Zilip; ***Neth.:*** Famvir; Vectavir; ***Norw.:*** Vectavir; ***NZ:*** Vectavir†; ***Port.:*** Denovir; Fenivir; ***Rus.:*** Fenistil Pencivir (Фенистил Пенцивир); ***Spain:*** Vectavir; ***Swed.:*** Vectavir; ***Switz.:*** Famvir; ***Turk.:*** Vectavir; ***UK:*** Fenistil; Vectavir; ***USA:*** Denavir.

Peptide T

D-Ala-peptide-T-amide; Péptido T.

Пептид Т

Profile

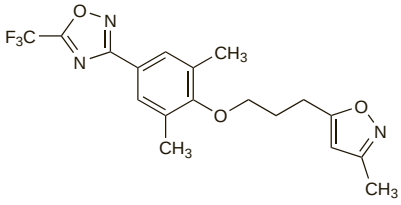
Peptide T is an octapeptide segment of the envelope glycoprotein of HIV. It has been investigated for the treatment of HIV infection and HIV-associated neurological disorders. Peptide T has also been tried in the treatment of psoriasis.

Pleconaril *(USAN, rINN)*

Pléconaril; Pleconarilo; Pleconarilum; VP-63843; Win-63843. 3-{4-[3-(3-Methyl-5-isoxazolyl)propoxy]-3,5-xylyl}-5-(trifluoromethyl)-1,2,4-oxadizole.

Плеконарил

$C_{18}H_{18}F_3N_3O_3$ = 381.3.
CAS — 153168-05-9.
ATC — J05AX06.
ATC Vet — QJ05AX06.



Profile

Pleconaril is an antiviral with activity against a range of picornaviruses. It has been investigated for the oral treatment of viral meningitis and encephalitis, upper respiratory-tract viral infections, and other enteroviral infections. However, there have been concerns over efficacy, viral resistance, and interactions with oral contraceptives. Development of an intranasal formulation for the common cold has also been investigated.

◊ References.

1. Nowak-Wegrzyn A, *et al.* Successful treatment of enterovirus infection with the use of pleconaril in 2 infants with severe combined immunodeficiency. *Clin Infect Dis* 2001; **32:** E13–E14.
2. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001; **32:** 228–35.
3. Aradottir E, *et al.* Severe neonatal enteroviral hepatitis treated with pleconaril. *Pediatr Infect Dis J* 2001; **20:** 457–9.
4. Starlin R, *et al.* Acute flaccid paralysis syndrome associated with echovirus 19, managed with pleconaril and intravenous immunoglobulin. *Clin Infect Dis* 2001; **33:** 730–2.
5. Hayden FG, *et al.* Oral pleconaril treatment of picornavirus-associated viral respiratory illness in adults: efficacy and tolerability in phase II clinical trials. *Antivir Ther* 2002; **7:** 53–65.
6. Abzug MJ, *et al.* Double blind placebo-controlled trial of pleconaril in infants with enterovirus meningitis. *Pediatr Infect Dis J* 2003; **22:** 335–41.
7. Hayden FG, *et al.* Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin Infect Dis* 2003; **36:** 1523–32.

Poly I.poly C12U

Poli(I)^{2}poli(C_{12}U); Poly(I):poly(C_{12},U).

Поли I.Поли C12U

Profile

Poly I.poly C12U is a synthetic mismatched polymer of double-stranded RNA with antiviral and immunomodulatory activity (see also Poly I. Poly C, p.2370). It is under investigation in the treatment of HIV infection, and also in renal cell carcinoma, chronic fatigue syndrome, invasive melanoma, and hepatitis B and C.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Ampligen.

Propagermanium *(rINN)*

Propagermanio. A polymer obtained from 3-(trihydroxygermyl)propionic acid.

Пропагерманий

$(C_3H_5GeO_{3.5})_n$.
CAS — 12758-40-6.

Profile

Propagermanium is an immunomodulator that has been used in chronic hepatitis B infections. Acute exacerbation of hepatitis, including some fatalities, has been reported in patients receiving propagermanium.

◊ References.

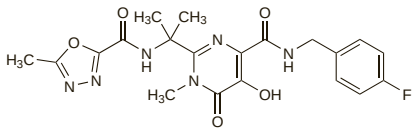
1. Hirayama C, *et al.* Propagermanium: a nonspecific immune modulator for chronic hepatitis B. *J Gastroenterol* 2003; **38:** 525–32.

Raltegravir *(USAN, rINN)*

Raltégravir; Raltegravirum. *N*-{2-[4-(4-Fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl}-5-methyl-1,3,4-oxadiazole-2-carboxamide.

Ральтегравир

$C_{20}H_{21}FN_6O_5$ = 444.4.
CAS — 518048-05-0.
ATC — J05AX08.
ATC Vet — QJ05AX08.



Raltegravir Potassium *(USAN, rINNM)*

Kalii Raltegravirum; MK-0518; Raltegravir potásico; Raltégravir Potassique. Potassium 4-[(4-fluorobenzyl)carbamoyl]-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidin-5-olate.

Калия Ральтегравир

$C_{20}H_{20}FKN_6O_5$ = 482.5.
CAS — 871038-72-1.

Adverse Effects and Precautions

On the basis of limited data, raltegravir appears to be well tolerated; non-specific adverse effects associated with raltegravir-based regimens include headache, abdominal pain, vomiting, asthenia, fatigue, and dizziness. Abnormal creatine phosphokinase values may occur and myopathy and rhabdomyolysis have been reported although a causal relationship has not been established; nonetheless, caution is advised in patients at increased risk of these conditions.

Interactions

Raltegravir is not a substrate for cytochrome P450 isoenzymes, and does not appear to interact with drugs metabolised by this mechanism. However, rifampicin induces the glucuronidase responsible for raltegravir metabolism (UGT1A1) and reduces plasma concentrations of raltegravir.

Antivirals. Plasma concentrations of raltegravir were modestly increased by *atazanavir* and ritonavir-boosted atazanavir in healthy subjects; this increase is not considered to be clinically significant.[1]

1. Iwamoto M, *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin Infect Dis* 2008; **47:** 137–40.

Pharmacokinetics

Raltegravir is absorbed on oral dosage, with peak concentrations achieved about 3 hours after a dose. There is considerable inter-individual variation in the pharmacokinetics. It is metabolised via glucuronidation, catalysed by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and excreted in both urine and faeces as unchanged drug and metabolites.

Uses and Administration

Raltegravir is an inhibitor of HIV integrase, an enzyme essential for insertion of viral DNA into the host genome, and thus for replication. It is added to treatment with other antiretrovirals for salvage therapy in patients with HIV infection and AIDS (p.856) who have evidence of viral replication and HIV-1 strains resistant to multiple antiretrovirals.

It is given orally as the potassium salt but doses are calculated in terms of the base; 434 mg of raltegravir potassium is equivalent to about 400 mg of raltegravir. The usual dose is the equivalent of 400 mg of raltegravir twice daily, with or without food.

◊ References.

1. Markowitz M, *et al.* Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 2006; **43:** 509–15. Correction. *ibid.* 2007; **44:** 492.
2. Grinsztejn B, *et al.* Protocol 005 Team. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet* 2007; **369:** 1261–9.
3. Markowitz M, *et al.* Protocol 004 Part II Study Team. Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr* 2007; **46:** 125–33.
4. Iwamoto M, *et al.* Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. *Clin Pharmacol Ther* 2008; **83:** 293–9.
5. Croxtall JD, *et al.* Raltegravir. *Drugs* 2008; **68:** 131–8.

Preparations

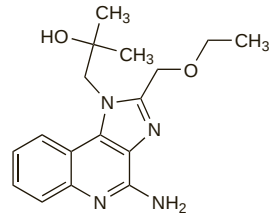
Proprietary Preparations (details are given in Part 3)
Cz.: Isentress; ***Fr.:*** Isentress; ***UK:*** Isentress; ***USA:*** Isentress.

Resiquimod *(rINN)*

R-848; Résiquimod; Resiquimodum; S-28463; VML-600. 4-Amino-2-(ethoxymethyl)-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

Резихимод

$C_{17}H_{22}N_4O_2$ = 314.4.
CAS — 144875-48-9.



Profile

Resiquimod is an immune response modifier that has been investigated for the topical treatment of genital herpes.

◊ References.

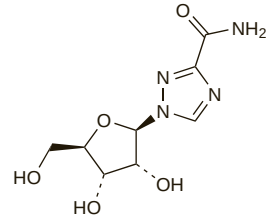
1. Spruance SL, *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; **184:** 196–200.
2. Mark KE, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital shedding: a randomized, controlled trial. *J Infect Dis* 2007; **195:** 1324–31.

Ribavirin *(BAN, USAN, rINN)*

ICN-1229; Ribaviriini; Ribavirina; Ribavirinas; Ribavirine; Ribavirinum; RTCA; Tribavirin. 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

Рибавирин

$C_8H_{12}N_4O_5$ = 244.2.
CAS — 36791-04-5.
ATC — J05AB04.
ATC Vet — QJ05AB04.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Ribavirin). A white or almost white crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; slightly soluble or very slightly soluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 6.5. Protect from light.
USP 31 (Ribavirin). A white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. Store in airtight containers.

Adverse Effects

When given *by inhalation*, ribavirin has sometimes led to worsening of lung function, bacterial pneumonia, and pneumothorax, to cardiovascular effects (including a fall in blood pressure and cardiac arrest), and, rarely, to anaemia, haemolysis, and reticulocytosis. Conjunctivitis and skin rash have also occurred. Precipitation of inhaled ribavirin and consequent accumulation of fluid has occurred in the tubing of ventilating equipment.

The most common adverse effects reported by patients taking *oral* ribavirin, with either interferon alfa or peginterferon alfa, are psychiatric reactions (such as

anxiety, depression, insomnia, and irritability) and flu-like symptoms. Life-threatening or fatal adverse effects include severe depression, suicidal ideation, relapse of drug abuse or overdose, and bacterial infection. Severe adverse effects include haemolytic anaemia, leucopenia, thrombocytopenia, aplastic anaemia, diabetes mellitus, auto-immune disorders, gastrointestinal symptoms, pancreatitis, pulmonary embolism, chest pain, liver dysfunction, and interstitial pneumonitis. Lupus erythematosus, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), and photosensitivity have also been reported. Growth retardation (including decrease in height and weight) has been reported in children. A wide range of other adverse effects may occur as a result of the use of ribavirin with interferon alfa (see under Adverse Effects in Interferon Alfa, p.885).

Incidence of adverse effects. A review[1] of adverse effects reported in 110 patients with suspected or probable SARS who were treated with ribavirin found that 61% of the patients had evidence of haemolytic anaemia. In a smaller cohort of 76 patients hypocalcaemia and hypomagnesaemia were reported in 58% and 46% of patients, respectively, while 29% had evidence of both hypocalcaemia and hypomagnesaemia. A retrospective cohort study[2] found that the adverse effects strongly associated with the use of ribavirin (mostly high-dose) in 306 patients with confirmed or probable SARS, were progressive anaemia, hypomagnesaemia, and bradycardia.

1. Knowles SR, *et al.* Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis* 2003; **37:** 1139–42.
2. Muller MP, *et al.* Canadian SARS Research Network. Adverse events associated with high-dose ribavirin: evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy* 2007; **27:** 494–503.

Precautions

SPECIFIC CAUTIONS FOR INHALED TREATMENT. Standard supportive respiratory and fluid management should be maintained during aerosol treatment with ribavirin and electrolytes should be monitored closely. Equipment should be monitored for precipitation of ribavirin. Precautions should be taken to minimise atmospheric pollution with ribavirin during aerosol inhalation.

SPECIFIC CAUTIONS FOR ORAL TREATMENT. Ribavirin should not be given orally to patients with pre-existing medical conditions that could be exacerbated by ribavirin-induced haemolysis, including significant or unstable cardiac disease or haemoglobinopathies (thalassaemia or sickle-cell anaemia). Blood cell counts and chemistry should be measured at the start of treatment, after 2 and 4 weeks of treatment, and periodically thereafter. Patients with renal impairment and a creatinine clearance of less than 50 mL/minute should not receive oral ribavirin. It should be avoided in patients with severe hepatic impairment or decompensated cirrhosis of the liver (Child-Pugh 6 or more). The potential for development of gout should be considered in predisposed patients. Patients should be monitored for signs and symptoms of psychiatric disorders. Ribavirin therapy is contra-indicated in children and adolescents with a history of, or existing, psychiatric disorders. The growth of children should be monitored and thyroid function should be tested every 3 months. Patients infected with hepatitis C virus and HIV should be carefully monitored for signs of mitochondrial toxicity and lactic acidosis. Dental and periodontal disorders have been reported and regular dental examinations and good oral hygiene are advised.

Contact lenses. Report of damage to a nurse's soft contact lenses after intermittent occupational exposure to aerosolised ribavirin over a period of 1 month.[1]

1. Diamond SA, Dupuis LL. Contact lens damage due to ribavirin exposure. *DICP Ann Pharmacother* 1989; **23:** 428–9.

Pregnancy. Oral ribavirin has been reported to be teratogenic and embryocidal in *rodents* and is contra-indicated in pregnancy or in those who may become pregnant. Ribavirin was not found to be teratogenic in *baboons*. Although there are no case reports of teratogenicity after exposure to aerosolised ribavirin during pregnancy, licensed product information advises that pregnant women and those planning pregnancy should avoid exposure to the aerosol. Pregnancy should also be avoided in partners of male patients taking ribavirin orally. Effective contraception should be used during treatment and for 6 months after the end of treatment. Male patients whose partners are pregnant should use a condom to minimise vaginal exposure to ribavirin.

Interactions

Use of ribavirin with zidovudine is not recommended as patients are at increased risk of anaemia. Increased toxicity has also been seen with didanosine, and the combination should be avoided. Ribavirin inhibits the phosphorylation of NRTIs such as zidovudine, lamivudine, and stavudine, but although UK licensed product information suggests this may reduce their activity against HIV, US product information indicates that no such reduction has been seen in practice.

Anticoagulants. For reference to the effect of ribavirin on the activity of *warfarin*, see under Antivirals, p.1430.

Antiviral Action

Ribavirin inhibits many viruses *in vitro* and in *animal* models. However, this activity has not necessarily correlated with activity against human infections. Ribavirin is phosphorylated but its mode of action is still unclear; it may act at several sites, including cellular enzymes, to interfere with viral nucleic acid synthesis. The mono- and triphosphate derivatives are believed to be responsible for its antiviral activity. Susceptible DNA viruses include herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include Lassa virus, members of the bunyaviridae group, influenza, parainfluenza, measles, mumps, and RSV, and HIV.

Pharmacokinetics

Aerosolised ribavirin is absorbed systemically, but local concentrations in the respiratory tract secretions are much higher than plasma concentrations. Plasma half-life is about 9.5 hours. The bioavailability of aerosolised ribavirin is unknown and may depend on the mode of delivery.

Ribavirin is rapidly absorbed after oral doses and peak plasma concentrations have been reported within 1 to 2 hours. Absorption is extensive but oral bioavailability is about 45 to 65% as a result of first-pass metabolism. Steady state plasma concentrations are achieved after about 4 weeks with twice-daily oral doses resulting in peak plasma concentrations 6 times higher than that after single doses. On stopping dosing the plasma half-life is about 300 hours as a result of slow elimination from non-plasma compartments. Ribavirin does not bind to plasma proteins. Ribavirin is not metabolised by the cytochrome P450 system; it is metabolised by reversible phosphorylation and degradation involving deribosylation and amide hydrolysis to give a triazole carboxyacid metabolite. After a single oral dose the terminal half-life is about 120 to 170 hours. Ribavirin is mainly excreted in the urine as unchanged drug and metabolites. Insignificant amounts of the drug are removed by haemodialysis.

◊ References.

1. Kramer TH, *et al.* Hemodialysis clearance of intravenously administered ribavirin. *Antimicrob Agents Chemother* 1990; **34:** 489–90.
2. Glue P, *et al.* The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *Br J Clin Pharmacol* 2000; **49:** 417–21.
3. Tsubota A, *et al.* Pharmacokinetics of ribavirin in combined interferon-alpha 2b and ribavirin therapy for chronic hepatitis C virus infection. *Br J Clin Pharmacol* 2003; **55:** 360–7.
4. Kamar N, *et al.* Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it depends on renal function. *Am J Kidney Dis* 2004; **43:** 140–6.
5. Uchida M, *et al.* Assessment of adverse reactions and pharmacokinetics of ribavirin in combination with interferon alpha-2b in patients with chronic hepatitis C. *Drug Metab Pharmacokinet* 2004; **19:** 438–43.
6. Wade JR, *et al.* Pharmacokinetics of ribavirin in patients with hepatitis C virus. *Br J Clin Pharmacol* 2006; **62:** 710–14.

Uses and Administration

Ribavirin is a synthetic nucleoside analogue structurally related to guanine. It is given by aerosol in the treatment of RSV infections (p.860); this route appears to give better results than the oral route although its efficacy is questionable. It is used orally with an interferon alfa or peginterferon alfa in the treatment of chronic hepatitis C, including HIV co-infection (p.851). Ribavirin has been tried in haemorrhagic fevers (such as haemorrhagic fever with renal syndrome and Lassa fever) and in SARS.

For details of doses in children, see below.

Ribavirin is used, with an interferon alfa or peginterferon 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 those with hepatitis C infection alone (*mono-infection*), patients with viral genotype 1, and probably genotype 4, should generally be treated for 48 weeks and those with genotype 2 or 3 for 24 weeks; data on genotypes 5 or 6 are insufficient to make recommendations. In *co-infection* with HIV, treatment should generally be given for 48 weeks regardless of genotype.

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

The following doses are recommended in the UK:

- adults up to 65 kg: 400 mg both in the morning and in the evening
- 65 to 85 kg: 400 mg in the morning and 600 mg in the evening
- from 85 to 105 kg: 600 mg both in the morning and in the evening
- over 105 kg: 600 mg in the morning and 800 mg in the evening

In the USA, the doses are:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

Copegus (*Roche*) is used in the UK with interferon alfa-2a or peginterferon alfa-2a and in the USA with peginterferon alfa-2a.

The following doses are used with peginterferon alfa-2a for mono-infection in genotype 1 or 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For mono-infection in genotype 2 or 3 (with peginterferon alfa-2a):

- all adults: 400 mg both in the morning and in the evening

The following doses are used with interferon alfa-2a for mono-infection in genotype 1 to 4:

- adults up to 75 kg: 400 mg in the morning and 600 mg in the evening
- over 75 kg: 600 mg both in the morning and in the evening

For co-infection with HIV:

- all adults: 800 mg daily, irrespective of genotype

Dose reductions of ribavirin may be necessary in patients who develop low haemoglobin concentrations. Ribavirin is contra-indicated in patients with a creatinine clearance less than 50 mL/minute.

◊ Reviews.

1. Plosker GL, Keating GM. Peginterferon-α-2a (40kD) plus ribavirin: a review of its use in hepatitis C virus and HIV co-infection. *Drugs* 2004; **64:** 2823–43.
2. Keating GM, Plosker GL. Peginterferon α-2a (40KD) plus ribavirin: a review of its use in the management of patients with chronic hepatitis C and persistently 'normal' ALT levels. *Drugs* 2005; **65:** 521–36.
3. Gish RG. Treating HCV with ribavirin analogues and ribavirin-like molecules. *J Antimicrob Chemother* 2006; **57:** 8–13.
4. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
5. Keam SJ, Cvetković RS. Peginterferon-α-2a (40 kD) plus ribavirin: a review of its use in the management of chronic hepatitis C mono-infection. *Drugs* 2008; **68:** 1273–1317.

Administration in children. Preparations of ribavirin are available for aerosol administration to infants and children with severe **RSV** infection via a small particle aerosol generator. Solutions containing 20 mg/mL are used; 300 mL, representing 6 g

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.

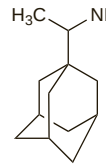
Римантадина Гидрохлорид

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