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.

1. Anaizi NH, *et al.* Stability of valganciclovir in an extemporaneously compounded oral liquid. *Am J Health-Syst Pharm* 2002; **59:** 1267–70.
2. 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.

1. 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.
2. Jung D, Dorr A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. *J Clin Pharmacol* 1999; **39:** 800–4.
3. Pescovitz MD, *et al.* Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; **44:** 2811–15.
4. 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.
5. 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.

1. Freeman RB. Valganciclovir: oral prevention and treatment of cytomegalovirus in the immunocompromised host. *Expert Opin Pharmacother* 2004; **5:** 2007–16.
2. 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]

1. Einsele 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.
2. 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.
3. 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)
4. 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.
5. 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.
6. Said T, *et al.* Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transplant Proc* 2007; **39:** 997–9.
7. 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.
8. Len O, *et al.* RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46:** 20–7.
9. Snydman DR. Use of valganciclovir for prevention and treatment of cytomegalovirus disease. *Clin Infect Dis* 2008; **46:** 28–9.

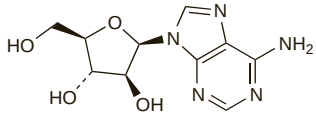
Preparations

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.:*** Darilin; 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
$C_{10}H_{13}N_5O_4,H_2O$ = 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, rINNM)*

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
$C_{10}H_{14}N_5O_7P$ = 347.2.
CAS — 29984-33-6.
ATC — J05AB03; S01AD06.
ATC Vet — QJ05AB03; QS01AD06.

Vidarabine Sodium Phosphate *(BANM, USAN, rINNM)*

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
$C_{10}H_{12}N_5Na_2O_7P$ = 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

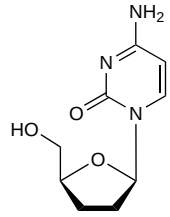
USP 31: Vidarabine Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Gr.: Erpimycin; Tekarin; 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
$C_9H_{13}N_3O_3$ = 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.