tions of alkali hydroxides and slightly soluble in dilute acids. Protect from light.

USP 31 (Torsemide). A white to off-white, crystalline powder. Practically insoluble in water and in ether; slightly soluble in alcohol, in methyl alcohol, in 0.1N sodium hydroxide, and in 0.1N hydrochloric acid; very slightly soluble in acetone and in chloroform.

Adverse Effects and Precautions

As for Furosemide, p.1292.

Interactions

As for Furosemide, p.1293.

Pharmacokinetics

Torasemide is well absorbed from the gastrointestinal tract. Peak serum concentrations are achieved within 1 hour of oral doses. Torasemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. Metabolism takes place in the liver and inactive metabolites are excreted in the urine. The elimination half-life of torasemide is about 3.5 hours. Torasemide is extensively bound to plasma proteins. In patients with heart failure both hepatic and renal clearance are reduced. In patients with renal impairment, the renal clearance is reduced but total plasma clearance is not significantly altered.

◊ References.

1. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clin Pharmacokinet* 1998; **34:** 1–24.
2. Vormfelde SV, *et al.* CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther* 2004; **76:** 557–66.

Uses and Administration

Torasemide is a loop diuretic with actions similar to those of furosemide (p.1294).

Torasemide is used for oedema associated with heart failure (p.1165), including pulmonary oedema, and with renal and hepatic disorders. It is also used in the treatment of hypertension (p.1171), either alone or with other antihypertensives.

Diuresis after oral use starts within 1 hour, reaches a maximum in about 1 to 2 hours, and lasts for up to 8 hours; after intravenous injection its effects are evident within 10 minutes but like oral use can last up to 8 hours.

In the treatment of **oedema** the usual oral dose is 5 mg once daily increased according to response to 20 mg once daily; doses of up to 40 mg daily have been required in some patients. Torasemide may also be given intravenously in usual initial doses of 10 to 20 mg daily. Higher doses may sometimes be necessary, especially in oedema of renal origin; the dose should be increased stepwise as necessary to a maximum of 200 mg daily, although doses should not exceed 40 mg daily in patients with hepatic cirrhosis.

In the treatment of **hypertension** torasemide is given in initial oral doses of 2.5 to 5 mg daily; US licensed product information allows the dose to be increased to 10 mg daily if required, although UK licensed product information suggests that doses above 5 mg are unlikely to produce additional benefit.

◊ Reviews.

1. Blose JS, *et al.* Torsemide: a pyridine-sulfonylurea loop diuretic. *Ann Pharmacother* 1995; **29:** 396–402.
2. Dunn CJ, *et al.* Torasemide: an update of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; **49:** 121–42.
3. Brater DC. Benefits and risks of torasemide in congestive heart failure and essential hypertension. *Drug Safety* 1996; **14:** 104–120.
4. Ishido H, Senzaki H. Torasemide for the treatment of heart failure. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 127–32.

Preparations

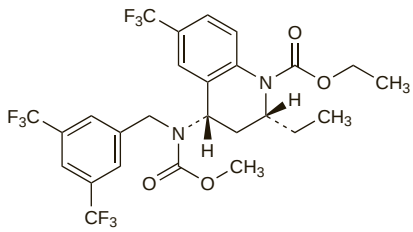
Proprietary Preparations (details are given in Part 3)
Arg.: Torem; ***Austria:*** Unat; ***Belg.:*** Torrem; ***Chile:*** Unat†; ***Cz.:*** Diuver; Trifas†; ***Ger.:*** Toracard; Toragamma; Torasid; Torem; Unat; ***Hong Kong:*** Unat; ***India:*** Dytor; ***Ital.:*** Diuremid; Diuresix; Toradiur; ***Jpn:*** Luprac; ***Pol.:*** Diuver; Trifas; ***Rus.:*** Diuver (Диувер); ***S.Afr.:*** Unat; ***Spain:*** Dilutol; Isodiur; Sutril; Tadegan; ***Swed.:*** Torem; ***Switz.:*** Toramide; Torasem; Torasis; Torem; ***Thai.:*** Unat; ***UK:*** Torem; ***USA:*** Demadex.

Torcetrapib *(USAN, rINN)*

CP-529414; Torcétrapib; Torcetrapibum. Ethyl (2*R*,4*S*)-4-{[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl)amino}-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate.

Торцетрапиб

$C_{26}H_{25}F_9N_2O_4$ = 600.5.
CAS — 262352-17-0.



Profile

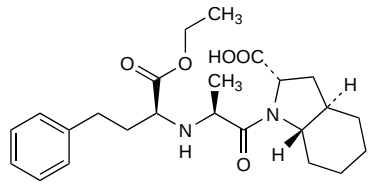
Torcetrapib is a cholesteryl ester transfer protein inhibitor. It increases plasma concentrations of high-density lipoprotein (HDL)-cholesterol and has been investigated in the management of lipid disorders. Development was stopped after the finding of increased mortality associated with torcetrapib in randomised, controlled studies.

Trandolapril *(BAN, rINN)*

RU-44570; Trandolapriili; Trandolaprilum; Trandolapryl. Ethyl (2*S*,3a*R*,7a*S*)-1-{(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl}hexahydro-2-indolinecarboxylate; (2*S*,3a*R*,7a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}perhydroindole-2-carboxylic acid.

Трандолаприл

$C_{24}H_{34}N_2O_5$ = 430.5.
CAS — 87679-37-6.
ATC — C09AA10.
ATC Vet — QC09AA10.



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

Ph. Eur. 6.2 (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Trandolapril acts as a prodrug of the diacid trandolaprilat, its active metabolite. After oral doses of trandolapril the bioavailability of trandolaprilat is 40 to 60%. Trandolapril is metabolised in the liver to trandolaprilat and to some inactive metabolites. Peak plasma concentrations of trandolaprilat are achieved 4 to 6 hours after an oral dose of trandolapril. Trandolaprilat is more than 80% bound to plasma proteins. About 33% of an oral dose of trandolapril is excreted in the urine, mainly as trandolaprilat; the rest is excreted in the faeces. The effective half-life for accumulation of trandolaprilat is 16 to 24 hours after multiple doses of trandolapril.

Impaired renal function decreases the excretion of trandolaprilat. Trandolaprilat is removed by haemodialysis.

◊ References.

1. Bevan EG, *et al.* Effect of renal function on the pharmacokinetics and pharmacodynamics of trandolapril. *Br J Clin Pharmacol* 1993; **35:** 128–35.

Uses and Administration

Trandolapril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and in left ventricular dysfunction following myocardial infarction (p.1175).

Trandolapril owes its activity to trandolaprilat to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after 8 to 12 hours. The haemodynamic action lasts for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** the initial oral dose is 500 micrograms 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. In patients already taking a diuretic, the diuretic should be stopped, if possible, 2 to 3 days before starting trandolapril and resumed later if necessary. In patients with co-existing heart failure treatment with trandolapril should begin under close medical supervision. The usual maintenance dose for hypertension is 1 to 2 mg once daily, although up to 4 mg daily may be given, as a single dose or in 2 divided doses.

In **myocardial infarction**, treatment with trandolapril may be started 3 days after the infarction in an initial dose of 500 micrograms once daily, gradually increased to a maximum of 4 mg once daily.

A reduction in dosage may be necessary in patients with renal impairment (see below).

◊ References.

1. Zannad F. Trandolapril: How does it differ from other angiotensin converting enzyme inhibitors? *Drugs* 1993; **46** (suppl 2): 172–82.
2. Wiseman LR, McTavish D. Trandolapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. *Drugs* 1994; **48:** 71–90.
3. Køber L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; **333:** 1670–6.
4. Peters DC, *et al.* Trandolapril: an update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 1998; **56:** 871–93.

Administration in renal impairment. The initial dose of trandolapril in patients with renal impairment should not exceed 500 micrograms daily. UK licensed product information states that the maximum maintenance dose should be 2 mg daily in patients with a creatinine clearance of less than 10 mL/minute.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nortensin†; ***Austral.:*** Gopten; Odrik; Tranalpha; ***Austria:*** Gopten; ***Braz.:*** Gopten; Odrik†; ***Canad.:*** Mavik; ***Cz.:*** Gopten; Tanap; ***Denm.:*** Gopten; Odrik; ***Fin.:*** Gopten†; ***Fr.:*** Gopten†; Odrik; ***Ger.:*** Gopten†; Udrik; ***Gr.:*** Afenil; Odrik; ***Hung.:*** Gopten; ***Indon.:*** Gopten; ***Irl.:*** Gopten; Odrik; ***Ital.:*** Gopten; ***Jpn:*** Odric; Preran; ***Mex.:*** Gopten†; ***Neth.:*** Gopten; Odrik; ***Norw.:*** Gopten; ***NZ:*** Gopten; Odrik; ***Pol.:*** Gopten; ***Port.:*** Gopten; Odrik; ***Rus.:*** Gopten (Гоптен); ***S.Afr.:*** Gopten†; Mavik; ***Spain:*** Gopten; Odrik; ***Swed.:*** Gopten; ***Switz.:*** Gopten; ***Turk.:*** Gopten; ***UK:*** Gopten; Odrik†; ***USA:*** Mavik.

Multi-ingredient: ***Arg.:*** Tarka†; ***Austral.:*** Tarka; ***Austria:*** Tarka; ***Canad.:*** Tarka; ***Cz.:*** Tarka; ***Denm.:*** Tarka; ***Fin.:*** Tarka†; ***Fr.:*** Ocadrik†; Tarka; ***Ger.:*** Tarka; Udramil†; ***Gr.:*** Tarka; Ziaxel; ***Hung.:*** Tarka; ***Indon.:*** Tarka; ***Ital.:*** Tarka; ***Mex.:*** Tarka; ***Neth.:*** Tarka; Ziaxel; ***NZ:*** Ziaxel; ***Philipp.:*** Tarka; ***Pol.:*** Tarka; ***Port.:*** Tarka; Ziaxal; ***Rus.:*** Tarka (Тарка); ***S.Afr.:*** Tarka; ***Spain:*** Tarka; Tricen; ***Swed.:*** Tarka; ***Switz.:*** Tarka; ***Turk.:*** Tarka; ***UK:*** Tarka; ***USA:*** Tarka; ***Venez.:*** Tarka.

Trapidil *(BAN, rINN)*

AR-12008; Tarpidil; Trapidiili; Trapidilis; Trapidilum. 7-Diethylamino-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine.

Трапидил

$C_{10}H_{15}N_5$ = 205.3.
CAS — 15421-84-8.
ATC — C01DX11.
ATC Vet — QC01DX11.