

Tromantadine Hydrochloride (rINNM)

D-41; Hidrocloruro de tromantadina; Tromantadine, Chlorhydrate de; Tromantadini Hydrochloridum. N-1-Adamantyl-2-(2-dimethylaminoethoxy)acetamide hydrochloride; 2-(2-Dimethylaminoethoxy)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)acetamide hydrochloride.

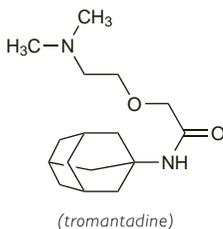
Тромантадина Гидрохлорид

C₁₆H₂₈N₂O₂·HCl = 316.9.

CAS — 53783-83-8 (tromantadine); 41544-24-5 (tromantadine hydrochloride).

ATC — D06BB02; J05AC03.

ATC Vet — QD06BB02; QJ05AC03.

**Profile**

Tromantadine hydrochloride is a derivative of amantadine (p.792) used for its antiviral activity. It is applied topically at a concentration of 1% in the treatment of herpes simplex infections of the skin and mucous membranes (p.854). Contact dermatitis has been reported after the topical use of tromantadine hydrochloride.

Effects on the skin. References to contact dermatitis associated with the use of tromantadine.

- Fanta D, Mischer P. Contact dermatitis from tromantadine hydrochloride. *Contact Dermatitis* 1976; **2**: 282–4.
- Lembo G, et al. Allergic dermatitis from Viruseol ointment probably due to tromantadine hydrochloride. *Contact Dermatitis* 1984; **10**: 317.
- Jauregui I, et al. Allergic contact dermatitis from tromantadine. *J Investig Allergol Clin Immunol* 1997; **7**: 260–1.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Viru-Merz Serol; **Belg:** Viru-Merz; **Braz:** Herpeq; **Chile:** Viru-Merz; **Cz:** Viru-Merz; **Ger:** Viru-Merz Serol; **Gr:** Viru-Merz Serol; **Hong Kong:** Viru-Merz; **Hung:** Viru-Merz; **Indon:** Viru-Merz; **Israel:** Viru-Merz; **Italy:** Viruserol; **Malaysia:** Viru-Merz; **Mex:** Viru-Serol; **Neth:** Viru-Merz; **Philipp:** Viru-Merz; **Pol:** Viru-Merz; **Port:** Viru-Merz; **Rus:** Viru-Merz Serol (Вирю-Мерц Серол); **Singapore:** Viru-Merz; **Spain:** Viru-Serol; **Switz:** Viru-Merz Serol.

Valaciclovir Hydrochloride

(BANM, rINNM)

Hidrocloruro de valaciclovir; 256U87 (valaciclovir); Valaciclovir, chlorhydrate de; Valacicloviri hydrochloridum; Valaciclovir Hydrochloride (USAN). L-Valine, ester with 9-[[2-(hydroxyethoxy)methyl]guanine hydrochloride.

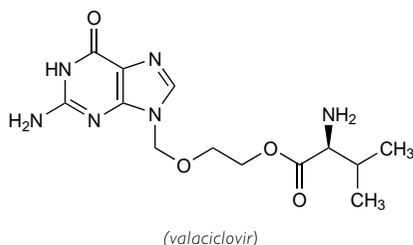
Валацикловира Гидрохлорид

C₁₃H₂₀N₆O₄·HCl = 360.8.

CAS — 124832-26-4 (valaciclovir); 124832-27-5 (valaciclovir hydrochloride);

ATC — J05AB11.

ATC Vet — QJ05AB11.



Pharmacopoeias. In *Chin*.

Adverse Effects and Precautions

As for Aciclovir, p.863.

Breast feeding. In a study in 5 women who took oral valaciclovir 500 mg twice daily for 7 days, concentrations of the active metabolite aciclovir in breast milk were 3.4 times those in maternal serum at 4 hours after the initial dose, although the ratio declined to 1.85 at steady-state concentrations. Nonetheless, it was calculated that the amount ingested by an infant would be negligible (about 2% of a standard neonatal dose of intravenous aciclovir, with exposure further reduced by the poor oral bioavailability of the drug), and valaciclovir was thus considered compatible with breast feeding.¹

1. Sheffield JS, et al. Acyclovir concentrations in human breast milk after valaciclovir administration. *Am J Obstet Gynecol* 2002; **186**: 100–102.

Effects on the nervous system. Mononeuritis multiplex due to vasculitis has been reported¹ in a woman a week after a one-day course of valaciclovir for the treatment of herpes labialis. Symptoms improved within 10 days of treatment with oral prednisolone but reoccurred upon rechallenge with valaciclovir.

- Pary LF, et al. Vasculitic mononeuritis multiplex induced by valaciclovir. *Neurology* 2004; **62**: 1906–7.

Interactions

As for Aciclovir, p.863.

Antiviral Action

As for Aciclovir, p.863.

Pharmacokinetics

As for Aciclovir, p.863.

Valaciclovir is readily absorbed from the gastrointestinal tract after oral doses, and is rapidly converted to aciclovir and valine by first-pass intestinal or hepatic metabolism. The bioavailability of aciclovir after dosage with valaciclovir is reported to be 54% and peak plasma concentrations of aciclovir are achieved after 1.5 hours. Valaciclovir is eliminated mainly as aciclovir and its metabolite 9-carboxymethoxymethylguanine; less than 1% of a dose of valaciclovir is excreted unchanged in the urine.

References

- Steingrimsdottir H, et al. Bioavailability of aciclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. *Antimicrob Agents Chemother* 2000; **44**: 207–9.
- Höglund M, et al. Comparable aciclovir exposures produced by oral valaciclovir and intravenous aciclovir in immunocompromised cancer patients. *J Antimicrob Chemother* 2001; **47**: 855–61.
- Bras AP, et al. Comparative bioavailability of acyclovir from oral valaciclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol* 2001; **8**: 207–11.
- Nadal D, et al. An investigation of the steady-state pharmacokinetics of oral valaciclovir in immunocompromised children. *J Infect Dis* 2002; **186** (suppl 1): S123–S130.
- MacDougall C, Guglielmo BJ. Pharmacokinetics of valaciclovir. *J Antimicrob Chemother* 2004; **53**: 899–901.

Uses and Administration

Valaciclovir is a prodrug of the antiviral aciclovir (p.864). It is used in the treatment of herpes zoster (p.855) and herpes simplex infections (p.854) of the skin and mucous membranes, including genital herpes. Treatment should be started as soon as symptoms occur. Valaciclovir is used for the suppression of recurrent herpes simplex infections and can reduce the risk of transmission of genital herpes to susceptible partners when used as suppressive therapy and as part of safer sex practices. It is also used for the prophylaxis of CMV infection after renal transplantation. Valaciclovir is given orally as the hydrochloride; doses are expressed in terms of the base. Valaciclovir hydrochloride 1.11 g is equivalent to about 1 g of valaciclovir.

For **herpes zoster**, the dose is 1 g three times daily for 7 days. For treatment of **herpes simplex infections**, 500 mg is given twice daily for 5 days (3 days in the USA) for recurrent episodes or for up to 10 days for a first episode; in the USA, the recommended dose for a first episode of genital herpes is 1 g twice daily for 10 days. For the treatment of herpes labialis, a dose of 4 g in two divided doses 12 hours apart is recommended. For the **suppression** of herpes simplex infection in immunocompetent patients, a dose of 500 mg daily as a single dose or in two divided doses, is recommended; in the USA, a dose of 1 g daily as a single dose is recommended for suppression of recurrent genital herpes. A dose of 500 mg twice daily may be used in immunocompromised patients. To **reduce transmission** of genital herpes a dose of 500 mg daily is taken by the infected partner.

A dose of 2 g four times daily is recommended for prophylaxis of **CMV infection** in renal transplant re-

ipients; prophylaxis should begin within 72 hours and is usually continued for 90 days.

Doses of valaciclovir may need to be reduced in patients with renal impairment (see below).

References

- Ormrod D, et al. Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000; **59**: 839–63.
- Ormrod D, Goa K. Valaciclovir: a review of its use in the management of herpes zoster. *Drugs* 2000; **59**: 1317–40.
- Tyring SK, et al. Valaciclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; **186** (suppl 1): S40–S46.
- Corey L, et al. Once-daily valaciclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350**: 11–20.
- Brantley JS, et al. Valaciclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4**: 367–76.
- Fife KH, et al. Effect of valaciclovir on viral shedding in immunocompetent patients with recurrent herpes simplex virus 2 genital herpes: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2006; **81**: 1321–7.

Administration in renal impairment. Oral doses of valaciclovir may need to be reduced in patients with renal impairment. The following dosage reductions are suggested by the UK licensed product information according to creatinine clearance (CC):

herpes zoster:

- CC 15 to 30 mL/minute: 1 g twice daily
- CC less than 15 mL/minute: 1 g daily
- patients on haemodialysis: 1 g daily after haemodialysis

herpes simplex infections:

- CC less than 15 mL/minute: 500 mg daily
- patients on haemodialysis: 500 mg daily after haemodialysis

suppression of herpes simplex:

- CC less than 15 mL/minute: immunocompetent patients: 250 mg once daily; immunocompromised patients: 500 mg once daily

patients on haemodialysis: immunocompetent patients: 250 mg once daily after haemodialysis; immunocompromised patients: 500 mg once daily after haemodialysis

reduction of transmission of genital herpes:

- CC less than 15 mL/minute: 250 mg daily
- patients on haemodialysis: 250 mg daily after haemodialysis

prophylaxis of CMV:

- CC 50 to 74 mL/minute: 1.5 g four times daily
- CC 25 to 49 mL/minute: 1.5 g three times daily
- CC 10 to 24 mL/minute: 1.5 g twice daily
- CC less than 10 mL/minute: 1.5 g once daily
- patients on haemodialysis: 1.5 g once daily after haemodialysis

Preparations

Proprietary Preparations (details are given in Part 3)

Arg: Valtrex; Viramixal; Viranet; **Austral:** Valtrex; **Austria:** Valtrex; **Belg:** Zelitrex; **Braz:** Valtrex; **Canada:** Valtrex; **Chile:** Pervioral; Vadiral; Valtrex; **Denm:** Valtrex; **Denm:** Zelitrex; **Fin:** Valavir; Valtrex; **Fr:** Zelitrex; **Ger:** Valtrex; **Gr:** Valtrex; **Hong Kong:** Valtrex; **India:** Valovir; **Indon:** Herclor; Valtrex; **Irl:** Valtrex; **Israel:** Valtrex; **Italy:** Talavir; Zelitrex; **Malaysia:** Valtrex; **Mex:** Rapivir; **Neth:** Zelitrex; **Norw:** Valtrex; **Philipp:** Valtrex; **Port:** Valavir; **Rus:** Valtrex (Валтрек); **S.Afr:** Zelitrex; **Singapore:** Valtrex; **Spain:** Valherpes; Valtrex; Virval; **Swed:** Valtrex; **Switz:** Valtrex; **Thai:** Valtrex; **Turk:** Valtrex; **UK:** Valtrex; **USA:** Valtrex; **Venez:** Valtrex.

Valganciclovir Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de valganciclovir; Ro-107-9070/194; RS-079070-194; Valganciclovir, Chlorhydrate de; Valgancicloviri Hydrochloridum. L-Valine, ester with 9-[[[2-(hydroxy-1-(hydroxymethyl)ethoxy)methyl]guanine hydrochloride].

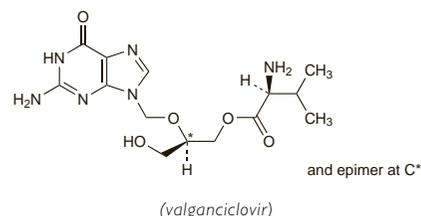
Вальганцикловира Гидрохлорид

C₁₄H₂₂N₆O₅·HCl = 390.8.

CAS — 175865-60-8 (valganciclovir); 175865-59-5 (valganciclovir hydrochloride).

ATC — J05AB14.

ATC Vet — QJ05AB14.



Pharmacopoeias. In *US*.

USP 31 (Valganciclovir Hydrochloride). A white to off-white powder. Freely soluble in alcohol; practically insoluble in acetone or in ethyl acetate; slightly soluble in hexane; very soluble in isopropyl alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Stability. References.

- Anazi NH, *et al.* Stability of valganciclovir in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59**: 1267–70.
- Henkin CC, *et al.* Stability of valganciclovir in extemporaneously compounded liquid formulations. *Am J Health-Syst Pharm* 2003; **60**: 687–90.

Adverse Effects, Treatment, and Precautions

As for Ganciclovir, p.879.

In the USA, valganciclovir is not indicated for use in liver transplant recipients, because of reports of a higher incidence of tissue-invasive CMV infection compared with patients treated with ganciclovir (although see Cytomegalovirus Infections, below). In the UK, valganciclovir is licensed for use in the prevention of CMV disease in all solid organ graft recipients.

Interactions

As for Ganciclovir, p.879.

Antiviral Action

As for Ganciclovir, p.880.

Pharmacokinetics

Valganciclovir is well absorbed from the gastrointestinal tract after oral doses and is rapidly converted to ganciclovir by first-pass intestinal or hepatic metabolism. The bioavailability of ganciclovir after an oral dose with food is reported to be about 60% and peak plasma concentrations of ganciclovir are achieved after 1 to 3 hours. Valganciclovir is eliminated in the urine as ganciclovir (see p.880).

◇ References.

- Brown F, *et al.* Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet* 1999; **37**: 167–76.
- Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. *J Clin Pharmacol* 1999; **39**: 800–4.
- Pescovitz MD, *et al.* Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; **44**: 2811–15.
- Wiltshire H, *et al.* Pharmacokinetic profile of ganciclovir after its oral administration and from its prodrug, valganciclovir, in solid organ transplant recipients. *Clin Pharmacokinet* 2005; **44**: 495–507.
- Winston DJ, *et al.* Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. *Biol Blood Marrow Transplant* 2006; **12**: 635–40.

Uses and Administration

Valganciclovir is a prodrug of the antiviral ganciclovir (p.880) that is used for the treatment of CMV retinitis in patients with AIDS, and for the prevention of CMV disease in transplant recipients who have received an organ from a CMV-positive donor (see below).

Valganciclovir is given orally with food as the hydrochloride; doses are expressed in terms of the base. Valganciclovir hydrochloride 1.1 g is equivalent to about 1 g of valganciclovir.

For *induction* in patients with active CMV retinitis, the dose is 900 mg twice daily for 21 days. For *maintenance* following induction, or in patients with inactive CMV retinitis, the dose is 900 mg daily. Patients whose retinitis deteriorates during maintenance may repeat induction but the possibility of viral resistance should be considered. For *prevention* of CMV disease in organ transplant recipients, the dose is 900 mg daily starting within 10 days and continuing until 100 days after transplantation.

Doses of valganciclovir should be reduced in renal impairment (see Administration in Renal Impairment, below).

◇ Reviews.

- Freeman RB. Valganciclovir: oral prevention and treatment of cytomegalovirus in the immunocompromised host. *Expert Opin Pharmacother* 2004; **5**: 2007–16.
- Cvetković RS, Wellington K. Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. *Drugs* 2005; **65**: 859–78.

Administration in renal impairment. Doses of oral valganciclovir should be reduced in renal impairment according to creatinine clearance (CC). Licensed product information recommends the following doses:

- CC 40 to 59 mL/minute: 450 mg twice daily for *induction* and 450 mg daily for *maintenance* or *prevention*
- CC 25 to 39 mL/minute: 450 mg daily for *induction* and 450 mg every two days for *maintenance* or *prevention*
- CC 10 to 24 mL/minute: 450 mg every two days for *induction* and 450 mg twice weekly for *maintenance* or *prevention*
- haemodialysis patients: not recommended

Cytomegalovirus infections. Valganciclovir produces high systemic concentrations of ganciclovir after oral doses; exposure may be higher than with intravenous ganciclovir regimens.¹ It is therefore active against CMV infections (p.853). It has been shown to be of benefit for both induction therapy and maintenance treatment of CMV retinitis in patients with AIDS,^{2,3} and although this has become less widespread in the developed world with the advent of HAART, it continues to be a problem in resource-poor settings in particular; there have been calls for valganciclovir to be made more widely available for treatment in preference to less effective and convenient drugs.³

Valganciclovir is also used in the prophylaxis and preemptive treatment of CMV infections in transplant recipients,^{4,8} and many centres consider it to be the standard of care for this indication (including in liver transplantation although it is contra-indicated for such use in the USA—see Adverse Effects, Treatment, and Precautions, above).⁹

- Einsle H, *et al.* Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood* 2006; **107**: 3002–8.
- Martin DF, *et al.* Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 2002; **346**: 1119–26. Correction. *ibid.*; **347**: 862.
- Heiden D, *et al.* Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. *PLoS Med* 2007; **4**: e334. Available at: http://medicine.plosjournals.org/archive/1549-1676/4/12/pdf/10.1371_journal.pmed.0040334-S.pdf (accessed 28/08/08)
- Paya C, *et al.* Valganciclovir Solid Organ Transplant Study Group. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 611–20.
- Khoury JA, *et al.* Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant* 2006; **6**: 2134–43.
- Said T, *et al.* Oral valganciclovir versus intravenous ganciclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplant Proc* 2007; **39**: 997–9.
- Asberg A, *et al.* VICTOR Study Group. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; **7**: 2106–13.
- Len O, *et al.* RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46**: 20–7.
- Snydman DR. Use of valganciclovir for prevention and treatment of cytomegalovirus disease. *Clin Infect Dis* 2008; **46**: 28–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Valixa; **Austral.:** Valcyte; **Austria:** Valcyte; **Belg.:** Valcyte; **Braz.:** Valcyte; **Canad.:** Valcyte; **Chile:** Valixa; **Cz.:** Valcyte; **Denm.:** Valcyte; **Fin.:** Valcyte; **Fr.:** Rovalcyte; **Ger.:** Valcyte; **Gr.:** Valcyte; **Hong Kong:** Valcyte; **Hung.:** Valcyte; **Indon.:** Valcyte; **Irl.:** Valcyte; **Israel:** Valcyte; **Ital.:** Danilin; **Valcyte; Mex.:** Valcyte; **Neth.:** Valcyte; **Valixa; Norw.:** Valcyte; **NZ:** Valcyte; **Philipp.:** Valcyte; **Pol.:** Valcyte; **Port.:** Rovalcyte; **S.Afr.:** Valcyte; **Singapore:** Valcyte; **Spain:** Valcyte; **Swed.:** Valcyte; **Switz.:** Valcyte; **Thai.:** Valcyte; **UK:** Valcyte; **USA:** Valcyte; **Venez.:** Valixa.

Vidarabine (BAN, USAN, rINN)

Adenine Arabinoside; Ara-A; CI-673; Vidarabiini; Vidarabin; Vidarabina; Vidarabinum. 9-β-D-Arabinofuranosyladenine monohydrate.

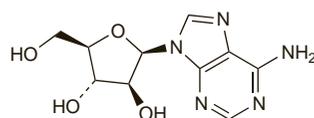
Видарабин

C₁₀H₁₃N₅O₄·H₂O = 285.3.

CAS — 5536-17-4 (anhydrous vidarabine); 24356-66-9 (vidarabine monohydrate).

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.



(anhydrous vidarabine)

Pharmacopoeias. In *US*.

USP 31 (Vidarabine). A white to off-white powder. Very slightly soluble in water; slightly soluble in dimethylformamide. Store in airtight containers.

Vidarabine Phosphate (BANM, USAN, rINN(M))

Ara-AMP; Arabinosyladenine Monophosphate; CI-808; Fosfato de vidarabina; Vidarabine 5'-Monophosphate; Vidarabine, Phosphate de; Vidarabini Phosphas. 9-β-D-Arabinofuranosyladenine 5'-(dihydrogen phosphate).

Видарабина Фосфат

C₁₀H₁₄N₅O₇P = 347.2.

CAS — 29984-33-6.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

Vidarabine Sodium Phosphate (BANM, USAN, rINN(M))

CI-808 Sodium; Fosfato sódico de vidarabina; Natrii Vidarabini Phosphas; Vidarabine, Phosphate Sodique de. 9-β-D-Arabinofuranosyladenine 5'-(dihydrogen phosphate) disodium.

Натрия Видарабина Фосфат

C₁₀H₁₂N₅Na₂O₇P = 391.2.

CAS — 71002-10-3.

ATC — J05AB03; S01AD06.

ATC Vet — QJ05AB03; QS01AD06.

Adverse Effects

Adverse effects that may occur when vidarabine is applied to the eyes include irritation, pain, superficial punctate keratitis, photophobia, lachrymation, and occlusion of the lachrymal duct.

Pharmacokinetics

Systemic absorption does not occur after application of vidarabine to the eye; trace amounts of its principal metabolite hypoxanthine arabinoside (arabinosyl hypoxanthine), and vidarabine, if the cornea is damaged, may be found in the aqueous humour.

Uses and Administration

Vidarabine is a purine nucleoside obtained from *Streptomyces antibioticus*. It has been used in the treatment of herpes simplex and varicella-zoster infections (p.854 and p.855), although aciclovir and related drugs are generally preferred.

Vidarabine has been used topically in the treatment of herpes simplex keratitis and keratoconjunctivitis as a 3% ophthalmic ointment.

It has also been used as the sodium phosphate as a 10% gel for the treatment of genital herpes.

Vidarabine was formerly used intravenously in the treatment of severe and disseminated herpes simplex infections and herpes zoster but aciclovir is preferred.

Preparations

USP 31: Vidarabine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)

Gr.: Erimycin; Tekanin; Virerpin; **Jpn:** Arasena-A.

Zalcitabine (BAN, USAN, rINN)

ddC; ddCyd; Dideoxycytidine; NSC-606170; Ro-24-2027; Ro-24-2027/000; Tsalsitabiini; Zalcitabin; Zalcitabina; Zalcitabinum; Zalsitabin; 2',3'-Dideoxycytidine.

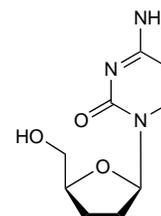
Зальцитабин

C₉H₁₃N₃O₃ = 211.2.

CAS — 7481-89-2.

ATC — J05AF03.

ATC Vet — QJ05AF03.

**Pharmacopoeias.** In *US*.

USP 31 (Zalcitabine). A white to off-white, crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol, in acetonitrile, in chloroform, and in dichloromethane; slightly soluble in cyclohexane. Store in airtight containers. Protect from light.

Adverse Effects

The most serious adverse effects of zalcitabine are peripheral neuropathy, which can affect up to one-third of patients, and pancreatitis which is rare, affecting up to about 1% of patients, but which can be fatal. Other severe adverse effects include oral and oesophageal ulceration, hypersensitivity reactions including anaphylaxis, cardiomyopathy and heart failure, lactic acidosis and severe hepatomegaly with steatosis (both potentially life-threatening), and hepatic failure.