. *Br J Clin Pharmacol* 1996; **42:** 615–20.

Uses and Administration

Cilazapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165).

Cilazapril owes its activity to cilazaprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after about 3 to 7 hours. The haemodynamic action persists for about 24 hours, allowing once-daily dosing. Cilazapril is given orally as the monohydrate, but doses are expressed in terms of the anhydrous substance. Cilazapril 1.04 mg as the monohydrate is equivalent to about 1 mg of anhydrous cilazapril.

In the treatment of **hypertension** the initial dose is 1 mg 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. Usual maintenance doses range from 2.5 to 5 mg daily. In the elderly, in patients with mild to moderate renal impairment, or those taking *diuretics*, a usual initial dose is 500 micrograms daily. If possible the diuretic should be withdrawn 2 to 3 days before cilazapril is started and resumed later if necessary.

In the treatment 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 therapy should be initiated with a low dose under close medical supervision. Cilazapril is given in an initial dose of 500 micrograms once daily, increased if tolerated to a usual maintenance dose of 1 to 2.5 mg once daily. The usual maximum dose is 5 mg daily.

Reduced doses may be necessary in patients with renal impairment (see below).

◊ References.

1. Deget F, Brogden RN. Cilazapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cardiovascular disease. *Drugs* 1991; **41:** 799–820.

Administration in renal impairment. In patients with a creatinine clearance of 10 to 40 mL/minute, the initial dose of cilazapril is 500 micrograms once daily and the maintenance dose should not exceed 2.5 mg once daily. Cilazapril should be avoided in patients with a creatinine clearance below 10 mL/minute. In patients receiving haemodialysis, cilazapril should be given on the non-dialysis days and the dose should be adjusted according to response.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Inhibace; ***Belg.:*** Inhibace; ***Braz.:*** Vascase; ***Canad.:*** Inhibace; ***Chile:*** Inhibace; ***Cz.:*** Cazaprol; Inhibace; ***Fr.:*** Justor; ***Ger.:*** Dynorm; ***Gr.:*** Vascase; ***Hong Kong:*** Inhibace; ***Hung.:*** Inhibace; ***Irl.:*** Vascace; ***Israel:*** Vascace; ***Ital.:*** Inibace; Initiss; ***Jpn:*** Inhibace; ***Mex.:*** Inhibace†; ***Neth.:*** Vascase; ***NZ:*** Inhibace; ***Philipp.:*** Vascace; ***Pol.:*** Inhibace; ***Port.:*** Inibace; Vascase; ***S.Afr.:*** Inhibace; ***Singapore:*** Inhibace†; ***Spain:*** Inhibace; Inocar; ***Swed.:*** Inhibace; ***Switz.:*** Inhibace; ***Thai.:*** Inhibace; ***Turk.:*** Inhibace; ***UK:*** Vascace; ***Venez.:*** Inhibace.

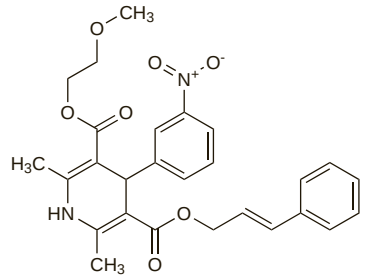
Multi-ingredient: ***Austria:*** Inhibace Plus; ***Belg.:*** Co-Inhibace; ***Braz.:*** Vascase Plus; ***Canad.:*** Inhibace Plus; ***Chile:*** Inhibace Plus; ***Cz.:*** Inhibace Plus; ***Ger.:*** Dynorm Plus; ***Gr.:*** Vascase Plus; ***Hung.:*** Inhibace Plus; ***Israel:*** Vascace Plus; ***Ital.:*** Inibace Plus; Initiss Plus; ***NZ:*** Inhibace Plus; ***Philipp.:*** Vascace Plus; ***Pol.:*** Inhibace Plus; ***Port.:*** Inibace Plus; Vascase Plus; ***Rus.:*** Ampliton (Амплитон); Sonoprel (Сонопрел); ***S.Afr.:*** Inhibace Plus; ***Spain:*** Inhibace Plus; Inocar Plus; ***Swed.:*** Inhibace comp; ***Switz.:*** Inhibace Plus; ***Turk.:*** Inhibace Plus.

Cilnidipine *(rINN)*

Cilnidipino; Cilnidipinum; FRC-8653. (±)-(*E*)-Cinnamyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate.

Цилнидипин

$C_{27}H_{28}N_2O_7$ = 492.5.
CAS — 132203-70-4.
ATC — C08CA14.
ATC Vet — QC08CA14.



Profile

Cilnidipine is a dihydropyridine calcium-channel blocker (p.1154) given orally in the management of hypertension (p.1171). The usual dose is 5 to 10 mg once daily, increased to 20 mg once daily if necessary.

Preparations

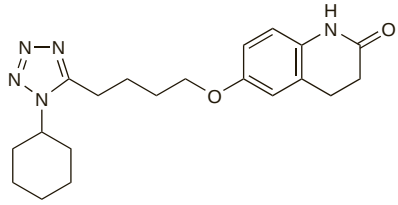
Proprietary Preparations (details are given in Part 3)
Jpn: Atelec; Cinalong; ***Port.:*** Tenvasc.

Cilostazol *(BAN, USAN, pINN)*

Cilostazolum; OPC-21; OPC-13013. 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril.

Цилостазол

$C_{20}H_{27}N_5O_2$ = 369.5.
CAS — 73963-72-1.



Pharmacopoeias. In *Jpn* and *US.*
USP 31 (Cilostazol). White to off-white crystals. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; freely soluble in chloroform. Store in airtight containers.

Adverse Effects and Precautions

Adverse effects of cilostazol include headache, dizziness, palpitations, and diarrhoea; oedema, nausea and vomiting, other cardiac arrhythmias, chest pain, rhinitis, ecchymosis, and skin rashes have also been reported. Cardiovascular toxicity has been reported in *animal* studies of cilostazol, and prolonged oral use of other phosphodiesterase inhibitors (such as amrinone, p.1215) for the treatment of heart failure has been associated with increased mortality. The use of cilostazol in patients with any degree of heart failure is therefore contra-indicated. It is also contra-indicated in patients with a known predisposition to bleeding, a history of ventricular arrhythmias, QT interval prolongation, severe renal impairment, or moderate to severe hepatic impairment. Cilostazol should be avoided or used in reduced doses in patients taking inhibitors of the cytochrome P450 isoenzymes CYP3A4 or CYP2C19 (see Interactions, below).

Interactions

Cilostazol is extensively metabolised to active and inactive metabolites by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19. Therefore use with other drugs that inhibit or are metabolised by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects. Cilostazol should therefore be used with caution in patients taking drugs metabolised by these enzymes; in patients taking enzyme inhibitors it should be avoided or a reduced dose of 50 mg twice daily should be considered.

Pharmacokinetics

Cilostazol is absorbed after oral doses and absorption is increased if taken with a high fat meal. Cilostazol is extensively metabolised in the liver by cytochrome P450 isoenzymes, mainly CYP3A4 and to a lesser extent CYP2C19, to both active and inactive metabolites; these are mainly excreted in the urine (74%) with the remainder in the faeces (20%). The active metabolites have apparent elimination half-lives of 11 to 13 hours. Cilostazol is 95 to 98% protein bound.

◊ References.

1. Woo SK, *et al.* Pharmacokinetic and pharmacodynamic modeling of the antiplatelet and cardiovascular effects of cilostazol in healthy humans. *Clin Pharmacol Ther* 2002; **71:** 246–52.

Uses and Administration

Cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilating activity. It is used in the management of peripheral vascular disease (p.1178).

The usual dose of cilostazol for the reduction of symptoms of intermittent claudication is 100 mg orally twice daily, at least 30 minutes before or 2 hours after food; doses should be reduced in patients taking enzyme inhibitors (see Interactions, above). Response to treatment may occur in 2 to 4 weeks, but up to 12 weeks may be required.

Cilostazol is under investigation for its antiplatelet effect after coronary stent implantation.

◊ Reviews.

1. El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. *Ann Pharmacother* 2001; **35:** 1108–13.
2. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005; **6:** 3–11.
3. Matsumoto M. Cilostazol in secondary prevention of stroke: impact of the Cilostazol Stroke Prevention Study. *Atheroscler Suppl* 2005; **6:** 33–40.
4. Weintraub WS. The vascular effects of cilostazol. *Can J Cardiol* 2006; **22** (suppl B): 56B–60B.
5. Dalainas I. Cilostazol in the management of vascular disease. *Int Angiol* 2007; **26:** 1–7.

Peripheral vascular disease. Intermittent claudication is a major feature of occlusive arterial disease of the lower limbs (a form of peripheral vascular disease, p.1178) and is characterised by pain in the legs, which develops during exercise but usually disappears at rest. Many drugs have been used for symptom control, but none is of established benefit.

Several randomised, double-blind studies[1-4] have shown that cilostazol improves walking distances in patients with intermittent claudication, and one study[5] suggested that it was more effective than pentoxifylline. Cilostazol may therefore have a role for symptom control in patients with intermittent claudication.[6] However, long-term benefit has not been assessed[4] and, since patients with intermittent claudication are at high risk of other cardiovascular events, appropriate therapy to reduce cardiovascular risk (p.1164) is still required.

1. Money SR, *et al.* Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg* 1998; **27:** 267–75.
2. Beebe HG, *et al.* A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med* 1999; **159:** 2041–50.
3. Strandness DE, *et al.* Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind, placebo-controlled study. *Vasc Endovascular Surg* 2002; **36:** 83–91.
4. Robless P, *et al.* Cilostazol for peripheral arterial disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/03/08).
5. Dawson DL, *et al.* A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000; **109:** 523–30.
6. Crouse JR, *et al.* Clinical manifestation of atherosclerotic peripheral arterial disease and the role of cilostazol in treatment of intermittent claudication. *J Clin Pharmacol* 2002; **42:** 1291–8.

Preparations

USP 31: Cilostazol Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Cibrogan; Cilostal; Cilovas; Licuagen; Pletaal; Policor; Trastocir; Trombonot; ***Braz.:*** Cebralat; Vasogard; ***Chile:*** Artesol; Ilostal; Kostal; ***Hong Kong:*** Pletaal; ***India:*** Cilodac; Pletoz; Stiloz†; Zilast; ***Indon.:*** Aggravan; Agrezol; Alista; Citaz; Naletal; Pletaal; Qital; Stazol; ***Jpn:*** Pletaal; ***Malaysia:*** Pletaal; ***Philipp.:*** Ciletin; Pletaal; ***Thai.:*** Pletaal; ***UK:*** Pletal; ***USA:*** Pletal.

Cinepazet Maleate *(BANM, USAN, pINNM)*

Cinépazet, Maléate de; Cinepazeti Maleas; Cinepazic Acid Ethyl Ester Maleate; Maleato de cinepazet. Ethyl 4-(3,4,5-trimethoxycinnamoyl)piperazin-1-ylacetate hydrogen maleate.

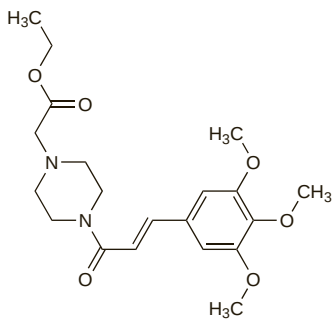
Цинепазета Малеат

$C_{20}H_{28}N_2O_6,C_4H_4O_4$ = 508.5.

CAS — 23887-41-4 (cinepazet); 50679-07-7 (cinepazet maleate).

ATC — C01DX14.

ATC Vet — QC01DX14.



(cinepazet)

Profile

Cinepazet maleate is a vasodilator that has been used in angina pectoris.

Cinepazide Maleate *(BANM, rINNM)*

Cinépazide, Maléate de; Cinepazidi Maleas; Maleato de cinepazida; MD-67350. 1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

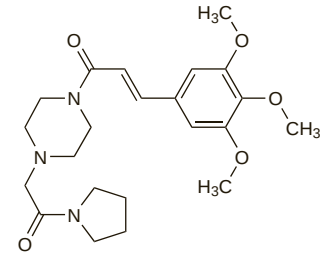
Цинепазида Малеат

$C_{22}H_{31}N_3O_5,C_4H_4O_4$ = 533.6.

CAS — 23887-46-9 (cinepazide); 26328-04-1 (cinepazide maleate).

ATC — C04AX27.

ATC Vet — QC04AX27.



(cinepazide)

Profile

Cinepazide maleate is a vasodilator that has been used in peripheral vascular disorders, but has been withdrawn from the market in some countries after reports of agranulocytosis.

Ciprofibrate *(BAN, USAN, rINN)*

Ciprofibrát; Ciprofibrat; Ciprofibratas; Ciprofibrato; Ciprofibratum; Siprofibraatti; Win-35833. 2-[4-(2,2-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid.

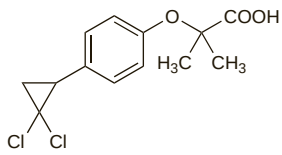
Ципрофибрат

$C_{13}H_{14}Cl_2O_3$ = 289.2.

CAS — 52214-84-3.

ATC — C10AB08.

ATC Vet — QC10AB08.



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

Ph. Eur. 6.2 (Ciprofibrate). A white or slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in toluene. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Interactions

As for Bezafibrate, p.1232.

Pharmacokinetics

Ciprofibrate is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours. Ciprofibrate is highly protein bound. It is excreted in the urine as unchanged drug and as glucuronide conjugates. The elimination half-life varies from about 38 to 86 hours in patients on long-term therapy.

Uses and Administration

Ciprofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, and type IV hyperlipoproteinaemias. The usual oral dose is 100 mg daily. The dose should be reduced in renal impairment (see below).

Administration in renal impairment. Ciprofibrate is contra-indicated in patients with severe renal impairment. Licensed product information suggests reducing the dose to 100 mg every other day for patients with moderate renal impairment.

Renal clearance of ciprofibrate was reduced and elimination half-life about doubled in patients with severe renal impairment.[1] Mild renal impairment slowed the urinary excretion of ciprofibrate but not its extent. The clearance of ciprofibrate was unaffected by haemodialysis.

1. Ferry N, *et al.* The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate. *Br J Clin Pharmacol* 1989; **28:** 675–81.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Estaprol; ***Belg.:*** Hyperlipen; ***Braz.:*** Lipless; Oroxadin; ***Chile:*** Estaprol; ***Cz.:*** Lipanor; ***Fr.:*** Lipanor; ***Gr.:*** Savilen; ***Hung.:*** Lipanor; ***Indon.:*** Modalim; ***Israel:*** Lipanor; ***Malaysia:*** Modalim; ***Mex.:*** Oroxadin; ***Neth.:*** Hyperlipen; Modalim; ***Philipp.:*** Modalim; ***Pol.:*** Lipanor; ***Port.:*** Fibranin; Lipanor; ***Singapore:*** Modalim; ***Switz.:*** Hyperlipen; ***UK:*** Modalim; ***Venez.:*** Hiperlipen.

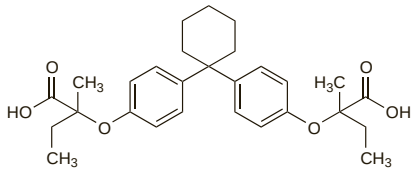
Clinofibrate *(rINN)*

Clinofibrato; Clinofibratum; S-8527. 2,2′-[Cyclohexylidenebis(4-phenyleneoxy)]bis[2-methylbutyric acid].

Клинофибрат

$C_{28}H_{36}O_6$ = 468.6.

CAS — 30299-08-2.



Pharmacopoeias. In *Jpn.*

Profile

Clinofibrate, a fibric acid derivative (see Bezafibrate, p.1232), is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Lipoclin.

Clofibrate *(BAN, USAN, rINN)*

AY-61123; Clofibrato; Clofibratum; Ethyl *p*-Chlorophenoxyisobutyrate; Ethyl Clofibrate; ICI-28257; Klofibraatti; Klofibrát; Klofibrat; Klofibratas; NSC-79389. Ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

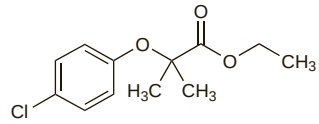
Клофибрат

$C_{12}H_{15}ClO_3$ = 242.7.

CAS — 637-07-0 (clofibrate); 882-09-7 (clofibric acid).

ATC — C10AB01.

ATC Vet — QC10AB01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Clofibrate). A clear, almost colourless liquid. Very slightly soluble in water; miscible with alcohol.

USP 31 (Clofibrate). A colourless to pale yellow liquid with a characteristic odour. Insoluble in water; soluble in alcohol, in acetone, in chloroform, and in benzene. Store in airtight containers. Protect from light.

Aluminium Clofibrate *(BAN, rINN)*

Alufibrate; Aluminii Clofibras; Aluminium, Clofibrate d'; Aluminiumklofibraatti; Aluminiumklofibrat; Aluminum Clofibrate; Clofibrato de aluminio. Bis[2-(4-chlorophenoxy)-2-methylpropionato]hydroxyaluminium.

Алюминия Клофибрат

$C_{20}H_{21}AlCl_2O_7$ = 471.3.

CAS — 24818-79-9; 14613-01-5.

ATC — C10AB03.

ATC Vet — QC10AB03.

Calcium Clofibrate *(rINN)*

Calcii Clofibras; Clofibrate de Calcium; Clofibrato de calcio.

Кальция Клофибрат

$C_{20}H_{20}CaCl_2O_6$ = 467.4.

CAS — 39087-48-4.

Magnesium Clofibrate *(rINN)*

Clofibrato de magnesio; Clomag; Magnesii Clofibras; Magnésium, Clofibrate de; UR-112.

Магния Клофибрат

$C_{20}H_{20}Cl_2MgO_6$ = 451.6.

CAS — 14613-30-0.

Profile

Clofibrate, a fibric acid derivative, is a lipid regulating drug with similar properties to bezafibrate (p.1233). It is used to reduce triglycerides and possibly total cholesterol in the management of hyperlipidaemias (p.1169), particularly in patients with hypertriglyceridaemia. Because of the incidence of adverse effects during long-term treatment it should not be used for the prophylaxis of ischaemic heart disease (see Adverse Effects, below).

The usual oral dose is 2 g daily in divided doses.

The aluminium, calcium, and magnesium salts of clofibrate have also been used.

Adverse effects. Large-scale, long-term studies[1,2] with clofibrate indicated that it was generally well-tolerated but that there was an increased incidence of serious effects, including cholelithiasis, cholecystitis, thromboembolic disorders, and certain cardiac arrhythmias. In one of the studies,[2] an increased mortality rate was unexpectedly found in patients taking clofibrate, producing serious concern over its long-term safety and its use is now generally restricted; the causes of death were spread over a range of malignant and non-malignant disorders.

1. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; **231:** 360–80.
2. Oliver MF, *et al.* A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978; **40:** 1069–1118.

Neonatal jaundice. Clofibrate has been used in the treatment of jaundice in term infants[1,2] and for prophylaxis in premature infants.[1] In a study[1] involving 93 term infants with jaundice, clofibrate 50 mg/kg as a single oral dose reduced the intensity and duration of jaundice compared with placebo. As a prophylactic measure, clofibrate was shown[1] to reduce the degree of jaundice in premature infants when the plasma concentration of clofibric acid reached 140 micrograms/mL within 24 hours of an oral dose. The dose required to achieve this was estimated to be 100 to 150 mg/kg.

1. Gabilan JC, *et al.* Clofibrate treatment of neonatal jaundice. *Pediatrics* 1990; **86:** 647–8.
2. Mohammadzadeh A, *et al.* Effect of clofibrate in jaundiced term newborns. *Indian J Pediatr* 2005; **72:** 123–6.

Preparations

BP 2008: Clofibrate Capsules;
USP 31: Clofibrate Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Elpi; ***Austria:*** Arterioflexin; ***Hong Kong:*** Lipilim; ***Port.:*** Atromid-S†.

Multi-ingredient: ***Braz.:*** Lipofacton.