Profile

Sulodexide is a heparinoid consisting of a mixture of low-molecular-weight heparin and dermatan sulfate. It is used as a hypolipidaemic and antithrombotic and has been given orally and parenterally for peripheral vascular disease and cerebrovascular disease. It is also included in preparations used topically for local vascular inflammation and soft-tissue disorders. Sulodexide has also been investigated for the treatment of diabetic nephropathy.

◊ References.

1. Ofosu FA. Pharmacological actions of sulodexide. *Semin Thromb Hemost* 1998; **24:** 127–38.
2. Weiss R, *et al*. The role of sulodexide in the treatment of diabetic nephropathy. *Drugs* 2007; **67:** 2681–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Cz.: Vessel Due F; ***Hung.:*** Vessel Due F; ***Ital.:*** Clarens; Provenal; Ravenol; Treparin; Vessel; ***Malaysia:*** Vessel Due F; ***Philipp.:*** Vessel Due F; ***Pol.:*** Vessel Due F; ***Port.:*** Vessel; ***Rus.:*** Vessel Due F (Вессел Дуэ Ф); ***Spain:*** Aterina; Luzone; ***Venez.:*** Vessel Due.

Multi-ingredient: ***Ital.:*** Dermoangiopan†; Vessiflex†.

Sympathomimetics ⊗

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, generally resembling the effect of excessive stimulation of the sympathetic nervous system. These effects are mediated by the different types of adrenergic receptor, and the effects of individual drugs depend to a large extent on their relative activity at the different receptors, as well as the body's homoeostatic response. While many sympathomimetics are relatively selective for specific receptors, this depends on the dose, and at higher doses most have effects on all receptors.

Central effects may occur with all sympathomimetics and include anxiety, fear, restlessness, insomnia, confusion, irritability, headache, and psychotic states; dyspnoea, weakness, anorexia, nausea, and vomiting are also common. Although some sympathomimetics have direct effects, others do not cross the blood-brain barrier and their central effects appear to be a somatic response.

The most important adverse effects of the sympathomimetics are those that affect the cardiovascular system. Palpitations, tachycardia, and arrhythmias mainly result from stimulation of cardiac beta receptors, and there is also an increase in cardiac contractility; this may result in angina or cardiac arrest.

The effects on blood vessels depend on the relative effects at alpha and beta receptors, since most blood vessels have both. Stimulation of alpha receptors produces vasoconstriction, with resultant hypertension, and this may be severe enough to lead to cerebral haemorrhage or pulmonary oedema, particularly in overdosage. There may also be reflex bradycardia. Conversely, hypotension, with dizziness and fainting, and flushing, may occur due to $beta_2$-induced vasodilatation, and may contribute to tachycardia.

Alpha-mediated vasoconstriction causes cold extremities, since blood vessels supplying the skin and mucosa have only alpha receptors; this may lead to gangrene, particularly when sympathomimetics are infiltrated into digits. Extravasation similarly may cause tissue necrosis and sloughing. Topical application to mucosal surfaces also causes vasoconstriction, pain, and irritation; hypoxia may lead to rebound mucosal congestion.

Other effects include mydriasis, difficulty in micturition and urinary retention, piloerection, sweating, and increased salivation, all of which result from $alpha_1$ stimulation. Hypokalaemia and muscle tremor may occur as a result of $beta_2$ stimulation, although tremor may also occur as a somatic response. Effects on the uterus are complex and depend on the stage of the menstrual cycle; labour may be inhibited by $beta_2$ stimulation. Hyperglycaemia may occur due to complex metabolic effects, and lactic acidosis has also been reported.

Effects on the heart. The heart has mainly $beta_1$ adrenoceptors and cardiac arrhythmias are most likely with $beta_1$ agonists; increased mortality has been reported with the use of beta agonists in heart failure (see Ibopamine, p.1312). A review[1] of vasopressor sympathomimetics, which are mainly used for their alpha-agonist properties, concluded that dopamine and adrenaline were associated with the highest risk, mainly of dose-related sinus tachycardia and ventricular arrhythmias. However, the clinical significance of most arrhythmias occurring with dopamine was considered questionable; supraventricular or ventricular arrhythmias with adrenaline were most likely in patients receiving general anaesthesia or with underlying disorders of cardiac conduction. The risk with noradrenaline was uncertain, though there are few clinical reports, while phenylephrine and methoxamine were thought unlikely to cause problems. Overall the frequency of serious problems with this class of drugs did not seem to be high, and benefits outweighed the risks in most patients.

Sympathomimetics may cause myocardial ischaemia, particularly in patients with ischaemic heart disease, and severe cardiovascular effects have occurred with the use of dobutamine for cardiac stress testing (see Diagnosis and Testing, p.1272). In addition, myocardial infarction has been reported in an 11-year-old boy treated with nebulised racepinefrine for symptoms of croup,[2] and there have also been reports of myocardial ischaemia associated with adrenaline overdosage (see p.1203).

1. Tisdale JE, *et al*. Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995; **29:** 269–81.
2. Butte MJ, *et al*. Pediatric myocardial infarction after racemic epinephrine administration. Abstract: *Pediatrics* 1999; **104:** 103–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e9 (accessed 07/10/05)

Topical use. Systemic effects may occasionally follow the local or topical use of sympathomimetics, for example as eye drops for the treatment of glaucoma.[1] Psychiatric effects including hallucinations and paranoia have also occurred after both proper and improper use of sympathomimetics in decongestant preparations.[2]

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; **112:** 120–5.
2. Anonymous. Drugs that cause psychiatric symptoms. *Med Lett Drugs Ther* 1993; **35:** 65–70.

Treatment of Adverse Effects

Most sympathomimetics have a short duration of action and treatment of adverse effects is mainly supportive; if given by infusion, stopping it or reducing the rate will be sufficient in many cases. A rapidly-acting alpha blocker, such as phentolamine, may be given to reverse $alpha_1$-mediated effects such as hypertension, while a beta blocker may be given for $beta_1$-mediated effects such as cardiac arrhythmias. In severe hypertension, rapidly-acting vasodilators such as glyceryl trinitrate have also been used.

In the case of extravasation of an alpha agonist, or injection into a digit, an alpha blocker such as phentolamine should be given as soon as possible to prevent tissue necrosis and ischaemic damage.

Non-catecholamine sympathomimetics may have a longer duration of action and adverse effects, particularly hypertension, may be prolonged.

Precautions

Sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia. $Beta_1$ agonists are a particular hazard in tachycardia. Sympathomimetics with $beta_2$ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful.

Sympathomimetics should be avoided in phaeochromocytoma. Caution is also needed in patients with hyperthyroidism, who may be at increased risk of effects on the heart; elevated thyroid hormone concentrations may also enhance adrenoceptor sensitivity. Diabetics and elderly patients have a high incidence of atherosclerotic disease and may also be at higher risk; the effects of sympathomimetics on blood glucose should also be considered.

Alpha agonists in particular should be used with caution in angle-closure glaucoma, as well as in patients with prostate disorders, who may be at increased risk of urinary retention. Sympathomimetics with vasoconstrictor effects may reduce placental perfusion and should possibly be avoided in pregnancy; adrenaline and others with $beta_2$-mediated effects may also inhibit labour.

If sympathomimetics are used for circulatory support, hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be corrected either before starting the sympathomimetic or while it is being given. Blood pressure should be monitored regularly during treatment.

Interactions

Interactions with sympathomimetics are complex and may be hazardous; they result mainly from their pharmacological actions at alpha and beta receptors.

Increased cardiac effects may occur with drugs that increase the sensitivity of the myocardium to $beta_1$ agonists; hazardous arrhythmias may occur with volatile anaesthetics, particularly cyclopropane or halothane. Caution is also required with thyroid hormones, and with drugs that affect cardiac conduction, such as cardiac glycosides and antiarrhythmics.

All sympathomimetics affect blood pressure and should be used with caution with antihypertensive drugs or drugs that cause hypotension, particularly those whose action involves the sympathetic nervous system. Direct-acting sympathomimetics with alpha-agonist actions specifically reverse the hypotensive effect of adrenergic neurone blockers such as guanethidine, and severe hypertension may result. There are also complex interactions between both alpha and beta blockers and sympathomimetics, particularly those that have actions at both types of receptor. Alpha blockers antagonise the effects at alpha receptors but leave the beta-mediated effects unopposed, leading to an increased risk of hypotension and tachycardia. Beta blockers, especially those that are non-selective, antagonise the effects at beta receptors but leave the alpha-mediated effects unopposed, increasing the risk of hypertension and reflex bradycardia. They also antagonise the bronchodilating effects of $beta_2$ agonists. Severe anaphylaxis in patients taking non-cardioselective beta blockers may not respond to adrenaline (see below).

Hazardous interactions resulting in severe hypertension may occur with MAOIs (including RIMAs) and sympathomimetics, especially those that have indirect actions, since MAOIs increase the amount of noradrenaline stored in adrenergic nerve endings. Sympathomimetics for which the risk is particularly high include dexamfetamine, dopamine, dopexamine, ephedrine, isometheptene, mephentermine, metaraminol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine. The effects of direct-acting sympathomimetics such as adrenaline and noradrenaline may also be slightly enhanced. For additional warnings see under Phenelzine (p.418) and Moclobemide (p.411).

Tricyclic antidepressants block the inactivation of adrenaline and noradrenaline by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur. Conversely, the effect of indirectly-acting sympathomimetics could theoretically be reduced by tricyclics, although there is little clinical evidence that this occurs. There is also no evidence that an interaction occurs when local anaesthetic solutions containing adrenaline or noradrenaline are used in patients taking MAOIs or tricyclics, although great care needs to be taken to avoid inadvertent intravenous injection of these local anaesthetic preparations.

Interactions may also occur between sympathomimetics and drugs that have similar or opposing effects through non-adrenergic mechanisms. Sympathomimetics with central actions may potentiate the effects of CNS stimulants, while the vasoconstrictor and pressor effects of alpha agonists may be enhanced by drugs with similar effects, such as ergot alkaloids or oxytocin. $Beta_2$-mediated hypokalaemia may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, and aminophylline or theophylline; patients given high doses of $beta_2$ agonists with such drugs should have their plasma-potassium concentration monitored (see Interactions of Salbutamol, p.1132). Hypokalaemia may also contribute to the increased susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides.

Antiparkinsonian drugs. Additive cardiovascular toxicity may occur when some sympathomimetics are given with antiparkinsonian drugs such as *levodopa* (see p.808) and *bromocriptine* (see p.800). Severe hypertension may also occur with some sympathomimetics and *selegiline* (see p.818), possibly due to inhibition of peripheral monoamine oxidase.

Beta blockers. The interactions between beta blockers and sympathomimetics are complex and depend on the selectivity of both drugs. Patients given adrenaline (including the low doses used with local anaesthetics) while taking non-selective beta blockers such as *propranolol* can develop raised blood pressure due to alpha-mediated vasoconstriction, followed by reflex bradycardia, and occasionally cardiac arrest;[1] the bronchodilator effects of adrenaline and other $beta_2$ agonists are also inhibited. In contrast, cardioselective beta blockers such as *metoprolol*, have minimal effects on blood pressure and heart rate since they only inhibit the $beta_1$- mediated effects, leaving the $beta_2$-mediated vasodilatation to balance the vasoconstrictor effect. However, beta blockers that also have alpha-blocking effects, such as *carvedilol*, may cause hypotension since only the $beta_2$-induced vasodilatation remains; such an interaction has been reported with dobutamine.[2] Low doses of cardioselective beta blockers do not appear to interfere with sympathomimetic (isoprenaline)-induced bronchodilatation,[3] although the effect of larger doses is uncertain.

Propranolol has also been shown to inhibit the favourable pressor and bronchodilator responses to adrenaline when given for anaphylaxis.[4] Thus, patients on long-term treatment with some non-cardioselective beta blockers who develop anaphylaxis may be relatively refractory to adrenaline.

1. Jay GT, Chow MSS. Interaction of epinephrine and β-blockers. *JAMA* 1995; **274:** 1830–2.
2. Lindenfeld J, *et al.* Hypotension with dobutamine: β-adrenergic antagonist selectivity at low doses of carvedilol. *Ann Pharmacother* 1999; **33:** 1266–9.
3. Decalmer PBS, *et al.* Beta blockers and asthma. *Br Heart J* 1978; **40:** 184–9.
4. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; **47:** 35–7.

General anaesthetics. Anaesthesia may sensitise the myocardium to the effects of sympathomimetics, increasing the risk of arrhythmias, and fatalities have been attributed to the use of adrenaline with *halothane* anaesthesia.[1] It has been suggested[2] that the use of adrenaline for haemostasis during surgery is a particular risk, although use of a low dose may be safe in patients anaesthetised with *cyclopropane*, *halothane*, or similar volatile anaesthetics; other factors likely to increase the irritability of the myocardium, such as carbon-dioxide retention, hypoxia, or the use of cocaine, should be avoided.[2,3] For *halothane* or *trichloroethylene* anaesthesia a maximum strength for the adrenaline solution of 1 in 100 000, given at a rate not exceeding 10 mL in any 10-minute period or 30 mL in 1 hour, has been recommended;[3] this may also apply for cyclopropane, although the risk of arrhythmias is higher.[3] Other volatile anaesthetics generally appear to carry less risk.

1. Buzik SC. Fatal interaction? Halothane, epinephrine and tooth implant surgery. *Can Pharm J* 1990; **123:** 68–9 and 81.
2. Anonymous. Anaesthetics and the heart. *Lancet* 1967; **i:** 484–5.
3. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. *Anesthesiology* 1968; **29:** 763.

Theophylline. For discussion of possible interactions between sympathomimetics with beta-agonist actions and theophylline, see p.1145.

Vasodilators. Paradoxical hypotension may occur when sympathomimetics with both alpha- and beta-agonist properties are given with *tolazoline*, and there has been a report[1] of fatal hypotension in a patient given tolazoline and dopamine together. The mechanism of the interaction appears to be antagonism of the alpha-mediated vasoconstrictor effect of the sympathomimetic by the alpha-blocking effects of tolazoline, leaving the vasodilator effects unopposed.

1. Carlon GC. Fatal association of tolazoline and dopamine. *Chest* 1979; **76:** 336.

Actions and Uses

Sympathomimetics have actions that mimic the effects of stimulation of postganglionic (adrenergic) nerves. They include the endogenous catecholamines adrenaline, noradrenaline, and dopamine, and other drugs that directly stimulate adrenergic receptors, as well as drugs that have an indirect action by stimulating the release of noradrenaline from storage vesicles in adrenergic nerve endings. Phenylephrine is an example of a direct-acting sympathomimetic, whereas ephedrine and many other sympathomimetics have both direct and indirect effects.

The endogenous sympathomimetics are catecholamines, consisting of a catechol portion (characterised by hydroxy groups at adjacent positions on a benzene ring) and an aliphatic amine portion. Adrenaline and noradrenaline both have direct actions on adrenergic receptors, whereas dopamine has direct and indirect actions, as well as stimulating specific dopamine receptors. Although sympathetic nerves are generally termed adrenergic, the principal neurotransmitter is actually noradrenaline; it also acts as a neurotransmitter in the CNS. The major physiological role of adrenaline is metabolic. Dopamine is an important neurotransmitter within the CNS, but also has a role peripherally within the renal, mesenteric, and coronary vasculature.

Adrenergic receptors are classified as either alpha or beta receptors, and these are subdivided into a number of types. Dopamine receptors are a distinct group of receptors that are mainly found in the CNS, and at least 5 subtypes are known (see p.791); D_1 receptors also occur in some vascular beds. The effects of adrenergic stimulation depend on the location and activity of the receptors:

- $alpha_1$ receptors are found primarily in blood vessels, as well as in the skin, eye, bladder, uterus, and liver. Stimulation leads to vasoconstriction, particularly in the vessels of the skin and mucosa, abdominal viscera, and kidney; this results in an increase in blood pressure, sometimes with compensatory reflex bradycardia. $Alpha_1$ stimulation also results in contraction of other smooth muscle, including the urinary sphincter and the uterus, and induces mydriasis in the eye
- $alpha_2$ receptors are mainly found presynaptically. Stimulation appears to play a role in feedback inhibition of neurotransmitter release and may be involved in the inhibition of intestinal activity; it also plays a role in the inhibition of insulin secretion
- $beta_1$ receptors are found predominantly in the heart. Stimulation produces an increase in the rate and force of contraction, increased conduction velocity, and greater automaticity
- $beta_2$ receptors are mainly found in blood vessels and the lung, as well as in the uterus, the gastrointestinal tract, the liver, and the ciliary body of the eye. Stimulation leads to vasodilatation, bronchodilatation, uterine relaxation, and a decrease in gastrointestinal motility; it also results in release of insulin and enhances gluconeogenesis and glycogenolysis
- $beta_3$ receptors are found in fat cells and are thought to have a role in lipolysis and thermogenesis; they have also been found in the heart, uterus, and bladder but their role is not clear
- D_1 receptors are found in the renal, mesenteric, and coronary vascular beds. Stimulation leads to vasodilatation

Sympathomimetics differ in their relative affinity for each type of receptor, and also in whether they have direct or indirect actions (see Table 5, below). Their effects generally reflect these characteristics, although both may depend on the dose. Feedback mechanisms and the homoeostatic response of the body are also important. The specific effects of the different sympathomimetics are described in more detail in the individual monographs.

The endogenous catecholamines all have a very short action and are inactive by mouth; they are also highly polar and do not cross the blood-brain barrier. Other sympathomimetics are analogues of catecholamines but generally have a longer duration of action and are orally active; many also cross the blood-brain barrier and have central effects. For example, dexamfetamine has marked central stimulant effects, while the seemingly paradoxical antihypertensive action of $alpha_2$ agonists such as clonidine may be due to central effects that outweigh their effects in vascular smooth muscle.

The differing characteristics of the sympathomimetics mean that they are used in a wide range of disorders. Those with $alpha_1$-agonist effects are mainly used to increase the blood pressure in hypotensive disorders and in shock (p.1183). Some alpha agonists, such as phenylephrine (p.1568), are also applied topically to produce vasoconstriction of mucosal surfaces and are used for the symptomatic relief of nasal congestion and in eye disorders; they may also be used as mydriatics. $Alpha_2$ agonists are used as central antihypertensives (see Clonidine, p.1247), or in the treatment of glauco-

Table 5. Actions of sympathomimetics.

	Action		Receptor specificity			
	Direct	Indirect	α	β_1	β_2	DA*
Adrenaline	+		+	+	+	
Dobutamine	+		+	+	+	
Dopamine	+	+	+	+		+
Dopexamine	+	+			+	+
Ephedrine	+	+	+	+	+	
Etilefrine	+		+	+	+	
Ibopamine		+	+	+	+	+
Isoprenaline	+			+	+	
Mephentermine	+	+	+	+		
Metaraminol	+	+	+	+		
Methoxamine	+		+			
Midodrine	+		+			
Noradrenaline	+		+	+		
Phenylephrine	+		+			

* = Dopaminergic

ma (see Apraclonidine, p.1877). Beta$_1$ agonists are mainly used for their inotropic actions in acute heart failure and shock, while beta$_2$ agonists such as salbutamol (p.1131) are used for their bronchodilator effects and as uterine relaxants in premature labour. Sympathomimetics with mainly CNS effects may be used as central stimulants (see Dexamfetamine, p.2153).

Talinolol *(rINN)* ⊗

Talinololum. (±)-1-{*p*-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-phenyl}-3-cyclohexylurea.

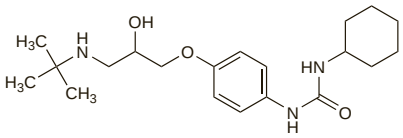
Талинолол

$C_{20}H_{33}N_3O_3$ = 363.5.

CAS — 57460-41-0.

ATC — C07AB13.

ATC Vet — QC07AB13.



Profile

Talinolol is a cardioselective beta blocker (p.1225). It is given orally in the management of hypertension (p.1171) and other cardiovascular disorders, in doses of up to 300 mg daily. It has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Cordanum†; ***Ger.:*** Cordanum; ***Rus.:*** Cordanum (Корданум).

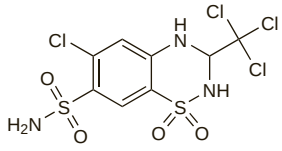
Teclothiazide Potassium *(BANM, rINNM)* ⊗

Kalii Teclothiazidum; Téclothiazide Potassique; Teclotiazida potásica; Tetrachlormethiazide Potassium. 6-Chloro-3,4-dihydro-3-trichloromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide potassium.

Калия Теклотиазид

$C_8H_7Cl_4N_3O_4S_2,K$ = 454.2.

CAS — 4267-05-4 (teclothiazide); 5306-80-9 (teclothiazide potassium).



(teclothiazide)

Profile

Teclothiazide potassium is a thiazide diuretic (see Hydrochlorothiazide, p.1307) used in the treatment of oedema.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Quimodril.

Tedisamil *(USAN, rINN)*

KC-8857; Tédisamil; Tedisamilum. 3′,7′-Bis(cyclopropylmethyl)-spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane].

Тедизамил

$C_{19}H_{32}N_2$ = 288.5.

CAS — 90961-53-8.

ATC — C01EB12.

ATC Vet — QC01EB12.

Profile

Tedisamil is an antiarrhythmic under investigation for the treatment of atrial arrhythmias.

◊ References.

1. Hohnloser SH, *et al*. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol* 2004; **44:** 99–104.

Telmisartan *(BAN, USAN, rINN)*

BIBR-277; BIBR-277-SE; Telmisartaani; Telmisartán; Telmisartanum. 4′-{[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl}-2-biphenylcarboxylic acid.

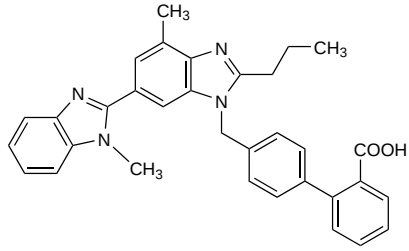
Тельмизартан

$C_{33}H_{30}N_4O_2$ = 514.6.

CAS — 144701-48-4.

ATC — C09CA07.

ATC Vet — QC09CA07.



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

Ph. Eur. 6.2 (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. it dissolves in 1M sodium hydroxide. It exhibits polymorphism.

Adverse Effects and Precautions

As for Losartan Potassium, p.1326. Telmisartan should be used with caution in patients with hepatic impairment or biliary obstruction.

◊ References.

1. Michel MC, *et al*. Safety of telmisartan in patients with arterial hypertension : an open-label observational study. *Drug Safety* 2004; **27:** 335–44.

Interactions

As for Losartan Potassium, p.1327.

Digoxin. Telmisartan may increase serum concentrations of digoxin (see Angiotensin II Receptor Antagonists under Interactions of Digoxin, p.1261) but the interaction is probably not clinically significant.

Pharmacokinetics

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% after a 40-mg dose and 58% after a 160-mg dose. Peak plasma concentrations of telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours.

◊ References.

1. Stangier J, *et al*. Absorption, metabolism, and excretion of intravenously and orally administered [C]telmisartan in healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1312–22.

Uses and Administration

Telmisartan 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).

Telmisartan is given orally. After a dose the hypotensive effect peaks within 3 hours and persists for at least 24 hours. The maximum hypotensive effect occurs within about 4 to 8 weeks after starting therapy.

In hypertension, telmisartan is given in an initial dose of 40 mg once daily. This may be increased, if necessary, to a maximum dose of 80 mg once daily. Lower doses should be considered in patients with hepatic or renal impairment (see below).

◊ Reviews.

1. McClellan KJ, Markham A. Telmisartan. *Drugs* 1998; **56:** 1039–44.
2. Sharpe M, *et al*. Telmisartan: a review of its use in hypertension. *Drugs* 2001; **61:** 1501–29.
3. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs* 2006; **66:** 51–83.
4. Gosse P. A review of telmisartan in the treatment of hypertension: blood pressure control in the early morning hours. *Vasc Health Risk Manag* 2006; **2:** 195–201.
5. Yamagishi S, *et al*. Potential utility of telmisartan, an angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor-γ (PPAR-γ)-modulating activity for the treatment of cardiometabolic disorders. *Curr Mol Med* 2007; **7:** 463–9.
6. Francischetti EA, *et al*. Treatment of hypertension in individuals with the cardiometabolic syndrome: role of an angiotensin II receptor blocker, telmisartan. *Expert Rev Cardiovasc Ther* 2008; **6:** 289–303.

Administration in hepatic or renal impairment. Giving telmisartan to patients with hepatic impairment resulted in an increase in bioavailability and a reduction in clearance compared with healthy subjects.[1] Although telmisartan was well tolerated, it was suggested that lower doses should be considered in patients with hepatic impairment. In the UK telmisartan is contraindicated in severe hepatic impairment and a maximum dose of 40 mg once daily is recommended for patients with mild to moderate impairment

Telmisartan appears to be well tolerated in patients with renal impairment, including those on dialysis.[2] However, in the UK, an initial dose of 20 mg once daily is recommended for patients with severe renal impairment or on haemodialysis.

1. Stangier J, *et al*. Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. *J Clin Pharmacol* 2000; **40:** 1355–64.
2. Sharma AM, *et al*. Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol* 2005; **63:** 250–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Gliosartan; Micardis; Pritor†; ***Austral.:*** Micardis; Pritor†; ***Austria:*** Micardis; ***Belg.:*** Kinzalmono; Micardis; ***Braz.:*** Micardis; Pritor; ***Canad.:*** Micardis; ***Chile:*** Micardis; Pritoral†; Samertan; ***Cz.:*** Kinzalmono; Micardis; Pritor; ***Denm.:*** Kinzalmono†; Micardis; ***Fin.:*** Kinzalmono; Micardis; ***Fr.:*** Micardis; Pritor; ***Ger.:*** Kinzalmono; Micardis; ***Gr.:*** Micardis; Pritor; ***Hong Kong:*** Micardis; ***Hung.:*** Micardis; Pritor; ***India:*** Telma; Telpres; ***Indon.:*** Micardis; ***Irl.:*** Micardis; ***Ital.:*** Micardis; Pritor; ***Jpn:*** Micardis; ***Malaysia:*** Micardis; ***Mex.:*** Micardis; Predxal; ***Neth.:*** Kinzalmono; Micardis; Pritor; ***Norw.:*** Micardis; ***NZ:*** Micardis; ***Philipp.:*** Micardis; Pritor; ***Pol.:*** Micardis; Pritor; ***Port.:*** Kinzalmono; Micardis; Pritor; ***Rus.:*** Micardis (Микардис); Pritor (Прайтор); ***S.Afr.:*** Micardis; ***Singapore:*** Micardis; ***Spain:*** Micardis; Pritor; ***Swed.:*** Kinzalmono†; Micardis; ***Switz.:*** Kinzal; Micardis; ***Thai.:*** Micardis; ***Turk.:*** Micardis; Pritor; ***UK:*** Micardis; ***USA:*** Micardis; ***Venez.:*** Micardis; Pritor.

Multi-ingredient: ***Arg.:*** Gliosartan Plus; Micardis Plus; ***Austral.:*** Micardis Plus; ***Austria:*** MicardisPlus; ***Belg.:*** Kinzalkomb; Micardis Plus; ***Braz.:*** Micardis HCT; Pritor HCT; ***Canad.:*** Micardis Plus; ***Chile:*** Micardis Plus; ***Cz.:*** Kinzalkomb; MicardisPlus; PritorPlus; ***Denm.:*** Kinzalkomb†; MicardisPlus; ***Fin.:*** Kinzalkomb; MicardisPlus; ***Fr.:*** MicardisPlus; PritorPlus; ***Ger.:*** Kinzalkomb; MicardisPlus; ***Gr.:*** Micardis Plus; Pritor Plus; ***Hong Kong:*** Micardis Plus; ***Hung.:*** MicardisPlus; PritorPlus; ***India:*** Telma-H†; Telpres-H; ***Indon.:*** Micardis Plus; ***Irl.:*** MicardisPlus; ***Ital.:*** Micardis Plus; PritorPlus; ***Malaysia:*** Micardis Plus; ***Mex.:*** Micardis Plus; Predxal Plus; ***Neth.:*** Kinzalkomb; Micardis Plus; PritorPlus; ***Norw.:*** MicardisPlus; ***Philipp.:*** Micardis Plus; PritorPlus; ***Pol.:*** Micardis Plus; Pritor Plus; ***Port.:*** Kinzalkomb; Micardis Plus; PritorPlus; ***Rus.:*** MicardisPlus (МикардисПлюс); ***S.Afr.:*** Co-Micardis; ***Singapore:*** Micardis Plus; ***Spain:*** Micardis Plus; Pritor Plus; ***Swed.:*** Kinzalkomb†; Micardis Plus; ***Switz.:*** Kinzalplus; MicardisPlus; ***Thai.:*** Micardis Plus; ***Turk.:*** Micardis Plus; Pritor Plus; ***UK:*** MicardisPlus; ***USA:*** Micardis HCT; ***Venez.:*** Micardis Plus; Pritor Plus.

Temocapril Hydrochloride *(BANM, USAN, rINNM)*

CS-622; Hidrocloruro de temocapril; Témocapril, Chlorhydrate de; Temocaprili Hydrochloridum. (+)-(2*S*,6*R*)-6-{[(1*S*)-1-Ethoxycarbonyl-3-phenylpropyl]amino}tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid hydrochloride.

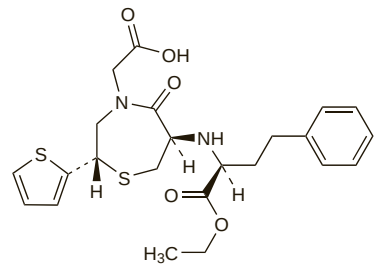
Темокаприла Гидрохлорид

$C_{23}H_{28}N_2O_5S_2$,HCl = 513.1.

CAS — 111902-57-9 (temocapril); 110221-44-8 (temocapril hydrochloride).

ATC — C09AA14.

ATC Vet — QC09AA14.



(temocapril)

Profile

Temocapril is an ACE inhibitor (p.1193) that has been used in the treatment of hypertension (p.1171). It owes its activity to the di-acid temocaprilat to which it is converted after oral doses.

◊ References.

1. Nakashima M, *et al*. Pharmacokinetics of temocapril hydrochloride, a novel angiotensin converting enzyme inhibitor, in renal insufficiency. *Eur J Clin Pharmacol* 1992; **43:** 657–9.