alkaline urine this is reduced to about 5% due to increased renal tubular reabsorption.

Quinidine is widely distributed throughout the body and is 80 to 90% bound to plasma proteins including α_1-acid glycoprotein. It has a plasma half-life of about 6 to 8 hours but this may show wide variation. Its therapeutic effect has been correlated with plasma concentrations of about 1 to 6 micrograms/mL, depending on the assay method used; older methods that do not differentiate quinidine from its metabolites may give misleading results.

Quinidine crosses the placenta and is distributed into breast milk. Only small amounts are removed by haemodialysis.

◊ Considerable intersubject and intrasubject variability in the pharmacokinetics of quinidine has been noted;[1] in one study the half-life ranged from about 1 to 16 hours regardless of whether the drug was given as a tablet, capsule, oral solution, or intramuscular injection. There may also be considerable variations in absorption depending upon the formulation and the salt used.[2,3] The effect of food on absorption is not clear.[4,5] The heart condition being treated or associated with the arrhythmia may alter quinidine's pharmacokinetics[6,7] as may the age of the patient.[8-10] Hepatic impairment may affect protein binding and prolong quinidine's half-life.[11] Protein binding increases in patients with renal impairment, although it returns to normal during dialysis procedures.[12] Accumulation of quinidine metabolites may occur in patients with renal dysfunction.[13-15]

1. Mason WD, *et al*. Comparative plasma concentrations of quinidine following administration of one intramuscular and three oral formulations to 13 human subjects. *J Pharm Sci* 1976; **65:** 1325–9.
2. Frigo GM, *et al*. Comparison of quinidine plasma concentration curves following oral administration of some short- and long-acting formulations. *Br J Clin Pharmacol* 1977; **4:** 449–54.
3. Mahon WA, *et al*. Comparative bioavailability study of three sustained release quinidine formulations. *Clin Pharmacokinet* 1987; **13:** 118–24.
4. Woo E, Greenblatt DJ. Effect of food on enteral absorption of quinidine. *Clin Pharmacol Ther* 1980; **27:** 188–93.
5. Martinez MN, *et al*. Effect of dietary fat content on the bioavailability of a sustained release quinidine gluconate tablet. *Biopharm Drug Dispos* 1990; **11:** 17–29.
6. Ueda CT, Dzindzio BS. Quinidine kinetics in congestive heart failure. *Clin Pharmacol Ther* 1978; **23:** 158–64.
7. Ueda CT, Dzindzio BS. Bioavailability of quinidine in congestive heart failure. *Br J Clin Pharmacol* 1981; **11:** 571–7.
8. Drayer DE, *et al*. Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. *Clin Pharmacol Ther* 1980; **27:** 72–5.
9. Szefler SJ, *et al*. Rapid elimination of quinidine in pediatric patients. *Pediatrics* 1982; **70:** 370–5.
10. Pickoff AS, *et al*. Age-related differences in the protein binding of quinidine. *Dev Pharmacol Ther* 1981; **3:** 108–15.
11. Kessler KM, *et al*. Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol. *Am Heart J* 1978; **96:** 627–35.
12. Kessler KM, Perez GO. Decreased quinidine plasma protein binding during haemodialysis. *Clin Pharmacol Ther* 1981; **30:** 121–6.
13. Kessler KM, *et al*. Quinidine elimination in patients with congestive heart failure or poor renal function. *N Engl J Med* 1974; **290:** 706–9.
14. Drayer DE, *et al*. Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. *Clin Pharmacol Ther* 1978; **24:** 31–9.
15. Hall K, *et al*. Clearance of quinidine during peritoneal dialysis. *Am Heart J* 1982; **104:** 646–7.

Uses and Administration

Quinidine is a class Ia antiarrhythmic (p.1153). It also has antimuscarinic and alpha-adrenoceptor blocking properties. Quinidine is used in the management of supraventricular and ventricular arrhythmias, including cardioversion and maintenance of sinus rhythm in atrial fibrillation, but other drugs or methods are usually preferred.

Quinidine is an isomer of quinine and may be used as an alternative to quinine in the treatment of malaria when quinine is not immediately available.

Quinidine is usually given orally and various salts have been used, including the bisulfate, the gluconate, the polygalacturonate, and the sulfate. Strengths of preparations and doses used may be expressed in terms of the salt actually contained in the preparation, but are commonly expressed as the equivalent amount of anhydrous quinidine base or quinidine sulfate dihydrate. Quinidine bisulfate (anhydrous) 260 mg, quinidine gluconate (anhydrous) 321 mg, quinidine sulfate (dihydrate) 241 mg, and quinidine sulfate (anhydrous) 230 mg are each equivalent to about 200 mg of quinidine (anhydrous).

For the management of **cardiac arrhythmias**, a typical dose of *quinidine sulfate dihydrate* is 200 to 400 mg three or four times daily, adjusted according to response; an initial test dose of 200 mg has been recommended for detecting hypersensitivity. Modified-release preparations may be preferred for maintenance.

Quinidine has also been given parenterally but absorption after intramuscular injection is erratic and incomplete, and intravenous use is associated with a risk of severe hypotension. If parenteral use is necessary for acute conversion of supraventricular or ventricular arrhythmias, *quinidine gluconate* may be given by intravenous infusion at a rate no faster than 250 micrograms/kg per minute; most patients respond to a total dose of less than 5 mg/kg, but up to 10 mg/kg may be given if required. ECG and blood pressure should be monitored throughout the infusion.

For the use of quinidine in the management of **malaria**, see below.

◊ General references.

1. Grace AA, Camm AJ. Quinidine. *N Engl J Med* 1998; **338:** 35–45.

Cardiac arrhythmias. Quinidine is a class Ia antiarrhythmic and has been used in the management of supraventricular and ventricular arrhythmias, but other drugs or non-pharmacological therapies are usually preferred (see Cardiac Arrhythmias, p.1160). Although use of quinidine may have increased after the CAST studies, which found an increased mortality with the use of encainide, flecainide, and moracizine in asymptomatic ventricular arrhythmias, a meta-analysis[1] of studies using quinidine for benign or potentially lethal ventricular arrhythmias found that it was associated with at least as high an incidence of adverse events, including death and early proarrhythmia, as the class Ic drugs flecainide and propafenone. Another meta-analysis[2] found that quinidine was more effective than placebo in maintaining sinus rhythm after cardioversion of atrial fibrillation, but again total mortality was increased.

Quinidine has been used[3] in patients with Brugada syndrome, a congenital channelopathy that predisposes to ventricular arrhythmias, and may have a role as an alternative to an implantable cardioverter defibrillator.

1. Morganroth J, Goin JE. Quinidine-related mortality in the short-to-medium-term treatment of ventricular arrhythmias: a meta-analysis. *Circulation* 1991; **84:** 1977–83.
2. Coplen SE, *et al*. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; **82:** 1106–16. Correction. *ibid*. 1991; **83:** 714.
3. Belhassen B, *et al*. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 2004; **110:** 1731–7.

Congenital myasthenia. Although quinidine may exacerbate the symptoms of myasthenia gravis and should be used with great caution in such patients, beneficial responses have been reported in patients with the slow-channel congenital myasthenic syndrome (see p.630).

Hiccup. Quinidine is one of several drugs that have been tried in intractable hiccups. For details of a protocol for the control of hiccups see Chlorpromazine, p.976.

Malaria. Quinidine may be more potent than quinine as an antimalarial but it is more likely to cause cardiac toxicity and hypersensitivity and WHO[1,2] has recommended that parenteral formulations of quinidine should only be used when parenteral quinine or artemisinin derivatives are not immediately available. In these situations intravenous infusions of quinidine could be used to begin treatment for severe chloroquine-resistant malaria. Patients should be transferred to oral therapy with quinine as soon as possible to complete a 7-day course; alternatively a single oral treatment of pyrimethamine-sulfadoxine may be given.

In the USA, the CDC[3,4] have recommended parenteral quinidine gluconate as the drug of choice for the treatment of complicated falciparum malaria, but only because of the lack of availability of parenteral quinine.

Quinidine is given intravenously as the gluconate and doses have been expressed in terms of the base or salt; it should be given under close control, preferably with continuous ECG monitoring and frequent measurements of blood pressure. Regimens used include one[1,5] where the equivalent of 15 mg of the base per kg is infused over 4 hours as a loading dose followed by the equivalent of 7.5 mg of the base per kg every 8 hours as infusions over 4 hours; the patient should be transferred to an oral form of antimalarial as soon as possible. An alternative regimen[6] consists of a loading dose of 10 mg of quinidine gluconate per kg given by intravenous infusion over a period of 1 to 2 hours followed by a constant intravenous infusion of 20 micrograms/kg per minute for a maximum of 72 hours or until oral therapy with quinine can be instituted to complete a total 3-day course of treatment. It is generally recommended that loading doses should not be used if the patient has received quinine or quinidine within the previous 24 hours or mefloquine within the preceding 7 days.

The overall management of malaria is discussed in the chapter on Antimalarials, p.594.

1. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO, 2000. Available at: http://www.who.int/malaria/docs/hbsm_toc.htm (accessed 16/07/07)
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 10/07/07)
3. CDC. Treatment with quinidine gluconate of persons with severe Plasmodium falciparum infection: discontinuation of parenteral quinine from CDC drug service. *MMWR* 1991; **40** (RR-4): 21–3. Also available at http://www.cdc.gov/mmwr/preview/mmwrhtml/00043932.htm (accessed 10/07/07)
4. CDC. Availability and use of parenteral quinidine gluconate for severe or complicated malaria. *MMWR* 2000; **49:** 1138–40.
5. Phillips RE, *et al*. Intravenous quinidine for the treatment of severe falciparum malaria: clinical pharmacokinetic studies. *N Engl J Med* 1985; **312:** 1273–8.
6. Miller KD, *et al*. Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. *N Engl J Med* 1989; **321:** 65–70.

Neurological disorders. For reference to the use of quinidine with dextromethorphan for the management of amyotrophic lateral sclerosis, see p.1556.

Preparations

BP 2008: Quinidine Sulphate Tablets;
USP 31: Quinidine Gluconate Extended-release Tablets; Quinidine Gluconate Injection; Quinidine Sulfate Capsules; Quinidine Sulfate Extended-release Tablets; Quinidine Sulfate Oral Suspension; Quinidine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Kinidin; ***Belg.:*** Kinidine†; ***Braz.:*** Quinicardine; ***Canad.:*** Biquin; ***Cz.:*** Kinidin†; ***Denm.:*** Kinidin; ***Fin.:*** Kiniduron; ***Gr.:*** Kinidine; Ydroquinidine; ***Hong Kong:*** Kinidin†; ***Irl.:*** Kinidin; ***Israel:*** Quiniduran; ***Ital.:*** Chinteina; Longachin; Naticardina†; Natisedina; Ritmocor; ***Mex.:*** Quini†; ***Neth.:*** Kinidine†; ***Philipp.:*** Kinidin; ***S.Afr.:*** Quinaglute; ***Spain:*** Longacor†; ***Swed.:*** Kinidin; ***Switz.:*** Kinidin; Longacor†; ***Turk.:*** Longacor; Natisedine; Quinicardine; ***UK:*** Kinidin†; ***USA:*** Quinidex†.

Multi-ingredient: ***Fr.:*** Quinimax; ***Ger.:*** Cordichin.

Ramipril *(BAN, USAN, rINN)*

Hoe-498; Ramipriili; Ramiprilis; Ramiprilum. (2*S*,3a*S*,6a*S*)-1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]L-alanyl}perhydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

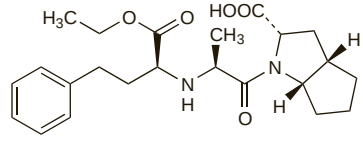
Рамиприл

$C_{23}H_{32}N_2O_5$ = 416.5.

CAS — 87333-19-5.

ATC — C09AA05.

ATC Vet — QC09AA05.



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

Ph. Eur. 6.2 (Ramipril). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Protect from light.

USP 31 (Ramipril). A white to almost white, crystalline powder. Sparingly soluble in water; freely soluble in methyl alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Ramipril acts as a prodrug of the diacid ramiprilat, its active metabolite. After oral doses at least 50 to 60% is absorbed. Ramipril is metabolised in the liver to ramiprilat; other metabolites are inactive. Peak plasma concentrations of ramiprilat are achieved 2 to 4 hours after an oral dose of ramipril. Ramiprilat is about 56% bound to plasma proteins. After oral doses ramipril is excreted primarily in the urine, as ramiprilat, other metabolites, and some unchanged drug. About 40% of an oral dose appears in the faeces; this may represent both biliary excretion and unabsorbed drug. The effective half-life for accumulation of ramiprilat is 13 to 17 hours after multiple doses of ramipril 5 to 10 mg, but is much longer for doses of 1.25 to 2.5 mg daily; the difference relates to the long terminal half-life associated

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.

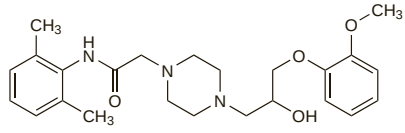
Ранолазин

$C_{24}H_{33}N_3O_4$ = 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)

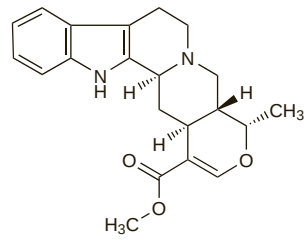
USA: Ranexa.

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.