tion recommends that it should only be given to breast-feeding mothers if the potential benefit justifies the potential risk.

Pregnancy. Studies in *rodents* given high doses of oseltamivir have not found it to be fetotoxic or embryotoxic. There is little data available on the use of oseltamivir in pregnant women and licensed product information recommends that it should only be given to pregnant women if the potential benefit justifies the potential risk.

Interactions

Oseltamivir may potentially inhibit replication of the influenza virus in live influenza virus vaccines. Therefore, US licensed product information states that live influenza virus vaccines should not be given until 48 hours after stopping oseltamivir and that oseltamivir should not be given for 2 weeks after live influenza virus vaccines have been given. Inactivated (split virion or surface antigen) vaccines are not expected to be affected by oseltamivir.

Antiviral Action

Oseltamivir has antiviral activity similar to that of zanamivir (p.913). Its active metabolite, oseltamivir carboxylate, selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells. Oseltamivir is active against influenza A and B viral neuraminidase.

Resistance. Oseltamivir-resistant type A virus, including H5N1 subtypes, have been reported in patients being treated for influenza.[1-3] A study[1] in Japan found that 9 of 50 (18%) children with influenza A (H3N2) virus infection who had been treated with oseltamivir had a virus with a drug-resistance mutation in the neuraminidase gene (predominantly R292K). Another study[4] in Japan reported resistant influenza A (H1N1) viruses with the H274Y mutation in 7 of 43 (16%) oseltamivir-treated children. In both these studies the children were given an oral dose of 2 mg/kg twice daily. However, a larger study[5] in the US reported no resistance in children who received age- and weight-tailored (and therefore sometimes substantially higher) doses than those used in the Japanese studies. No viruses resistant to zanamivir have been isolated from immunocompetent people,[6] although there is a case of resistance in an immunocompromised child.[7]

1. Kiso M, *et al.* Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004; **364:** 759–65.
2. de Jong MD, *et al.* Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; **353:** 2667–72.
3. Le QM, *et al.* Avian flu: isolation of drug-resistant H5N1 virus. *Nature* 2005; **437:** 1108. Correction. *ibid.*; **438:** 754.
4. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; **55** (suppl 1): i5–i21.
5. Hayden FG, *et al.* Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004; **189:** 440–9.
6. Moscona A. Oseltamivir-resistant influenza? *Lancet* 2004; **364:** 733–4.
7. Gubareva LV, *et al.* Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998; **178:** 1257–62.

Pharmacokinetics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral doses and is extensively metabolised in the liver to the active entity, oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as the carboxylate. Binding to plasma proteins is about 3% for the carboxylate and 42% for the parent drug. Oseltamivir has a plasma half-life of 1 to 3 hours and the carboxylate a plasma half-life of 6 to 10 hours. The carboxylate is not metabolised further and is eliminated in the urine.

◊ Reviews.

1. Abe M, *et al.* Pharmacokinetics of oseltamivir in young and very elderly subjects. *Ann Pharmacother* 2006; **40:** 1724–30.

Uses and Administration

Oseltamivir is a prodrug of oseltamivir carboxylate, an inhibitor of the enzyme neuraminidase (sialidase), which has a role in the infectivity and replication of influenza A and B viruses. It is used in adults and children over 1 year of age for the treatment and postexposure prophylaxis of influenza A and B (below).

Oseltamivir is given orally as the phosphate, but doses are expressed in terms of the base. Oseltamivir phosphate 98.5 mg is equivalent to about 75 mg of oseltamivir. For the *treatment* of adults a dose of 75 mg is given twice daily for 5 days, beginning as soon as possible (within 48 hours) after the onset of symptoms. For *postexposure prophylaxis* the usual dose is 75 mg given once daily for at least 10 days and for up to 6 weeks during an epidemic; therapy should begin within 48 hours of exposure.

For details of doses in children, see below.

Dosage should be reduced in patients with moderate renal impairment (see below).

Oseltamivir has been tried both for prophylaxis and treatment of H5N1 disease (avian influenza) and many countries are stockpiling the drug in order to contain any potential pandemic until an effective vaccine can be developed.

Administration in children. Oseltamivir is given orally in the treatment and prophylaxis of influenza A and B in children aged 1 year and over. Doses determined by body-weight may be given twice daily for treatment, or once daily for prophylaxis, of influenza A and B as follows:

- children over 40 kg: 75 mg
- more than 23 kg to 40 kg: 60 mg
- more than 15 kg to 23 kg: 45 mg
- 15 kg or less: 30 mg

Therapy should begin within 48 hours of exposure.

Administration in renal impairment. Dosage of oseltamivir should be reduced in patients with moderate renal impairment, according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: *treatment of influenza*: 75 mg once daily or 30 mg twice daily; *prevention*: 75 mg on alternate days or 30 mg daily
- CC less than 10 mL/minute: not recommended
- dialysis patients: not recommended

Influenza. Reviews[1-8] of oseltamivir and other neuraminidase inhibitors in the treatment and prophylaxis of influenza (p.859). There is some evidence[9] that zanamivir is more effective than oseltamivir for influenza B.

1. Gubareva LV, *et al.* Influenza virus neuraminidase inhibitors. *Lancet* 2000; **355:** 827–35.
2. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs* 2001; **61:** 263–83.
3. Jefferson TO, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
4. Matheson NJ, *et al.* Neuraminidase inhibitors for preventing and treating influenza in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
5. Cooper NJ, *et al.* Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003; **326:** 1235–9.
6. Dutkowski R, *et al.* Safety and pharmacology of oseltamivir in clinical use. *Drug Safety* 2003; **26:** 787–801.
7. Ward P, *et al.* Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005; **55** (suppl 1): i5–i21.
8. Democratis J, *et al.* Use of neuraminidase inhibitors to combat pandemic influenza. *J Antimicrob Chemother* 2006; **58:** 911–15.
9. Kawai N, *et al.* A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect* 2008; **56:** 51–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Agucort; Tamiflu; ***Austral.:*** Tamiflu; ***Austria:*** Tamiflu; ***Belg.:*** Tamiflu; ***Braz.:*** Tamiflu; ***Canad.:*** Tamiflu; ***Chile:*** Rimivat; Tamiflu; Virobin; ***Cz.:*** Tamiflu; ***Denm.:*** Tamiflu; ***Fin.:*** Tamiflu; ***Fr.:*** Tamiflu; ***Ger.:*** Tamiflu; ***Gr.:*** Tamiflu; ***Hong Kong:*** Tamiflu; ***Hung.:*** Tamiflu; ***Irl.:*** Tamiflu; ***Israel:*** Tamiflu; ***Ital.:*** Tamiflu; ***Jpn:*** Tamiflu; ***Malaysia:*** Fluhalt; Tamiflu; ***Neth.:*** Tamiflu; ***Norw.:*** Tamiflu; ***NZ:*** Tamiflu; ***Philipp.:*** Tamiflu; ***Pol.:*** Tamiflu; ***Port.:*** Tamiflu; ***S.Afr.:*** Tamiflu; ***Singapore:*** Tamiflu; ***Swed.:*** Tamiflu; ***Switz.:*** Tamiflu; ***Thai.:*** Tamiflu; ***Turk.:*** Tamiflu; ***UK:*** Tamiflu; ***USA:*** Tamiflu.

Penciclovir *(BAN, USAN, rINN)*

BRL-39123; BRL-39123-D (penciclovir sodium); Penciclovirum; Penciklovir; Pensikloviiri; Pensiklovir. 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.

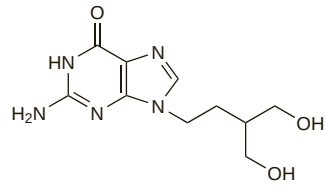
Пенцикловир

$C_{10}H_{15}N_5O_3$ = 253.3.

CAS — 39809-25-1 (penciclovir); 97845-62-0 (penciclovir sodium).

ATC — D06BB06; J05AB13.

ATC Vet — QD06BB06; QJ05AB13.



Adverse Effects and Precautions

Penciclovir applied topically may cause transient stinging, burning, and numbness.

For adverse effects of penciclovir after systemic use of famciclovir, see p.876.

Interactions

Plasma concentrations of penciclovir may be increased in patients receiving *probenecid* with the prodrug famciclovir.

Antiviral Action

Penciclovir has antiviral activity similar to that of aciclovir (p.863). It is active *in vitro* and *in vivo* against herpes simplex virus types 1 and 2 and against varicella-zoster virus. This activity is due to intracellular conversion by virus-induced thymidine kinase into penciclovir triphosphate, which inhibits replication of viral DNA and persists in infected cells for more than 12 hours. It also has activity against Epstein-Barr virus and hepatitis B virus.

◊ References.

1. Vere-Hodge RA. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. *Antiviral Chem Chemother* 1993; **4:** 67–84.
2. Boyd MR, *et al.* Penciclovir: a review of its spectrum of activity, selectivity, and cross-resistance pattern. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 3–11.
3. Bacon TH, Boyd MR. Activity of penciclovir against Epstein-Barr virus. *Antimicrob Agents Chemother* 1995; **39:** 1599–1602.

Pharmacokinetics

Penciclovir is poorly absorbed from the gastrointestinal tract. For systemic use it is usually given orally as the prodrug famciclovir, which is rapidly converted to penciclovir. Peak plasma concentrations proportional to the dose (over the range 125 to 750 mg) are achieved after 45 minutes to 1 hour. The plasma elimination half-life is about 2 hours. The intracellular half-life of the active triphosphate metabolite is longer. Penciclovir is less than 20% bound to plasma proteins. Penciclovir is mainly excreted unchanged in the urine.

Uses and Administration

Penciclovir is a nucleoside analogue structurally related to guanine, which is active against herpesviruses. It is applied topically as a 1% cream every 2 hours during waking hours for 4 days in the treatment of herpes labialis (see Herpes Simplex Infections, p.854).

For systemic use, penciclovir is given orally as the prodrug famciclovir (see p.876). Intravenous dosage of penciclovir has been investigated.

◊ References.

1. Spruance SL, *et al.* Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *JAMA* 1997; **277:** 1374–9.
2. Lazarus HM, *et al.* Intravenous penciclovir for treatment of herpes simplex infections in immunocompromised patients: results of a multicenter, acyclovir-controlled trial. *Antimicrob Agents Chemother* 1999; **43:** 1192–7.
3. Boon R, *et al.* Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2000; **22:** 76–90.
4. Raborn GW, *et al.* Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002; **133:** 303–9.
5. Lin L, *et al.* Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatol Treat* 2002; **13:** 67–72.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Pentavir; ***Austral.:*** Vectavir; ***Austria:*** Famvir; Vectavir; ***Belg.:*** Vectavir; ***Braz.:*** Penvir Labia; Vectavir; ***Cz.:*** Vectavir; ***Denm.:*** Vectavir; ***Fin.:*** Vectavir; ***Ger.:*** Fenistil Pencivir; Vectavir†; ***Gr.:*** Fenivir; Vectavir; ***Hong Kong:*** Vectavir†; ***Hung.:*** Fenivir; Vectavir†; ***Israel:*** Vectavir†; ***Ital.:*** Vectavir;

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

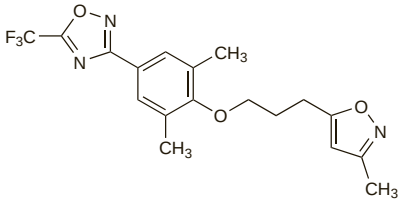
Peptide T is an octapeptide segment of the envelope glycoprotein of HIV. It has been investigated for the treatment of HIV infection and HIV-associated neurological disorders. Peptide T has also been tried in the treatment of psoriasis.

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.

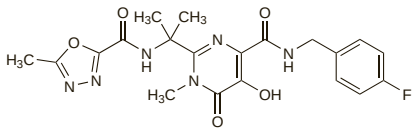
1. Hirayama C, *et al.* Propagermanium: a nonspecific immune modulator for chronic hepatitis B. *J Gastroenterol* 2003; **38:** 525–32.

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

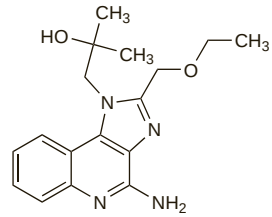
Proprietary Preparations (details are given in Part 3)
Cz.: Isentress; ***Fr.:*** Isentress; ***UK:*** Isentress; ***USA:*** Isentress.

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.

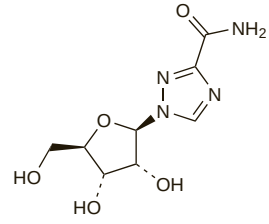
1. Spruance SL, *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; **184:** 196–200.
2. Mark KE, *et al.* Topical resiquimod 0.01% gel decreases herpes simplex virus type 2 genital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