of ribavirin, is delivered over a 12- to 18-hour period by aerosol at an average concentration of 190 micrograms/litre of air. Treatment is given for 3 to 7 days.

Ribavirin is used, with an interferon alfa, for the treatment of chronic **hepatitis C**. Doses of ribavirin depend upon the product used, but are given orally, usually twice daily, and are determined according to body-weight. Duration of treatment, and sometimes also dose, may be influenced by the genotype of the hepatitis C virus. In hepatitis C mono-infection, patients with viral genotype 1 should be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks.

Rebetol (Schering-Plough) is used, with interferon alfa-2b or peginterferon alfa-2b, for hepatitis C.

The following doses are recommended in the UK:

- 47 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 65 kg: 400 mg both in the morning and in the evening
- over 65 kg: the adult dose (above)

In the USA, the doses are:

- 25 to 36 kg: 200 mg both in the morning and in the evening
- 37 to 49 kg: 200 mg in the morning and 400 mg in the evening
- 50 to 61 kg: 400 mg both in the morning and in the evening
- over 61 kg: the adult dose

Copegus (Roche) is not licensed for use in those less than 18 years of age.

Encephalitis. A beneficial response to ribavirin was reported in a child with severe La Crosse encephalitis.[1] Ribavirin was given intravenously in a dose of 25 mg/kg over the first 24 hours and then reduced to 15 mg/kg daily for a further 9 days. A small open-label study[2] suggested that ribavirin might also be able to reduce mortality and neurological deficits in acute Nipah encephalitis.

Intraventricular ribavirin (plus intraventricular interferon and oral isoprinosine) was found to be effective in 4 of 5 patients with subacute sclerosing panencephalitis.[3] A concentration of ribavirin in the CSF of 50 to 200 micrograms/mL completely inhibited viral replication; doses of ribavirin given to achieve this concentration ranged from 1 to 9 mg/kg daily.

1. McJunkin JE, *et al.* Treatment of severe La Crosse encephalitis with intravenous ribavirin following diagnosis by brain biopsy. *Pediatrics* 1997; **99:** 261–7.
2. Chong HT, *et al.* Treatment of acute Nipah encephalitis with ribavirin. *Ann Neurol* 2001; **49:** 810–13.
3. Hosoya M, *et al.* Pharmacokinetics and effects of ribavirin following intraventricular administration for treatment of subacute sclerosing panencephalitis. *Antimicrob Agents Chemother* 2004; **48:** 4631–5.

Haemorrhagic fevers. The treatment of haemorrhagic fevers (p.850) is primarily symptomatic. However, ribavirin has been reported to reduce mortality in patients with Lassa fever,[1] haemorrhagic fever with renal syndrome,[2] and possibly Crimean-Congo haemorrhagic fever[3,4] and Bolivian haemorrhagic fever.[5] Intravenous ribavirin has also been tried in the related hantavirus pulmonary syndrome,[6,7] but a small randomised, double-blind, placebo-controlled study[8] with intravenous ribavirin reported no significant difference in survival between the 2 groups.

For treatment of *Lassa fever*, ribavirin has been given intravenously in a dose of 2 g initially, then 1 g every 6 hours for 4 days, then 500 mg every 8 hours for 6 days.[1] Treatment is most effective if started within 6 days of the onset of fever. Experience has shown that rigors may occur if the drug is given as a bolus injection, but that this can be overcome by giving it as an infusion over 30 minutes.[9] For prophylaxis, an oral dose of ribavirin 600 mg 4 times daily for 10 days has been suggested for adults,[10] although this was considered to be excessive by other commentators[11] who suggested that oral doses of 1 g daily (after an intravenous loading dose for those in whom the start of prophylaxis is delayed) might be suitable.

1. McCormick JB, *et al.* Lassa fever: effective therapy with ribavirin. *N Engl J Med* 1986; **314:** 20–6.
2. Huggins JW, *et al.* Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis* 1991; **164:** 1119–27.
3. Fisher-Hoch SP, *et al.* Crimean Congo-haemorrhagic fever treated with oral ribavirin. *Lancet* 1995; **346:** 472–5.
4. Mardani M, *et al.* The efficacy of oral ribavirin in the treatment of crimean-congo hemorrhagic fever in Iran. *Clin Infect Dis* 2003; **36:** 1613–18.
5. Kilgore PE, *et al.* Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis* 1997; **24:** 718–22.
6. Anonymous. Hantavirus pulmonary syndrome—northeastern United States, 1994. *JAMA* 1994; **272:** 997–8.
7. Prochoda K, *et al.* Hantavirus-associated acute respiratory failure. *N Engl J Med* 1993; **329:** 1744.
8. Mertz GJ, *et al.* Collaborative Antiviral Study Group. Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. *Clin Infect Dis* 2004; **39:** 1307–13.
9. Fisher-Hoch SP, *et al.* Unexpected adverse reactions during a clinical trial in rural West Africa. *Antiviral Res* 1992; **19:** 139–47.
10. Holmes GP, *et al.* Lassa fever in the United States: investigation of a case and new guidelines for management. *N Engl J Med* 1990; **323:** 1120–23.
11. Johnson KM, Monath TP. Imported Lassa fever—reexamining the algorithms. *N Engl J Med* 1990; **323:** 1139–41.

Hepatitis. For further discussion on the use of ribavirin with interferon alfa in the management of chronic hepatitis C, see under Interferon Alfa, p.889.

Preparations

BP 2008: Ribavirin Nebuliser Solution;
USP 31: Ribavirin for Inhalation Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Copegus; Laztie; Vibuzol; Xilopar; ***Austral.:*** Virazide; ***Austria:*** Copegus; Rebetol; ***Belg.:*** Copegus; Rebetol; Virazole; ***Braz.:*** Rebetol†; Ribav; Ribaviron C†; Viramid; Virazole†; ***Canad.:*** Virazole; ***Chile:*** Rebetol; ***Cz.:*** Copegus; Rebetol; ***Denm.:*** Copegus; Rebetol; ***Fin.:*** Copegus; Rebetol; ***Fr.:*** Copegus; Rebetol; ***Ger.:*** Copegus; Rebetol; Virazole; ***Gr.:*** Copegus; Rebetol; ***Hong Kong:*** Copegus; Rebetol; Virazole; ***Hung.:*** Copegus; Rebetol; Virazole†; ***India:*** Ribavin; ***Indon.:*** Rebetol; Virazide; ***Irl.:*** Copegus; Rebetol; ***Israel:*** Copegus; Rebetol; ***Ital.:*** Copegus; Rebetol; Virazole; ***Jpn:*** Copegus; ***Malaysia:*** Rebetol; ***Mex.:*** Copegus; Desiken; Trivorin; Vilona; Virazide; ***Neth.:*** Copegus; Rebetol; Virazole; ***Norw.:*** Copegus; Rebetol; ***NZ:*** Copegus; Rebetol; ***Philipp.:*** Ribazole; ***Pol.:*** Copegus; Rebetol; ***Port.:*** Copegus; Rebetol; ***Rus.:*** Arviron (Арвирон); Rebetol (Ребетол); Ribapeg (Рибапег); Virazole (Виразол); ***S.Afr.:*** Copegus; ***Singapore:*** Copegus; Rebetol; Virazole; ***Spain:*** Copegus; Rebetol; Virazole; ***Swed.:*** Copegus; Rebetol; Virazole; ***Switz.:*** Copegus; Rebetol; Virazole†; ***Thai.:*** Rebetol; ***UK:*** Copegus; Rebetol; Virazole; ***USA:*** Copegus; Rebetol; RibaPak; Ribaspheres; Ribatab; Virazole; ***Venez.:*** Rebetol.

Multi-ingredient: ***Arg.:*** Bioferon Hepakit; Pegatron†; Rebetron†; ***Austral.:*** Pegasys RBV; Pegatron; Rebetron; ***Canad.:*** Pegasys RBV; Pegetron; Rebetron†; ***Mex.:*** Hepatron C; Pegtron Cotronak Kit; ***NZ:*** Pegasys RBV; Pegatron; Rebetron; Roferon-A RBV; ***Philipp.:*** Pegasys RBV; ***S.Afr.:*** Rebetron†; ***Switz.:*** Intron A/Rebetol†; ***USA:*** Rebetron†.

Rimantadine Hydrochloride *(BANM, USAN, rINNM)*

EXP-126; Hidrocloruro de rimantadina; Rimantadine, Chlorhydrate de; Rimantadini Hydrochloridum. (*RS*)-1-(Adamantan-1-yl)ethylamine hydrochloride; α-Methyl-1-adamantanemethylamine hydrochloride.

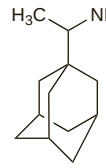
Римантадина Гидрохлорид

$C_{12}H_{21}N,HCl$ = 215.8.

CAS — 13392-28-4 (rimantadine); 1501-84-4 (rimantadine hydrochloride).

ATC — J05AC02.

ATC Vet — QJ05AC02.



(rimantadine)

Pharmacopoeias. In *US*.

USP 31 (Rimantadine Hydrochloride). Store at a temperature of 15° to 30°.

Adverse Effects and Precautions

The incidence and severity of adverse effects associated with rimantadine appear to be low. Those most commonly reported are gastrointestinal disturbances such as nausea, vomiting, abdominal pain, dry mouth, and anorexia, CNS effects such as headache, insomnia, nervousness, and dizziness, and asthenia. Other less frequently reported adverse effects include ataxia, agitation, concentration difficulties, diarrhoea, dyspepsia, depression, dyspnoea, skin rash, somnolence, and tinnitus.

There have been reports of convulsions, including grand mal convulsions, and rimantadine should be given with caution to patients with epilepsy. Doses are reduced in severe renal or hepatic impairment; reduced doses are also used in the elderly.

◊ A review[1] of clinical studies in adults concluded that rimantadine and amantadine were equally effective for prevention and treatment of influenza A, but rimantadine was significantly better tolerated than amantadine at usual doses. Another systematic review[2] evaluating the safety and efficacy of amantadine and rimantadine in children and the elderly with influenza A concluded that although rimantadine was safe in these groups, its efficacy was unproven and therefore its use could not be recommended.

In a study[3] to evaluate the safety of long-term rimantadine for elderly, chronically ill individuals during an influenza A epidemic, a significantly greater proportion of patients taking rimantadine developed anxiety and/or nausea compared with those taking placebo. There was also a significantly greater number of days in which anxiety, nausea, confusion, depression, or vomiting were reported. Most of these adverse effects lasted less than 9 days and were seldom severe except in 2 patients who withdrew from the study because of insomnia, anxiety, or both and a third who suffered a generalised convulsion. In a larger study[4] the incidence of these symptoms was similar in treatment and placebo groups.

Observations of seizures in 2 patients receiving influenza prophylaxis with rimantadine hydrochloride emphasised that chronically ill and elderly patients prone to seizures (especially those who may have had antiepileptic therapy withdrawn) may be at greater risk of developing seizures.[5] A precautionary measure of reducing the rimantadine hydrochloride dosage to 100 mg daily and temporary re-introduction of antiepileptics was suggested.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 3/10/07).
2. Alves Galvão MG, *et al.* Amantadine and rimantadine for influenza A in children and the elderly. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 27/02/08).
3. Patriarca PA, *et al.* Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. *Antimicrob Agents Chemother* 1984; **26:** 101–3.
4. Monto AS, *et al.* Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother* 1995; **39:** 2224–8.
5. Bentley DW, *et al.* Rimantadine and seizures. *Ann Intern Med* 1989; **110:** 323–4.

Breast feeding. Rimantadine is distributed into breast milk in *animals* in concentrations about twice those measured in the serum. US licensed product information states that rimantadine should be avoided in breast-feeding mothers.

Pregnancy. Although there is no data available on the use of rimantadine in pregnant women, US licensed product information states that it should only be used if potential benefit justifies the risk to the fetus as embryotoxicity has been reported in *rats* given high doses of rimantadine.

Antiviral Action

Rimantadine is an M2 ion channel inhibitor that inhibits influenza A virus replication mainly by blocking the M2-protein ion channel, thereby preventing fusion of the virus and the host-cell membranes and the release of viral RNA into the cytoplasm of infected cells.

Resistance to rimantadine can occur rapidly and resistant virus may be transmitted to close contacts of patients treated with rimantadine and cause influenza. Rimantadine and amantadine show complete cross-resistance.

Resistance. Resistance of influenza A viruses to the adamantane M2 ion channel inhibitors amantadine and rimantadine can occur spontaneously or emerge rapidly during treatment. A single point mutation in the code sequence for the amino acids at positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross-resistance to both amantadine and rimantadine. The resistant viruses can still replicate and be transmitted.[1-3] A report[4] describing the global prevalence of adamantane-resistant influenza A viruses over a 10 year period shows an increase in drug resistance from 0.4% during the 1994/5 influenza season to 12.3% during the 2003/4 season. During the 2005/6 influenza season, WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories in the United States reported tests on 120 influenza viruses of which 109 (91%) were found to have substitutions in the M2 protein that would confer resistance to amantadine and rimantadine.[3] In the USA, the reported adamantane resistance rate for influenza A increased from 11% for the 2004/5 influenza season to 92% for the 2005/6 influenza season.[5] On the basis of this information, the CDC no longer recommends amantadine or rimantadine for the treatment or prophylaxis of influenza A infections.[3,6]

1. Belshe RB, *et al.* Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* 1988; **62:** 1508–12.
2. Hayden FG, *et al.* Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med* 1989; **321:** 1696–1702.
3. CDC. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005–06 influenza season. *MMWR* 2006; **55:** 44–6. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5502a7.htm (accessed 13/06/08)
4. Bright RA, *et al.* Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005; **366:** 1175–81.
5. Bright RA, *et al.* Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. *JAMA* 2006; **295:** 891–4.
6. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; **56** (RR-6): 1–54. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5606.pdf (accessed 13/06/08)

Pharmacokinetics

Rimantadine hydrochloride is well, but slowly, absorbed from the gastrointestinal tract and maximum plasma concentrations are reached after about 6 hours. It has a large volume of distribution and long elimination half-life; reported figures for half-life in healthy adults range from 13 to 65 hours (mean 25.4 hours) and from 20 to 65 hours (mean 32 hours) in those over 70 years of age. Protein binding of rimantadine is about 40%. It is extensively metabolised in the liver with less than 25% of a dose being excreted unchanged in the urine; about 75% is excreted as hydroxylated metabolites over 72 hours. In severe renal or hepatic impairment the elimination half-life is about double, necessitating a dosage reduction.

Uses and Administration

Rimantadine hydrochloride is used similarly to amantadine hydrochloride (p.792) in the prophylaxis and treatment of influenza A infections (p.859) in adults and for prophylaxis of influenza A infection in children. It is given orally in usual adult doses of

200 mg daily in divided doses. In elderly patients the usual daily dose is 100 mg. A dosage reduction is also necessary in patients with severe renal or severe hepatic impairment (see below).

For details of doses in children, see below.

◊ Reviews.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/06/08).

Administration in children. For the prophylaxis of influenza A in children from 1 year of age, an oral dose of 5 mg/kg daily, up to a maximum daily dose of 150 mg, may be given. Although not licensed for the treatment of influenza A some experts consider that it may be given to children from 1 year of age.

Administration in hepatic or renal impairment. The usual oral dose of rimantadine in patients with severe renal or severe hepatic impairment and in elderly nursing home patients is 100 mg daily.

Preparations

USP 31: Rimantadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Germic†; Oclovir†; ***Cz.:*** Maridin; ***Mex.:*** Gabirol; ***Rus.:*** Algirem (Альгирем); ***USA:*** Flumadine.

Ritonavir *(BAN, USAN, rINN)*

A-84538; Abbott-84538; ABT-538; Ritonaviiri; Ritonavirum. 5-Thiazolylmethyl {(αS)-α-[(1S,3S)-1-hydroxy-3-((2S)-2-{3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido}-3-methylbutyramido)-4-phenylbutyl]phenethyl}carbamate; N^1-[(1S,3S,4S)-1-Benzyl-3-hydroxy-5-phenyl-4-(1,3-thiazol-5-ylmethoxycarbonylamino)pentyl]-N^2-{[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)carbamoyl}-L-valinamide.

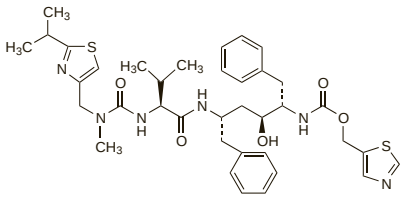
Ритонавир

$C_{37}H_{48}N_6O_5S_2$ = 720.9.

CAS — 155213-67-5.

ATC — J05AE03.

ATC Vet — QJ05AE03.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Ritonavir). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane; very slightly soluble in acetonitrile. It exhibits polymorphism. Protect from light.
USP 31 (Ritonavir). Practically insoluble in water; very soluble in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature between 5° and 30°. Protect from light.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing ritonavir are asthenia, gastrointestinal effects (abdominal pain, anorexia, diarrhoea, nausea, and vomiting), headache, taste disorder, and numbness around the mouth. One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Other commonly reported adverse effects include anxiety, dizziness, insomnia, fever, other gastrointestinal effects (dry mouth, dyspepsia, flatulence, local throat irritation), hyperaesthesia, mouth ulcer, malaise, pharyngitis, pruritus, rash, sweating, vasodilatation, and weight loss. Allergic reactions include urticaria, mild skin eruptions, bronchospasm, angioedema, and rarely anaphylaxis. A possible association with Stevens-Johnson syndrome has been reported with ritonavir. Reported abnormal laboratory results are decreased haemoglobin levels, increased eosinophil counts, raised liver enzymes and uric acid concentrations, and decreased free and total thyroxine concentrations; white blood cell and neutrophil counts may be reduced or increased.

Adverse effects associated with the use of ritonavir as a pharmacokinetic booster are dependent on the other HIV-protease inhibitor.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including ritonavir, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been seen in patients receiving antiretroviral therapy including ritonavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Ritonavir (as an antiviral agent or as a pharmacokinetic enhancer) should not be used in patients with decompensated liver disease. Caution is advised in patients with severe hepatic impairment (Child-Pugh Grade C) without decompensation, when ritonavir is used as a pharmacokinetic booster with another HIV-protease inhibitor, although specific recommendations depend on the other drug. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Patients should be monitored for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and increased serum lipase or amylase levels) and ritonavir treatment should be stopped in patients developing pancreatitis.

Interactions

Ritonavir is reported to have a high affinity for several cytochrome P450 isoenzymes with the following ranked order:

CYP3A > CYP2D6 > CYP2C9

Consequently ritonavir may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter; it may also induce glucuronidation and oxidation by CYP1A2 and CYP2C19.

Oral liquid formulations of ritonavir currently contain alcohol and use with disulfiram or metronidazole should be avoided.

Ritonavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include the alpha-adrenergic antagonist alfuzosin, antiarrhythmics (amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine), antifungals (voriconazole), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (clozapine and pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (lovastatin and simvastatin). St John's wort decreases the concentration of ritonavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. UK licensed product information also contra-indicates the use of ritonavir with the analgesics pethidine, piroxicam, and dextropropoxyphene, bupropion, fusidic acid, rifabutin, and some other sedatives and hypnotics (clorazepate, diazepam, estazolam, and flurazepam).

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Ritonavir is also a potent inhibitor of the cytochrome P450 subfamily CYP3A (chiefly the isoenzyme CYP3A4), and low-dose ritonavir is used with other HIV-protease inhibitors to decrease their metabolism and thus increase plasma concentrations of the other protease inhibitor; such use is referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur; in general the greater the number of mutations, the higher the level of resistance. Cross-resistance between HIV-protease inhibitors and NRTIs or NNRTIs is considered unlikely.

Pharmacokinetics

Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults. About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

◊ References.

1. Hsu A, *et al.* Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 1997; **41:** 898–905.
2. Hsu A, *et al.* Ritonavir: clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35:** 275–91.

Uses and Administration

Ritonavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when ritonavir is used alone, and it is therefore given with other antiretrovirals.

Ritonavir is given orally in an adult dose of 600 mg twice daily with food. In order to minimise nausea, ritonavir may be started at a dose of 300 mg twice daily and gradually increased over a period of up to 14 days by 100 mg twice daily to a total of 600 mg twice daily.

For details of doses in children, see below.

When used as a pharmacokinetic enhancer ritonavir is given in doses of 100 to 200 mg once or twice daily with other HIV-protease inhibitors.

◊ Reviews.

1. Lea AP, Faulds D. Ritonavir. *Drugs* 1996; **52:** 541–6.
2. Cooper CL, *et al.* A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; **36:** 1585–92.

Administration. Adjusting the dosage of ritonavir from 600 mg twice daily to 300 mg every 6 hours improved tolerability in 2 patients who would otherwise have stopped the drug.[1]

1. Merry C, *et al.* Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996; **42:** 787.