Precautions
Zalcitabine should be interrupted or stopped if peripheral neuropathy develops. Neuropathy is usually slowly reversible if treatment is stopped promptly but may be irreversible if treatment is continued after symptoms develop. Zalcitabine should be avoided in patients who already have peripheral neuropathy and used with caution in patients at risk of developing it (especially those with a low CD4+ cell count) or taking other drugs that may cause it (see Interactions, below).

Treatment should be interrupted in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded. Zalcitabine should be permanently withdrawn if pancreatitis develops. Patients with a history of pancreatitis or of raised serum amylase should be monitored closely. Zalcitabine should not be used with other drugs known to cause pancreatitis (see Interactions, below).

Zalcitabine should be used with caution in patients with hepatic impairment and treatment interrupted or stopped if hepatic function deteriorates or there are signs of hepatic damage or lactic acidosis. It should be used with caution in patients with renal impairment, and dosage reductions may be necessary. It should also be used with caution in patients with cardiomyopathy or heart failure.

Complete blood count and biochemical tests should be carried out before treatment starts and at regular intervals throughout therapy.

Handling. Exposure of the skin to zalcitabine and inhalation of zalcitabine powder should be avoided.

Interactions
Zalcitabine should not be used with other drugs known to cause pancreatitis (for example intravenous pentamidine). Caution is necessary when zalcitabine is given with other drugs that may cause peripheral neuropathy, such as other nucleoside reverse transcriptase inhibitors, chloramphenicol, dapsone, ethionamide, isoniazid (the clearance of which may also be affected—see p.290), metronidazole, nitrofurantoin, ribavirin, and vincristine. Use of zalcitabine with didanosine is not recommended.

The absorption of zalcitabine is reduced by about 25% when given with aluminium- or magnesium-containing antacids.

Cimetidine, probenecid, or trimethoprim can reduce the renal excretion of zalcitabine, resulting in elevated plasma concentrations. Renal excretion of zalcitabine may also be reduced by amphotericin B, aminoglycosides, or foscarnet, potentially increasing its toxicity.

The antiviral action of zalcitabine may be antagonised by lamivudine and the two drugs should not be used together.

Antiviral Action
Zalcitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA.

The emergence of zalcitabine-resistant strains of HIV has been reported.

◊ References.

1. Jeffries DJ. The antiviral activity of dideoxycytidine. *J Antimicrob Chemother* 1989; **23** (suppl A): 29–34.

Pharmacokinetics
Zalcitabine is absorbed from the gastrointestinal tract with a bioavailability of greater than 80%. The rate of absorption is reduced if given with food. Peak plasma concentrations in the fasting state are achieved within about 1 hour. Zalcitabine crosses the blood-brain barrier producing CSF concentrations ranging from 9 to 37% of those in plasma. Binding to plasma proteins is negligible. The plasma elimination half-life is about 2 hours.

Zalcitabine is metabolised intracellularly to the active antiviral triphosphate. It does not appear to undergo any substantial hepatic metabolism and is excreted mainly in the urine, in part by active tubular secretion.

Uses and Administration
Zalcitabine is a nucleoside reverse transcriptase inhibitor derived from cytidine with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when zalcitabine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

Zalcitabine is given orally in a dose of 750 micrograms every 8 hours. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. Doses of zalcitabine should be reduced for patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 40 mL/minute: 750 micrograms every 12 hours
- CC less than 10 mL/minute: 750 micrograms every 24 hours

Preparations
USP 31: Zalcitabine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hivid†; Inxibir†; ***Austral.:*** Hivid; ***Austria:*** Hivid; ***Belg.:*** Hivid; ***Braz.:*** Hivid†; ***Canad.:*** Hivid; ***Chile:*** Hivid†; ***Cz.:*** Hivid†; ***Denm.:*** Hivid†; ***Fin.:*** Hivid; ***Fr.:*** Hivid†; ***Ger.:*** Hivid; ***Gr.:*** Hivid; ***Hong Kong:*** Hivid†; ***Irl.:*** Hivid†; ***Israel:*** Hivid; ***Ital.:*** Hivid; ***Jpn:*** Hivid; ***Mex.:*** Arlevid; Hivid; ***Neth.:*** Hivid; ***Port.:*** Hivid†; ***S.Afr.:*** Hivid†; ***Singapore:*** Hivid†; ***Spain:*** Hivid; ***Swed.:*** Hivid†; ***Switz.:*** Hivid†; ***Thai.:*** Hivid; ***Turk.:*** Hivid; ***UK:*** Hivid†; ***USA:*** Hivid†; ***Venez.:*** Hivid.

Zanamivir *(BAN, USAN, rINN)*

GG-167; GR-121167X; 4-Guanidino-2,4-dideoxy-2,3-dehydro-*N*-acetylneuraminic Acid; Tsanamiviiri; Zanamivirum. 5-Acetamido-2,6-anhydro-3,4,5-trideoxy-4-guanidino-D-*glycero*-D-*galacto*-non-2-enonic acid.

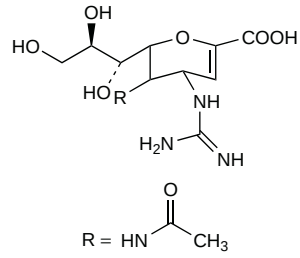
Занамивир

$C_{12}H_{20}N_4O_7$ = 332.3.

CAS — 139110-80-8.

ATC — J05AH01.

ATC Vet — QJ05AH01.



Adverse Effects
Inhaled zanamivir has generally been well tolerated. Acute bronchospasm or decline in respiratory function, with some fatalities, has been reported rarely in patients with a history of respiratory disease and very rarely in those with no such history. Other effects that have been noted include nasal symptoms, headache, gastrointestinal symptoms, cough, and bronchitis, but they may be difficult to distinguish from the symptoms of influenza. There have also been rare reports of hypersensitivity reactions, including oropharyngeal oedema and severe skin rashes.

There have been postmarketing reports (mostly from Japan) of neuropsychiatric adverse effects, such as delirium and abnormal behaviour, in patients taking neuraminidase inhibitors such as zanamivir.

◊ Reviews.

1. Freund B, *et al.* Zanamivir: a review of clinical safety. *Drug Safety* 1999; **21:** 267–81.
2. Gravenstein S, *et al.* Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Safety* 2001; **24:** 1113–25.

Precautions
Zanamivir should be used with caution in patients with chronic respiratory diseases as they may be at increased risk of bronchospasm; if zanamivir use is considered appropriate, patients with asthma or chronic obstructive pulmonary disease should have a fast-acting bronchodilator available during treatment. Patients on maintenance therapy with inhaled bronchodilators should inhale the bronchodilator before zanamivir. Patients experiencing bronchospasm should be advised to stop zanamivir and seek medical attention.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Antiviral Action
Zanamivir inhibits the viral surface enzyme neuraminidase (sialidase) which is essential for the release of newly formed viral particles from infected cells, and may facilitate access of virus through mucus to the cell surface. Zanamivir is active against influenza A and B virus replication.

Resistance. For information on the development of resistance to zanamivir and other neuramidase inhibitors, see under Oseltamivir, p.901.

Pharmacokinetics
Zanamivir is poorly absorbed after oral doses with a bioavailability of about 2%. Inhaled doses produce high local concentrations in the respiratory tract. About 4 to 20% of the inhaled dose is absorbed producing peak serum concentrations at about 1 to 2 hours. Zanamivir is less than 10% bound to plasma protein. It is not metabolized and the absorbed portion is excreted unchanged in the urine with a serum half-life of 2.6 to 5 hours; unabsorbed drug is excreted in the faeces.

◊ References.

1. Aoki FY, Hayden FG (eds.). The pharmacokinetics of zanamivir: a new inhaled antiviral for influenza. *Clin Pharmacokinet* 1999; **36** (suppl 1): 1–58.

Uses and Administration
Zanamivir is a neuraminidase inhibitor used by inhalation for the treatment and prophylaxis (postexposure and seasonal) of influenza A and B (p.859). For *treatment*, it is given to adults in a dose of 10 mg twice daily for 5 days, starting as soon as possible (within 48 hours) after the onset of symptoms.

Zanamivir is given by inhalation for *postexposure prophylaxis* of influenza A and B in household or close contacts and should be started within 36 hours of exposure. The dose for adults is 10 mg once daily for 10 days. For *seasonal prophylaxis* in a community setting 10 mg once daily may be given to adults and adolescents for 28 days and treatment should start within 5 days of an outbreak.

For details of doses in children, see below.

Administration in children. Zanamivir is given by inhalation for the treatment and postexposure prophylaxis of influenza A and B. For *treatment*, children may be given the same dose as adults (10 mg twice daily for 5 days), starting within 36 to 48 hours after the onset of symptoms. In the USA it is approved for those from 7 years of age whereas UK licensed product information permits use from 5 years of age.

Postexposure prophylaxis after close contact with infected patients should be started within 36 hours of exposure. Children from 5 years of age may be given the same dose as adults (10 mg once daily for 10 days).

Influenza. Reviews.[1,2] For further reviews on neuraminidase inhibitors (including zanamivir), see Influenza, under Oseltamivir, p.901.

1. Cheer SM, Wagstaff AJ. Zanamivir: an update of its use in influenza. *Drugs* 2002; **62:** 71–106.
2. Fleming DM. Zanamivir in the treatment of influenza. *Expert Opin Pharmacother* 2003; **4:** 799–805.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Relenza†; ***Austral.:*** Relenza; ***Austria:*** Relenza; ***Belg.:*** Relenza; ***Braz.:*** Relenza; ***Canad.:*** Relenza; ***Chile:*** Relenza†; ***Cz.:*** Relenza; ***Denm.:*** Relenza†; ***Fin.:*** Relenza; ***Fr.:*** Relenza; ***Ger.:*** Relenza; ***Gr.:*** Relenza; ***Hong Kong:*** Relenza; ***Hung.:*** Relenza; ***Irl.:*** Relenza†; ***Israel:*** Relenza†; ***Ital.:*** Relenza; ***Malaysia:*** Relenza; ***Mex.:*** Relenza; ***Neth.:*** Relenza; ***Norw.:*** Relenza; ***NZ:*** Relenza; ***Port.:*** Relenza; ***S.Afr.:*** Relenza; ***Singapore:*** Relenza; ***Spain:*** Relenza; ***Swed.:*** Relenza; ***Switz.:*** Relenza; ***Turk.:*** Relenza; ***UK:*** Relenza; ***USA:*** Relenza.

Zidovudine *(BAN, USAN, rINN)*

Azidodeoxythymidine; Azidothymidine; AZT; BW-A509U; BW-509U; Compound-S; Tsidovudiini; Zidovudin; Zidovudina; Zidovudinas; Zidovudinum; Zydowudyna. 3′-Azido-3′-deoxythymidine.

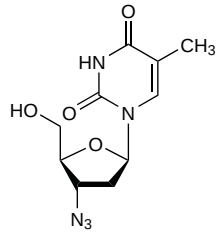
Зидовудин

$C_{10}H_{13}N_5O_4$ = 267.2.

CAS — 30516-87-1.

ATC — J05AF01.

ATC Vet — QJ05AF01.



NOTE. The abbreviation AZT has also been used for azathioprine.

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

Ph. Eur. 6.2 (Zidovudine). A white or brownish powder. It shows polymorphism. Sparingly soluble in water; soluble in dehydrated alcohol. Protect from light.

USP 31 (Zidovudine). A white to yellowish powder. Exhibits polymorphism. Sparingly soluble in water; soluble in alcohol.