21. Cheung P-Y, *et al.* The outcome of very low birth weight neonates (≤1500g) rescued by inhaled nitric oxide: neurodevelopment in early childhood. *J Pediatr* 1998; **133:** 735–9.
22. Mestan KKL, *et al.* Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005; **353:** 23–32.
23. Tanaka Y, *et al.* Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007; **119:** 1159–64.

Sickle-cell disease. Sickle-cell crisis due to vaso-occlusion is an acute complication of sickle-cell disease (p.1044), requiring hospitalisation, with the use of large volumes of intravenous fluids for dehydration, and analgesia including opioids for pain. Concentrations of nitric oxide metabolites and L-arginine have been found to be low in vaso-occlusive crisis and a study[1] in paediatric patients showed that inhaled nitric oxide may be of benefit.

1. Weiner DL, *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003; **289:** 1136–42.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: INOmax; ***Denm.:*** INOmax; ***Gr.:*** INOmax; ***Neth.:*** INOmax; ***Pol.:*** INOmax; ***Port.:*** INOmax; ***Spain:*** INOmax; ***Switz.:*** INOmax; ***USA:*** INOmax.

Noradrenaline *(BAN)* ⊗

Norepinephrine *(BAN, rINN)*; Levarterenol; Noradrenaliini; Noradrenalin; Noradrenalinum; Norepinefriini; Norepinefrin; Norepinefrina; Norépinéphrine; Norepinephrinum; Norepirenamine. (*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol.

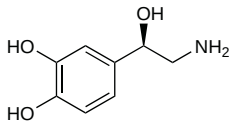
Норэпинефрин

$C_8H_{11}NO_3$ = 169.2.

CAS — 51-41-2.

ATC — C01CA03.

ATC Vet — QC01CA03.



Pharmacopoeias. *Jpn* includes the racemic form.

Noradrenaline Acid Tartrate *(BANM)* ⊗

Norepinephrine Bitartrate *(USAN, rINNM)*; Arterenol Acid Tartrate; *l*-Arterenol Bitartrate; Bitartrato de norepinefrina; Levarterenol Acid Tartrate; Levarterenol Bitartrate; Levarterenoli Bitartras; Noradrenaliinitartraatti; Noradrenaline Bitartrate; Noradrenaline Tartrate; Noradrénaline, tartrate de; Noradrenalini tartras; Noradrenalino tartratas; Noradrenalin-tartarát; Noradrenalintartrat; Norepinefrin tartarát monohydrát; Norepinefryny wodorowinian; Norepinephrine Acid Tartrate *(BANM)*; *l*-Norepinephrine Bitartrate; Norépinéphrine, Bitartrate de; Norepinephrini Bitartras; Norepinephrini Tartras Monohydricus.

Норэпинефрина Битартрат

$C_8H_{11}NO_3,C_4H_6O_6,H_2O$ = 337.3.

CAS — 51-40-1 (anhydrous noradrenaline acid tartrate); 69815-49-2 (noradrenaline acid tartrate monohydrate).

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Noradrenaline Tartrate; Noradrenaline Acid Tartrate BP 2008; Norepinephrine Acid Tartrate BP 2008). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.
USP 31 (Norepinephrine Bitartrate). A white or faintly grey, odourless, crystalline powder. It slowly darkens on exposure to air and light. Soluble 1 in 2.5 of water and 1 in 300 of alcohol; practically insoluble in chloroform and in ether. Its solutions in water have a pH of about 3.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Noradrenaline acid tartrate is strongly acidic in solution, and would be expected to be incompatible with drugs having an alkaline pH. Licensed product information in the UK states that solutions are reportedly incompatible with alkalis and oxidising agents, barbiturates, chlorphenamine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, and streptomycin. Incompatibility with insulin has also been reported.[1]

1. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.

Noradrenaline Hydrochloride *(BANM)* ⊗

Norepinephrine Hydrochloride *(BANM, rINNM)*; Hidrocloruro de norepinefrina; Noradrenaliinihydrokloridi; Noradrénaline, chlorhydrate de; Noradrenalin-hidroklorid; Noradrenalinhydroklorid; Noradrenalini hydrochloridum; Noradrenalino hidrochloridas; Norepinefrin hydrochlorid; Norépinéphrine, Chlorhydrate de; Norepinephrini Hydrochloridum.

Норэпинефрина Гидрохлорид

$C_8H_{11}NO_3$,HCl = 205.6.

CAS — 329-56-6.

ATC — C01CA03.

ATC Vet — QC01CA03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Noradrenaline Hydrochloride; Norepinephrine Hydrochloride BP 2008). A white or brownish-white, crystalline powder. It becomes coloured on exposure to air and light. Very soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 3.5 to 4.5. Store in airtight containers, or preferably, in a sealed tube under vacuum or an inert gas. Protect from light.

Adverse Effects

As for Sympathomimetics, p.1407. Noradrenaline is an extremely potent peripheral vasoconstrictor and its adverse effects include hypertension (possibly associated with reflex bradycardia), headache, and peripheral ischaemia, which may be severe enough to result in gangrene of the extremities. Extravasation may lead to severe phlebitis and sloughing.

Dental use. Severe headache,[1,2] including fatal cerebral haemorrhage,[1,3] has been reported after the use of lidocaine with noradrenaline 1 in 25 000 for dental anaesthesia. It was suggested[1-3] that preparations containing noradrenaline 1 in 25 000 should not be used, and that a concentration of 1 in 80 000 was to be preferred. However, in the UK the *Dental Practitioners' Formulary*[4] had stated that noradrenaline should not be used as a vasoconstrictor in local anaesthetic solutions since it presented no advantage over adrenaline and carried additional hazard.

1. Boakes AJ, *et al.* Adverse reactions to local anaesthetic/vasoconstrictor preparations: a study of the cardiovascular responses to Xylestesin and Hostacain-with-Noradrenaline. *Br Dent J* 1972; **133:** 137–40.
2. van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anesthesia. *Anesth Prog* 1992; **39:** 87–9.
3. Okada Y, *et al.* Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J* 1989; **34:** 323–5.
4. *Dental Practitioners' Formulary.* 2002–2004. London: British Dental Association, British Medical Association, and the Royal Pharmaceutical Society of Great Britain; 2002. D6.

Treatment of Adverse Effects

As for Sympathomimetics, p.1407. If extravasation occurs, infiltration with phentolamine (see p.1370) as soon as possible, and certainly within 12 hours, may relieve pain and prevent tissue necrosis.

Precautions

As for Sympathomimetics, p.1407. Noradrenaline has mainly alpha-agonist properties and must be avoided in the presence of hypertension; blood pressure and infusion rate must be monitored frequently. Noradrenaline-induced cardiac arrhythmias are more likely in patients with hypoxia or hypercapnia.

Noradrenaline is a severe tissue irritant and only very dilute solutions should be used. It should be infused centrally or into a large vein if possible, and care should be taken to avoid extravasation.

Noradrenaline may reduce placental perfusion throughout pregnancy and some consider that it and similar vasoconstrictor sympathomimetics are best avoided; also in late pregnancy noradrenaline provokes uterine contractions which can result in fetal asphyxia.

Interactions

As for Sympathomimetics, p.1407. Severe hypertension may occur if noradrenaline is given to patients taking tricyclic antidepressants since tricyclics block the uptake of noradrenaline into nerve endings.

Pharmacokinetics

Like adrenaline (p.1204), noradrenaline is inactive when given orally, and it is rapidly inactivated in the body by similar processes. When given intravenously it is extensively metabolised and only small amounts are excreted unchanged in the urine.

Uses and Administration

Noradrenaline is a direct-acting catecholamine sympathomimetic (p.1408) with pronounced effects on alpha-adrenergic receptors; it also stimulates $beta_1$ receptors but has little effect on $beta_2$ receptors. It is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Some is also present in the adrenal medulla and is released with adrenaline.

The major effects of noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

Noradrenaline is used for the emergency restoration of blood pressure in acute hypotensive states such as shock (p.1183). It has also been used in the management of cardiac arrest. Noradrenaline has been used in local anaesthesia to diminish the absorption and localise the effect of the local anaesthetic (p.1852) but adrenaline is now preferred (see also Dental use under Adverse Effects, above). Locally applied solutions have been used to control bleeding in upper gastrointestinal haemorrhage and similar disorders.

In **acute hypotensive states**, noradrenaline is used as the acid tartrate, or occasionally as the hydrochloride, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms or noradrenaline hydrochloride 1.2 micrograms are equivalent to about 1 microgram of noradrenaline. It is given by intravenous infusion of a solution containing the equivalent of 4 micrograms of the base per mL in glucose 5%, or sodium chloride 0.9% and glucose 5%. To avoid tissue necrosis the infusion should be given through a central venous catheter or into a large vein high up in a limb, preferably the arm. Some sources have suggested that addition of phentolamine 5 to 10 mg/litre to the infusion may prevent sloughing, should extravasation occur, without affecting the vasopressor action. The infusion is usually given initially at a rate of 2 to 3 mL/minute (8 to 12 micrograms/minute) and adjusted according to the blood pressure response. Blood pressure is initially recorded every 2 minutes and the rate of infusion continuously monitored. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure. The average maintenance dose is 0.5 to 1 mL/minute (2 to 4 micrograms/minute), but there is a wide variation and higher doses may be required. The concentration of the infusion may be altered according to clinical needs. Alternatively a solution containing the equivalent of 40 micrograms of the base per mL may be given at an initial rate of 0.16 to 0.33 mL/minute via a central venous catheter, using a syringe pump or drip counter.

Preparations

BP 2008: Noradrenaline Injection;
USP 31: Norepinephrine Bitartrate Injection; Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fioritina; ***Austral.:*** Levophed; ***Belg.:*** Levophed; Norepine†; ***Braz.:*** Levophed; Norephed†; ***Canad.:*** Levophed; ***Chile:*** Adine; ***Ger.:*** Arterenol; ***Gr.:*** Levophed; Noradren; ***Hong Kong:*** Levophed†; ***India:*** Adrenor; ***Indon.:*** Levophed; N-Epi; Raivas; Vascon; ***Irl.:*** Levophed; ***Israel:*** Levophed; ***Malaysia:*** Levophed; ***Mex.:*** Pridam; ***NZ:*** Levophed; ***Philipp.:*** Inotrop; Levophed; ***Pol.:*** Levonor; ***Singapore:*** Levophed†; ***Spain:*** Norages; ***Thai.:*** Levophed; ***USA:*** Levophed.

Used as an adjunct in: ***Austria:*** Neo-Xylestesin forte; Scandonest; ***Braz.:*** Xylestesin; Xylocaina; ***Ger.:*** Xylestesin-S†; Xylestesin, Xylestesin-F†; ***Ital.:*** Lident Andrenor†; Xylonor; ***Port.:*** Scandonest; Xilonibsa; ***S.Afr.:*** Xylotox; ***Spain:*** Xylonor Especial; ***Switz.:*** Scandonest; Xylestesin-F†; Xylestesin-S "special"†; ***Thai.:*** Neo-Lidocaton†.

Norfenefrine Hydrochloride *(rINNM)* ⊗

Hidrocloruro de norfenefrina; Norfenefrin Hidroklorür; Norfénéfrine, Chlorhydrate de; Norfenefrini Hydrochloridum; Norphenylephrine Hydrochloride; *m*-Norsynephrine Hydrochloride; WV-569. 2-Amino-1-(3-hydroxyphenyl)ethanol hydrochloride.

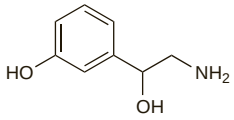
Норфенефрина Гидрохлорид

$C_8H_{11}NO_2,HCl$ = 189.6.

CAS — 536-21-0 (norfenefrine); 15308-34-6 (norfenefrine hydrochloride).

ATC — C01CA05.

ATC Vet — QC01CA05.



(norfenefrine)

NOTE. *m*-Octopamine has been used as a synonym for norfenefrine. Care should be taken to avoid confusion with octopamine, which is the *p*-isomer.

Profile

Norfenefrine is a sympathomimetic (p.1407) with predominantly alpha-adrenergic activity. It is used as the hydrochloride for its vasopressor effect in the treatment of hypotensive states (p.1174). The usual oral dose is 15 mg three times daily of norfenefrine hydrochloride, as a modified-release preparation. Norfenefrine hydrochloride has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Novadral; ***Ger.:*** Novadral†; ***Mex.:*** AS Cor; ***Switz.:*** Novadral; ***Turk.:*** Novadral.

Multi-ingredient: ***Ger.:*** Adyston†; Normotin-R†; Ordinal Forte†; ***Switz.:*** Ortho-Maren retard.

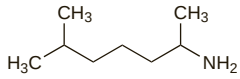
Octodrine *(USAN, rINN)* ⊗

Octodrina; Octodrinum; SKF-51. 1,5-Dimethylhexylamine.

Октодрин

$C_8H_{19}N$ = 129.2.

CAS — 543-82-8.



Profile

Octodrine is a sympathomimetic (p.1407) with mainly alpha-adrenergic activity. It has been given orally as the camsilate, in combination with norfenefrine (p.1361), in the treatment of hypotensive states. Octodrine phosphate has been used as an ingredient of preparations for obstructive airways disease.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austria:*** Ambredin; ***Ger.:*** Ordinal Forte†.

Olmesartan Medoxomil *(BAN, USAN, rINN)*

CS-866; Olmésartan Médoxomil; Olmesartán medoxomilo; Olmesartanum Medoxomilum; RNH-6270 (olmesartan). (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl ester of 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-{[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl}-1*H*-imidazole-5-carboxylic acid.

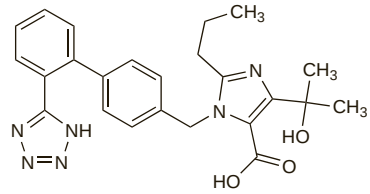
Ольмезартан Медоксомил

$C_{29}H_{30}N_6O_6$ = 558.6.

CAS — 144689-24-7 (olmesartan); 144689-63-4 (olmesartan medoxomil).

ATC — C09CA08.

ATC Vet — QC09CA08.



(olmesartan)

NOTE. The name olmesartan has been applied to both the base and to the medoxomil ester.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326.

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. The absolute bioavailability is about 26%. Peak plasma concentrations of olmesartan occur about 1 to 2 hours after oral doses. Olmesartan is at least 99% bound to plasma proteins. It is excreted in the urine and the bile as olmesartan; about 35 to 50% of the absorbed dose is excreted in the urine and the remainder in the bile. The terminal elimination half-life is between 10 and 15 hours.

◊ References.

1. Yoshihara K, *et al.* Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. *Clin Pharmacokinet* 2005; **44:** 1329–42.

Uses and Administration

Olmesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171).

Olmesartan is given orally as the ester prodrug olmesartan medoxomil. After a dose the hypotensive effect lasts for 24 hours. Most of the hypotensive effect is apparent within 2 weeks after starting therapy and is maximal within about 8 weeks.

In hypertension, olmesartan medoxomil is given in a usual dose of 20 mg once daily, although in the UK an initial dose of 10 mg once daily is recommended. The dose may be increased to 40 mg once daily if required.

For doses in hepatic or renal impairment, see below.

◊ References.

1. Brunner HR. The new oral angiotensin II antagonist olmesartan medoxomil: a concise overview. *J Hum Hypertens* 2002; **16** (suppl 2): S13–S16.
2. Warner GT, Jarvis B. Olmesartan medoxomil. *Drugs* 2002; **62:** 1345–53. Correction. *ibid.*; 1852.
3. Gardner SF, Franks AM. Olmesartan medoxomil: the seventh angiotensin receptor antagonist. *Ann Pharmacother* 2003; **37:** 99–105.
4. Unger T, *et al.* The role of olmesartan medoxomil in the management of hypertension. *Drugs* 2004; **64:** 2731–9.
5. Mire DE, *et al.* A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. *J Cardiovasc Pharmacol* 2005; **46:** 585–93.
6. Takai S, Miyazaki M. Effect of olmesartan medoxomil on atherosclerosis: clinical implications of the emerging evidence. *Am J Cardiovasc Drugs* 2006; **6:** 363–6.
7. Smith DH. Dose-response characteristics of olmesartan medoxomil and other angiotensin receptor antagonists. *Am J Cardiovasc Drugs* 2007; **7:** 347–56.
8. Zannad F, Fay R. Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies. *Fundam Clin Pharmacol* 2007; **21:** 181–90.
9. Chrysant SG, *et al.* Treatment of hypertension with olmesartan medoxomil, alone and in combination with a diuretic: an update. *J Hum Hypertens* 2007; **21:** 699–708.
10. Barrios V, Escobar C. Olmesartan medoxomil plus hydrochlorothiazide for treating hypertension. *Expert Opin Pharmacother* 2008; **9:** 129–36.

Administration in hepatic or renal impairment. Olmesartan is excreted in both urine and bile and raised plasma concentrations have been noted in patients with renal or hepatic impairment. In patients with *renal impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment (creatinine clearance (CC) below 20 mL/minute) since experience is limited, and the maximum dose in mild to moderate impairment (CC 20 to 60 mL/minute) is 20 mg once daily. Similarly, in patients with *hepatic impairment*, licensed product information in the UK does not recommend the use of olmesartan in severe impairment since there is no experience. Those with moderate hepatic impairment should be given an initial dose of 10 mg once daily and the maximum dose is 20 mg once daily.

Migraine. For reference to the use of angiotensin II receptor antagonists, including olmesartan, in the prophylaxis of migraine, see under Losartan, p.1328.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Olmec; Tensonit; Vasexten; ***Austral.:*** Olmetec; ***Austria:*** Olmetec; ***Belg.:*** Belsar; Olmetec; ***Braz.:*** Benicar; Olmetec; ***Cz.:*** Olmetec; Sarten; ***Denm.:*** Olmetec; ***Fin.:*** Benetor; Olmetec; ***Fr.:*** Alteis; Olmetec; ***Ger.:*** Olmetec; Votum; ***Gr.:*** Olartan; Olmetec; ***Hong Kong:*** Olmetec; ***Indon.:*** Olmetec; ***Irl.:*** Benetor; Omesar; ***Israel:*** Olmetec; ***Ital.:*** Olmetec; Olpress; Plaunac; ***Jpn:*** Olmetec; ***Malaysia:*** Olmetec; ***Neth.:*** Olmes; Olmetec; ***Norw.:*** Olmetec; ***Philipp.:*** Olmetec; ***Port.:*** Olmetec; Olsar; ***Singapore:*** Olmetec; ***Spain:*** Ixia; Olmetec; Openvas; ***Switz.:*** Olmetec; Votum; ***Thai.:*** Olmetec; ***UK:*** Olmetec; ***USA:*** Benicar; ***Venez.:*** Benicar; Olmetec.

Multi-ingredient: ***Austral.:*** Olmetec Plus; ***Belg.:*** Olmetec Plus; ***Braz.:*** Benicar HCT; Olmetec HCT; ***Cz.:*** Olmetec Plus H; Sarten Plus H; ***Fr.:*** Alteisduo; Coolmetec; ***Ger.:*** Olmetec Plus; Votum Plus; ***Gr.:*** Olartan Plus; Olmetec Plus; ***Malaysia:*** Olmetec Plus; ***Port.:*** Olsar Plus; ***Singapore:*** Olmetec Plus; ***Switz.:*** Olmetec Plus; Votum Plus; ***UK:*** Olmetec Plus; ***USA:*** Azor; Benicar HCT.

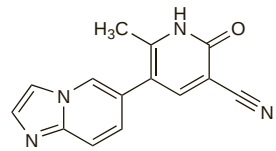
Olprinone Hydrochloride *(rINNM)*

Hidrocloruro de olprinona; Olprinone, Chlorhydrate d'; Olprinoni Hydrochloridum. 1,2-Dihydro-5-imidazo[1,2-*a*]pyridin-6-yl-6-methyl-2-oxonicotinonitrile hydrochloride.

Ольпринона Гидрохлорид

$C_{14}H_{10}N_4O,HCl$ = 286.7.

CAS — 106730-54-5 (olprinone); 119615-63-3 (olprinone hydrochloride).



(olprinone)

Profile

Olprinone is a phosphodiesterase inhibitor with positive inotropic and vasodilator activity, used in acute heart failure (p.1165). It is given intravenously as the hydrochloride in an initial dose of 10 micrograms/kg given over 5 minutes, followed by a continuous infusion at a rate of 100 to 400 nanograms/kg per minute, according to response.

Preparations

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

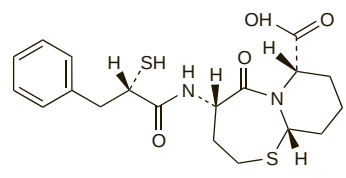
Omapatrilat *(BAN, USAN, rINN)*

BMS-186716; BMS-186716-01; Omapatrilate; Omapatrilato; Omapatrilatum. (4*S*,7*S*,10a*S*)-Octahydro-4-[(*S*)-α-mercaptohydrocinnamamido]-5-oxo-7*H*-pyrido[2,1-*b*][1,3]thiazepine-7-carboxylic acid.

Омапатрилат

$C_{19}H_{24}N_2O_4S_2$ = 408.5.

CAS — 167305-00-2.



Profile

Omapatrilat is a vasopeptidase inhibitor. It inhibits both angiotensin-converting enzyme and neutral endopeptidase and is under investigation in the management of hypertension and heart failure. However, its use may be limited by severe angioedema.

◊ References.

1. Tabrizchi R. Dual ACE and neutral endopeptidase inhibitors: novel therapy for patients with cardiovascular disorders. *Drugs* 2003; **63:** 2185–2202.
2. Kostis JB, *et al.* Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17:** 103–11.