with saturable binding to the angiotensin-converting enzyme. The clearance of ramiprilat is reduced in renal impairment.

◊ Reviews.

1. Meisel S, *et al*. Clinical pharmacokinetics of ramipril. *Clin Pharmacokinet* 1994; **26:** 7–15.
2. van Griensven JMT, *et al*. Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril. *Eur J Clin Pharmacol* 1995; **47:** 513–8.
3. Fillastre JP, *et al*. Kinetics, safety, and efficacy of ramipril after long-term administration in hemodialyzed patients. *J Cardiovasc Pharmacol* 1996; **27:** 269–74.

Uses and Administration

Ramipril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171), heart failure (p.1165), and after myocardial infarction (p.1175) to improve survival in patients with clinical evidence of heart failure. It is also used to reduce the risk of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p.1164).

Ramipril owes its activity to ramiprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 3 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic effect is maintained for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** an initial oral dose of 1.25 mg once daily is given. Since there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Patients taking diuretics should, if possible, have the diuretic stopped 2 to 3 days before starting ramipril, and resumed later if necessary. The usual maintenance dose is 2.5 to 5 mg daily as a single dose, although up to 10 mg daily may be required. In the USA an initial dose of 2.5 mg once daily in hypertensive patients not taking a diuretic and a maintenance dose of 2.5 to 20 mg daily, as a single dose or in two divided doses, have been suggested.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision; high doses of diuretics should be reduced before starting ramipril. Ramipril is given in an initial dose of 1.25 mg once daily. The usual maximum dose is 10 mg daily; doses of 2.5 mg or more daily may be taken in 1 or 2 divided doses.

After **myocardial infarction**, treatment with ramipril may be started in hospital 3 to 10 days after the infarction at a usual initial dose of 2.5 mg twice daily, increased after two days to 5 mg twice daily. The usual maintenance dose is 2.5 to 5 mg twice daily.

For the **prophylaxis of cardiovascular events** in patients considered to be at high risk, ramipril is given in an initial dose of 2.5 mg once daily. The dose should be increased, if tolerated, to 5 mg once daily after 1 week, then to the usual maintenance dose of 10 mg once daily after a further 3 weeks. In patients with hypertension or recent myocardial infarction it may also be given in divided doses.

A reduction in dosage of ramipril may be necessary in patients with impaired hepatic or renal function (see below).

◊ References.

1. Todd PA, Benfield P. Ramipril: a review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. *Drugs* 1990; **39:** 110–35.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; **342:** 821–8.
3. Frampton JE, Peters DH. Ramipril: an updated review of its therapeutic use in essential hypertension and heart failure. *Drugs* 1995; **49:** 440–66.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.
5. Warner GT, Perry CM. Ramipril: a review of its use in the prevention of cardiovascular outcomes. *Drugs* 2002; **62:** 1381–1405.
6. Vuong AD, Annis LG. Ramipril for the prevention and treatment of cardiovascular disease. *Ann Pharmacother* 2003; **37:** 412–19.
7. Rokoss MJ, Teo KK. Ramipril in the treatment of vascular diseases. *Expert Opin Pharmacother* 2005; **6:** 1911–19.
8. Anderson VR, *et al*. Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. *Am J Cardiovasc Drugs* 2006; **6:** 417–32.
9. Lüders S, *et al*.. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure - a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* 2008; **26:** 1487–1496.

Administration in hepatic or renal impairment. The UK licensed product information states that in patients with hepatic impairment, or renal impairment with a creatinine clearance of less than 30 mL/minute, the initial dose of ramipril should not exceed 1.25 mg daily. In hepatic impairment higher doses should be used with caution. In renal impairment the maintenance dose should not exceed 5 mg daily; for those with a creatinine clearance of less than 10 mL/minute, the maintenance dose should not exceed 2.5 mg daily.

Preparations

BP 2008: Ramipril Capsules; Ramipril Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Lostapres; Tritace; ***Austral.:*** Prilace; Ramace; Tritace; ***Austria:*** Hypren; Lannapril; Ramipharm; Tritace; ***Belg.:*** Ramace; Tritace; ***Braz.:*** Atensec; Ecator; Naprix; Triatec; ***Canad.:*** Altace; ***Chile:*** Ramipres; Triatec; ***Cz.:*** Acesial; Amprilan; Hartil; Miril; Piramil; Ramicard; Ramil; Ramistada; Ramitren; Tritace; ***Denm.:*** Ramace; Triatec; ***Fin.:*** Cardace; Ramace†; ***Fr.:*** Triatec; ***Ger.:*** Delix; Ramicard; Ramigamma; RamiLich; Vesdil; ***Gr.:*** Stibenyl; Triatec; ***Hong Kong:*** Tritace; ***Hung.:*** Amprilan; Corpril; Emren; Hartil; Meramyl; Piramil; Ramace; Ramicard; Ramiwin; Tritace; ***India:*** Cardace; Hopecard; Preface; R-Pril; Ramcor; Ramipres; Sclerace; ***Indon.:*** Cardace; Hyperil; Ramixal; Tenapril; Triatec; ***Irl.:*** ByTrite; Ramic; Ramilo; Tritace; ***Israel:*** Ramitens; Tritace; ***Ital.:*** Quark; Triatec; Unipril; ***Malaysia:*** Tritace; ***Mex.:*** Intempril; Ramace†; Tritace; ***Neth.:*** Remik†; Tritace; ***Norw.:*** Triatec; ***NZ:*** Tritace; ***Philipp.:*** Tritace; ***Pol.:*** Axtil; Mitrip; Piramil; Ramicor; Tritace; Vivace; ***Port.:*** Ramik; Triatec; Verzatec; ***Rus.:*** Hartil (Хартил); ***S.Afr.:*** Ramace; Ramiwin; Rampil; Tritace; ***Singapore:*** Tritace; ***Spain:*** Acovil; Carasel; ***Swed.:*** Pramace; Triatec; ***Switz.:*** Triatec; Vesdil; ***Thai.:*** Corpril; Piramil; Ramiril; Ramtace; Tritace; ***Turk.:*** Delix; ***UK:*** Tritace; ***USA:*** Altace; ***Venez.:*** Altace; Piramil.

Multi-ingredient: *Arg.:* Triacor; Tritace-HCT; ***Austral.:*** Triasyn; ***Austria:*** Hypren plus; Lannapril plus; Lasitace; Ramicomp; Ramipharm comb; Trialix; Triapin; Tritazide; Unimax; ***Belg.:*** Tritazide; ***Braz.:*** Ecator H; Naprix A; Naprix D; Triatec D; ***Cz.:*** Amprilan H; Hartil-H; Medoram plus H; Miril plus H; Ramil H; Ramixa Plus H; Triasyn; Tritazide; Unimax†; ***Denm.:*** Triatec Comp; ***Fin.:*** Cardace Comp; Unimax; ***Fr.:*** Cotriatec; ***Ger.:*** Arelix ACE; Aretensin; Delix Plus; Delmuno; Rami-Q comp; Ramicard Plus; Ramigamma HCT; RamiLich comp; Ramiplus; Ramipril comp; Ramipril HCT; Ramipril HCTad; Ramipril Plus; Unimax; Vesdil plus; ***Gr.:*** Stibenyl HCT; Triacor; Triatec Plus; Unitens; ***Hung.:*** Amprilan HD; Amprilan HL; Hartil HCT; Meramyl HCT; Ramace Plusz; Ramiwin HCT; Triasyn; Tritace-HCT; ***India:*** Ramcor H; Ramipres H; ***Irl.:*** Trialix; Triapin; ***Israel:*** Tritace Comp; ***Ital.:*** Idroquark; Prilace; Triatec HCT; Uniprildiur; ***Mex.:*** Triacor; Tritazide; ***Neth.:*** Delitab-HCT; Prilitab-HCT; Prilitaril-HCT; Ramitab-HCT; Rataril-HCT; Triapin; Tritazide; Unimax; ***Philipp.:*** Triapin; ***Pol.:*** Ramicor Comb; ***Port.:*** Ramicor D; Triatec Composto; Unimax; ***S.Afr.:*** Tri-Plen; ***Swed.:*** Triatec Comp; ***Switz.:*** Trialix; Triatec Comp; Unimax; ***Turk.:*** Delix Plus; ***UK:*** Triapin; ***Venez.:*** Altace Plus.

Ranolazine *(USAN, rINN)*

CVT-303; Ranolazina; Ranolazinum; RS-43285-003. (±)-*N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide.

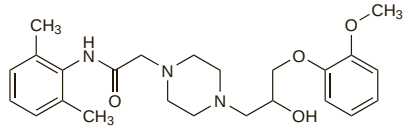
Ранолазин

$C_{24}H_{33}N_3O_4$ = 427.5.

CAS — 95635-55-5.

ATC — C01EB18.

ATC Vet — QC01EB18.



Ranolazine Hydrochloride *(USAN, rINNM)*

Hidrocloruro de ranolazina; Ranolazine, Chlorhydrate de; Ranolazini Hydrochloridum; RS-43285.

Ранолазина Гидрохлорид

$C_{24}H_{33}N_3O_4,2HCl$ = 500.5.

CAS — 95635-56-6.

ATC — C01EB18.

ATC Vet — QC01EB18.

Adverse Effects and Precautions

Adverse effects most commonly seen with ranolazine are nausea, constipation, dizziness, and headache. Palpitations, tinnitus, vertigo, dry mouth, abdominal pain, vomiting, peripheral oedema, and dyspnoea have also been reported. Rarely reported effects include bradycardia, haematuria, paraesthesia, hypotension, and blurred vision.

Dose-related prolongation of the QT interval may occur; ranolazine is therefore contra-indicated in patients with pre-existing QT prolongation, and in those at increased risk of QT prolongation, including patients with hepatic impairment (Child-Pugh classes A to C) and those taking interacting drugs (see Interactions, below). Blood pressure may be increased in patients with severe renal impairment and should be monitored regularly.

Interactions

Ranolazine is primarily metabolised by the P450 isoenzyme CYP3A and should not be given with other drugs that are potent or moderately potent inhibitors of this enzyme, such as ketoconazole, diltiazem, macrolide antibacterials, HIV protease inhibitors, and grapefruit juice or grapefruit products. Simvastatin is also metabolised by this enzyme and plasma concentrations are reported to be doubled when given with ranolazine. Ranolazine is an inhibitor of CYP2D6 and drugs metabolised by this enzyme, such as tricyclic antidepressants or some antipsychotics, may need dose reductions. Ranolazine is both a substrate for, and inhibitor of, P-glycoprotein, and the dose of other substrates, such as digoxin, may need reducing.

Pharmacokinetics

Absorption of ranolazine is highly variable with peak plasma concentrations occurring about 2 to 5 hours after an oral dose of the modified-release preparation. Ranolazine is extensively metabolised in the gastrointestinal tract and liver. Four main metabolites have been identified. Protein binding of ranolazine is about 62%. About 75% of a dose is excreted in the urine with the remainder in the faeces, with less than 5% as unchanged drug. The apparent terminal half-life for the modified-release preparation of ranolazine is 7 hours, and steady state occurs within 3 days.

◊ Reviews.

1. Jerling M. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet* 2006; **45:** 469–91.

Uses and Administration

Ranolazine is an antianginal drug. Its mechanism of action is unclear but may involve inhibition of the late sodium current in cardiac myocytes; it also inhibits fatty acid oxidation, but this does not appear to occur at therapeutic plasma concentrations. It is used for the treatment of angina pectoris (p.1157) in patients who have not responded satisfactorily to other antianginals and should be given as an adjunct to standard therapy. It is given in a modified-release form in an initial oral dose of 500 mg twice daily, increasing to a maximum of 1 g twice daily if necessary.

◊ Reviews.

1. Siddiqui MAA, Keam SJ. Ranolazine: a review of its use in chronic stable angina pectoris. *Drugs* 2006; **66:** 693–710.
2. Tafreshi MJ, Fisher E. Ranolazine: a new approach to management of patients with angina. *Ann Pharmacother* 2006; **40:** 689–93.
3. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006; **113:** 2462–72.
4. Zerumsky K, McBride BF. Ranolazine in the management of chronic stable angina. *Am J Health-Syst Pharm* 2006; **63:** 2331–8.

Preparations

Proprietary Preparations (details are given in Part 3)

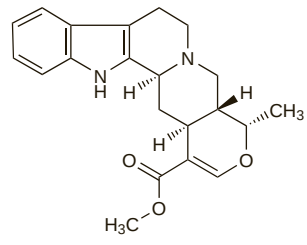
USA: Ranexa.

Raubasine

Ajmalicine; Alkaloid F; Raubasiini; Raubasin; Raubasina; Raubasinum; δ-Yohimbine. Methyl 16,17-didehydro-19α-methyl-18-oxayohimban-16-carboxylate.

$C_{21}H_{24}N_2O_3$ = 352.4.

CAS — 483-04-5.



Pharmacopoeias. In *Chin.*

Profile

Raubasine is an alkaloid obtained from *Rauwolfia serpentina* (Apocynaceae). It is a vasodilator related chemically to reserpine (p.1387) and has been given orally and by injection in peripheral and cerebral vascular disorders.