Trimetaphan Camsilate *(BAN, rINN)*

Cansilato de trimetafán; Méthioplégium; Trimetaphan Camphorsulfonate; Trimétaphan, Camsilate de; Trimetaphan Camsylate; Trimetaphani Camsilas; Trimetaphani Camsylas; Trimethaphan Camsylate. (+)-1,3-Dibenzylperhydro-2-oxothieno-[1′,2′:1,2]thieno[3,4-*d*]-imidazol-5-ium 2-oxobornane-10-sulfonate; 4,6-Dibenzyl-4,6-diaza-1-thioniatricyclo[6.3.0.0^{3,7}]undecan-5-one 2-oxobornane-10-sulfonate.

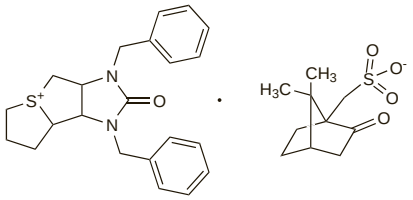
Триметафана Камзилат

$C_{22}H_{25}N_2OS,C_{10}H_{15}O_4S$ = 596.8.

CAS — 7187-66-8 (trimetaphan); 68-91-7 (trimetaphan camsilate).

ATC — C02BA01.

ATC Vet — QC02BA01.



Incompatibility. Trimetaphan is incompatible with thiopental sodium, gallamine triethiodide, iodides, bromides, and strongly alkaline solutions.

Adverse Effects and Treatment

The adverse effects of trimetaphan are mainly due to ganglionic blockade. A reduction in gastrointestinal motility may cause constipation and, on prolonged use, paralytic ileus. Urinary retention, cycloplegia, mydriasis, tachycardia, precipitation of angina, and gastrointestinal disturbances such as anorexia, nausea, or vomiting, may occur. Orthostatic hypotension may be severe. Rapid intravenous infusion can result in respiratory arrest. Other adverse effects include raised intra-ocular pressure, dry mouth, hypoglycaemia, hypokalaemia, fluid retention, weakness, urticaria, and itching. Trimetaphan crosses the placenta and can cause paralytic or meconium ileus in the neonate.

If severe hypotension occurs, trimetaphan should be stopped and the patient positioned with the head lower than the feet. A vasopressor may be given cautiously if necessary.

Effects on the eyes. Although trimetaphan may increase intraocular pressure, a sudden and dramatic reduction of intra-ocular pressure to very low levels was noted in 5 patients undergoing surgery when the systolic blood pressure was reduced to 60 mmHg with trimetaphan infusion.[1]

1. Dias PLR, *et al*. Effect on the intraocular pressure of hypotensive anaesthesia with intravenous trimetaphan. *Br J Ophthalmol* 1982; **66:** 721–4.

Precautions

Trimetaphan should be avoided in patients with asphyxia or respiratory insufficiency, uncorrected anaemia, shock or hypovolaemia, severe arteriosclerosis, severe ischaemic heart disease, or pyloric stenosis and should only be used with extreme caution in those with hepatic or renal impairment, degenerative disease of the CNS, Addison's disease, prostatic hyperplasia, glaucoma, cerebral or coronary vascular insufficiency, and diabetes. It should be used with care in elderly or debilitated patients and should be avoided in pregnancy. Owing to a histamine-liberating effect it should be used with caution in allergic subjects.

Interactions

Trimetaphan should be used with caution in patients being treated with other antihypertensives, drugs that depress cardiac function, or muscle relaxants, and in those taking NSAIDs or corticosteroids. The hypotensive effect is enhanced by general and spinal anaesthetics. Adrenaline should not be infiltrated locally at the site of incision when trimetaphan is being given since this may antagonise the effect of trimetaphan.

Neuromuscular blockers. For a reference to possible potentiation of neuromuscular blockade by trimetaphan, see Ganglion Blockers, under Interactions of Atracurium, p.1904.

Uses and Administration

Trimetaphan is a ganglion blocker that inhibits the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. The sympathetic blockade produces peripheral vasodilatation. Trimetaphan also has a direct vasodilator effect on peripheral blood vessels. It has been used for inducing controlled hypotension during surgical procedures; it acts rapidly to produce a hypotensive response which persists for about 10 to 15 minutes. Trimetaphan has also been used for the emergency treatment of hypertensive crises (p.1171), especially in the presence of pulmonary oedema or acute dissecting aortic aneurysms. However, sodium nitroprusside is now preferred.

Trimetazidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimetazidina; Trimetatsidiinidihydrokloridi; Trimetazidin Hidroklorür; Trimetazidindihidroklorid; Trimetazidindihydrochlorid; Trimetazidindihydroklorid; Trimétazidine, Chlorhydrate de; Trimétazidine, dichlorhydrate de; Trimetazidine Dihydrochloride; Trimetazidini dihydrochloridum; Trimetazidini Hydrochloridum; Trimetazidino hidrochloridas; Trimetazine Hydrochloride. 1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride.

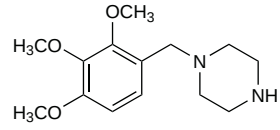
Триметазидина Гидрохлорид

$C_{14}H_{22}N_2O_3$,2HCl = 339.3.

CAS — 5011-34-7 (trimetazidine); 13171-25-0 (trimetazidine hydrochloride).

ATC — C01EB15.

ATC Vet — QC01EB15.



(trimetazidine)

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

Ph. Eur. 6.2 (Trimetazidine Dihydrochloride; Trimetazidine Hydrochloride BP 2008). A slightly hygroscopic, white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Trimetazidine hydrochloride is used in angina pectoris (p.1157) and in ischaemia of neurosensorial tissues as in Ménière's disease (p.564); 40 to 60 mg is given daily by mouth in divided doses.

◊ References.

1. McClellan KJ, Plosker GL. Trimetazidine: a review of its use in stable angina pectoris and other coronary conditions. *Drugs* 1999; **58:** 143–57.
2. Ciapponi A, *et al*. Trimetazidine for stable angina. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/06).
3. Danchin N. Clinical benefits of a metabolic approach with trimetazidine in revascularized patients with angina. *Am J Cardiol* 2006; **98** (suppl): 8J–13J.

Effects on the nervous system. Eight elderly patients aged between 72 and 94 years were reported[1] to have developed signs of parkinsonism while taking trimetazidine; the parkinsonism regressed completely when the drug was stopped. A retrospective study[2] found that adverse effects on motor function, including parkinsonism, gait disorders, and tremor, occurred in 56 of 130 patients taking trimetazidine and were more common in older patients.

1. Marti Massó JF. Parkinsonismo por trimetazidina. *Neurologia* 2004; **19:** 392–5.
2. Martí Massó J-F, *et al*. Trimetazidine induces parkinsonism, gait disorders and tremor. *Therapie* 2005; **60:** 419–22.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Vastarel; ***Austria:*** Vastarel; ***Braz.:*** Vastarel; ***Chile:*** Vastarel; ***Cz.:*** Adexor; Preductal; ***Denm.:*** Vastarel; ***Fr.:*** Centrophene†; Vastarel; ***Gr.:*** Atanol; Imovexil; Intervein; Latrimet†; Liomagen; Novazidine; Trimedin; Trimedor; Trimevert; Vastarel; Zidin; ***Hong Kong:*** Vastarel; ***Hung.:*** Adexor; Preductal; ***India:*** Flavedon; Mayozest; Metacard; Metagard; Trivedon; ***Indon.:*** Trizedon; ***Irl.:*** Vastarel; ***Ital.:*** Vastarel; ***Malaysia:*** Metagard; Vastarel; ***Philipp.:*** Angirel; Vastarel; ***Pol.:*** Metazydyna; Preductal; Trimetaratio; ***Port.:*** Tacirel; Vastarel; ***Rus.:*** Deprenorm (Депренорм); Medarum (Медарум); Preductal (Предуктал); Rimecor (Римекор); Trimetazide (Триметазид); ***Singapore:*** Metagard; Vastarel; ***Spain:*** Idaptan; Vaso Rimal†; ***Thai.:*** Matenol; Trizidine; Vastarel; Vastinol; ***Turk.:*** Vastarel; ***Venez.:*** Vastarel.

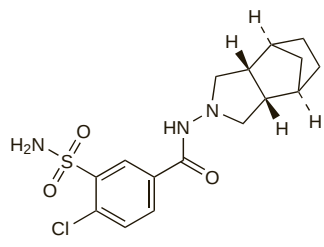
Tripamide *(USAN, rINN)* ⊗

ADR-033; E-614; Tripamida; Tripamidum. 4-Chloro-*N*-(*endo*-hexahydro-4,7-methanoisoindolin-2-yl)-3-sulphamoylbenzamide.

Трипамид

$C_{16}H_{20}ClN_3O_3S$ = 369.9.

CAS — 73803-48-2.



Profile

Tripamide is a diuretic structurally related to indapamide. It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Part 3)
Thai.: Normonal.

Urapidil *(BAN, rINN)*

B-66256M; Urapidili; Urapidilum. 6-[3-(4-o-Methoxyphenylpiperazin-1-yl)propylamino]-1,3-dimethyluracil.

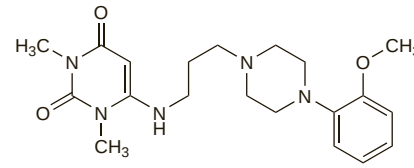
Урапидил

$C_{20}H_{29}N_5O_3$ = 387.5.

CAS — 34661-75-1.

ATC — C02CA06.

ATC Vet — QC02CA06.



Pharmacopoeias. In *Jpn.*

Urapidil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de urapidil; Urapidil, Chlorhydrate d'; Urapidili Hydrochloridum.

Урапидила Гидрохлорид

$C_{20}H_{29}N_5O_3$,HCl = 423.9.

CAS — 64887-14-5.

ATC — C02CA06.

ATC Vet — QC02CA06.

Adverse Effects and Precautions

Urapidil is reported to be well-tolerated, with adverse effects generally transient and most frequent at the beginning of therapy. Dizziness, nausea, headache, fatigue, orthostatic hypotension, palpitations, nervousness, pruritus, and allergic skin reactions have been reported.

It should be used with care in elderly patients and those with severe hepatic impairment. Intravenous urapidil should not be used in patients with aortic stenosis.

Urinary incontinence. Enuresis was reported[1] to be associated with the use of urapidil in 2 elderly patients.

1. Jonville A-P, *et al*. Urapidil and enuresis. *Lancet* 1992; **339:** 688.

Pharmacokinetics

After oral doses urapidil is rapidly absorbed with a reported bioavailability of 70 to 80%. It is reported to be about 80% bound to plasma proteins. Urapidil is extensively metabolised in the liver, mainly by hydroxylation, and excreted mostly in urine, as metabolites and 10 to 20% of unchanged drug. The elimination half-life is reported to be about 4.7 hours when given orally as capsules and about 2.7 hours after intravenous dosage.

◊ Reviews.

1. Kirsten R, *et al*. Clinical pharmacokinetics of urapidil. *Clin Pharmacokinet* 1988; **14:** 129–40.

Uses and Administration

Urapidil is an antihypertensive drug that is reported to block peripheral alpha$_1$ adrenoceptors (see Alpha Blockers, p.1153) and to have central actions. It produces a reduction in peripheral resistance and a fall in systolic and diastolic blood pressure, usually without reflex tachycardia.

Urapidil is used in the management of hypertension (p.1171), including hypertensive crises.

Urapidil is given orally as the base and intravenously as the hydrochloride, but doses are usually expressed in terms of the base. Urapidil hydrochloride 10.94 mg is equivalent to about 10 mg of urapidil. Urapidil fumarate has also been given orally.

In hypertension doses of 30 to 90 mg are given twice daily by mouth. In hypertensive crises a suggested regimen is to give an initial dose of 25 mg by slow intravenous injection over 20 seconds, repeated if necessary after 5 minutes. This may be followed by a dose of 50 mg after a further 5 minutes if the response is still inadequate. Treatment should continue with a maintenance infusion of 9 to 30 mg/hour once the blood pressure is sufficiently reduced.

◊ Reviews.

1. Dooley M, Goa KL. Urapidil: a reappraisal of its use in the management of hypertension. *Drugs* 1998; **56:** 929–55.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ebrantil; ***Belg.:*** Ebrantil; ***Cz.:*** Ebrantil; ***Fr.:*** Eupressyl; Mediatensyl; ***Ger.:*** Ebrantil; ***Hung.:*** Ebrantil; ***Ital.:*** Ebrantil; ***Neth.:*** Ebrantil; ***Pol.:*** Ebrantil; ***Port.:*** Ebrantil; ***Spain:*** Elgadil; ***Switz.:*** Ebrantil.

Urokinase *(BAN, USAN, rINN)*

Urokinaasi; Urokinas; Urokinasa; Urokinasum; Ürokinaz; Urokináz; Urokinazė; Uroquinasa.

Урокиназа

CAS — 9039-53-6.
ATC — B01AD04.
ATC Vet — QB01AD04.

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

Ph. Eur. 6.2 (Urokinase). An enzyme isolated from human urine that activates plasminogen. It consists of a mixture of low (33 000) and high (54 000) molecular mass forms, the high molecular mass form being predominant. The potency is not less than 70 000 international units per mg of protein. A white or almost white, amorphous powder. Soluble in water. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. Solutions of urokinase containing 2500 to 25 000 units/mL were found to be stable in single-use syringes when stored at –30° for 30 days and also when stored frozen for 7 days, thawed, and refrozen for a further 23 days.[1]

1. Dedrick SC, Ramirez-Rico J. Potency and stability of frozen urokinase solutions in syringes. *Am J Health-Syst Pharm* 2004; **61:** 1586–9.

Units

The potency of urokinase is expressed in international units. Preparations are assayed using the first International Reference Preparation (1968), a mixture of low-molecular-weight and high-molecular-weight urokinases. The first International Standard for high-molecular-weight urokinase was established in 1989 for use with preparations of this type of urokinase.

Potency used to be expressed in Ploug or Plough units or in CTA units, but these now appear to be obsolete.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402. Serious allergic reactions may be less likely to occur with urokinase than with streptokinase.

Hypersensitivity. Allergic reactions are considered to be less frequent with urokinase than with streptokinase. However, in a series of 6 patients who had previously been treated with streptokinase,[1] thrombolytic therapy with urokinase for recurrent myocardial infarction was associated with rigors in 4 patients, 2 of whom also developed bronchospasm. None of the patients had any history of atopy.

1. Matsis P, Mann S. Rigors and bronchospasm with urokinase after streptokinase. *Lancet* 1992; **340:** 1552.

Transmission of infection. Some preparations of urokinase are produced in cultures of human cells and there is a risk of transmission of infection associated with their use.

Interactions

As for Streptokinase, p.1404.

Pharmacokinetics

After intravenous infusion urokinase is cleared rapidly from the circulation by the liver. A plasma half-life of up to 20 minutes has been reported.

Uses and Administration

Urokinase is a thrombolytic produced by the kidney and found in human urine. It directly converts plasminogen to plasmin, a proteolytic enzyme with fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Urokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p.1156).

Urokinase is used similarly to streptokinase (p.1404) in the management of thromboembolic disorders including venous thromboembolism (pulmonary embolism and deep-vein thrombosis; p.1189) and peripheral arterial thromboembolism (p.1178). It is also used to clear occluded catheters and cannulas. Urokinase has been used in myocardial infarction and for clearing clots after haemorrhage within the eye.

In the treatment of **venous thromboembolism**, urokinase is given by intravenous infusion in an initial dose of 4400 units/kg over 10 minutes. This is followed by 4400 units/kg per hour for 12 hours in pulmonary embolism, and for 12 to 24 hours in deep-vein thrombosis. Alternatively, patients with pulmonary embolism may be given a bolus injection of 15 000 units/kg into the pulmonary artery; the injection may be repeated, with the dose adjusted according to plasma-fibrinogen concentration, up to 3 times in 24 hours.

In the treatment of **peripheral arterial thromboembolism**, a solution containing urokinase 2000 units/mL is infused into the clot via a catheter at a rate of 4000 units/minute for 2 hours. Angiography should then be performed and, if flow has not resumed, the catheter should be advanced into the occluded vessel and the infusion continued at the same rate for a further 2 hours. The procedure may be repeated, if necessary, up to 4 times. Once blood flow is re-established, the catheter should be partially withdrawn and infusion continued at a rate of 1000 units/minute until the remaining clot has lysed; a dose of 500 000 units given over 8 hours is usually sufficient.

For **clearing occluded intravenous catheters or cannulas**, 5000 to 25 000 units of urokinase dissolved in 2 mL of sodium chloride 0.9% may be instilled into the device and clamped off for up to 4 hours; the lysate is then aspirated and the procedure repeated if necessary. Alternatively, a solution of 5000 units of urokinase in 200 mL of sodium chloride 0.9% may be infused into the device over 30 minutes.

Catheters and cannulas. For reference to the use of urokinase to maintain patency of long-term venous access devices, see under Uses for Alteplase, p.1208.

Preparations

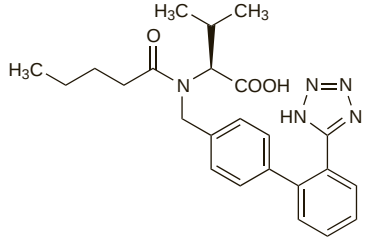
Proprietary Preparations (details are given in Part 3)
Austria: Abbokinase; Actosolv; ***Belg.:*** Actosolv; ***Cz.:*** Rheotromb; ***Ger.:*** Corase; Rheotromb; ***Gr.:*** Ukidan†; Urochinasi; ***Hung.:*** Rheotromb; ***India:*** Solokinase; Ukidan†; Uni-Kinase; ***Israel:*** Abbokinase; ***Ital.:*** Actosolv†; Alfakinasi†; Kisolv†; Persolv Richter†; ***Jpn:*** Uronase; ***Neth.:*** Medacinase; ***Port.:*** Ukidan†; ***Spain:*** Uroquidan; ***Swed.:*** Abbokinase†; ***UK:*** Syner-Kinase; ***USA:*** Abbokinase.

Valsartan *(BAN, USAN, rINN)*

CGP-48933; Valsartaani; Valsartán; Valsartanum. *N*-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine; *N*-Pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine.

Вальзартан

$C_{24}H_{29}N_5O_3$ = 435.5.
CAS — 137862-53-4.
ATC — C09CA03.
ATC Vet — QC09CA03.



Pharmacopoeias. In *US.*

USP 31 (Valsartan). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Suspension. The US licensed product information provides the following method for making 160 mL of a suspension containing valsartan 4 mg/mL:

- add 80 mL of *Ora-Plus* (*Paddock, USA*) to an amber glass bottle containing eight 80-mg tablets (*Diovan, Novartis*) and shake for at least 2 minutes
- allow to stand for at least 1 hour then shake again for at least 1 minute
- add 80 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and shake for at least 10 seconds

The suspension can be stored for 30 days at or below 30° or for up to 75 days at 2° to 8°.

Adverse Effects and Precautions

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

Interactions

As for Losartan Potassium, p.1327.

Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23%. Peak plasma concentrations of valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolised and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose about 83% is excreted in the faeces and 13% in urine.

◊ References.

1. Brookman LJ, *et al.* Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; **62:** 272–8.
2. Prasad PP, *et al.* Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *J Cardiovasc Pharmacol* 2002; **40:** 801–7.

Uses and Administration

Valsartan 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), to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction (p.1175), and in the management of heart failure (see under Losartan Potassium, p.1327).

Valsartan is given orally. After a dose the hypotensive effect occurs within 2 hours, reaches a peak within 4 to 6 hours, and persists for over 24 hours. The maximum hypotensive effect is achieved within 2 to 4 weeks.

In **hypertension**, valsartan is given in an initial dose of 80 mg once daily. This may be increased, if necessary, to 160 mg once daily; the maximum dose is 320 mg once daily. A lower initial dose of 40 mg once daily may be used in elderly patients over 75 years, and in those with intravascular volume depletion.

In **heart failure,** valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

In patients who have had **myocardial infarction**, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, in an initial dose of 20 mg twice daily; the dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated.

Valsartan should be used with caution in patients with hepatic or renal impairment and dose reduction may be required (see below).

◊ Reviews.

1. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54:** 299–311.
2. Ripley TL. Valsartan in chronic heart failure. *Ann Pharmacother* 2005; **39:** 460–9.
3. Mistry NB, *et al.* The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7:** 575–81.
4. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vasc Health Risk Manag* 2007; **3:** 425–30.

Administration in children. Valsartan may be used for hypertension in children aged 6 to 16 years. US licensed product information recommends an initial dose of 1.3 mg/kg once daily (up to a maximum of 40 mg). The dose should be adjusted according to response, but doses above 2.7 mg/kg daily have not been studied. A suspension formulation may be used (see Suspension, above) but exposure to valsartan may be higher with the suspension than with tablets. There is no experience with valsartan in children with renal impairment (creatinine clearance below 30 mL/minute per 1.73 m^2) and it should therefore not be used in such children.

Administration in hepatic or renal impairment. The elimination of valsartan may be reduced in patients with hepatic impairment or biliary obstruction and it should be used with caution, if at all, in such patients; dose reductions may be required. In the UK, valsartan is contra-indicated in patients with severe hepatic impairment, cirrhosis, or biliary obstruction. In mild to moderate hepatic impairment an initial dose of 40 mg once daily and a maximum dose of 80 mg once daily is recommended for hypertension, and the dose after myocardial infarction should not generally exceed 80 mg twice daily.

Lower doses of valsartan may also be considered in patients with renal impairment. In the UK, an initial dose of 40 mg once daily is recommended for the treatment of hypertension in patients