For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh class B or C), and should be used with caution in those with mild impairment (Child-Pugh A). Treatment should not be started in patients with pre-treatment liver enzyme values more than 5 times the upper limit of normal. Patients should be closely monitored for clinical signs and symptoms of hepatitis; monitoring of liver enzymes is recommended before and during treatment with tipranavir. In patients with mild hepatic impairment, chronic hepatitis, or other underlying liver disease more frequent monitoring is recommended. Treatment should be interrupted or stopped if liver function deteriorates and should be permanently stopped in those patients with liver enzyme values more than 10 times the upper limit of normal or in those who develop signs or symptoms of clinical hepatitis. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients who are at increased risk of bleeding such as those with haemophilia A and B or who are taking antiplatelet drugs or anticoagulants as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Tipranavir oral solution contains vitamin E and patients given the oral solution should not take high doses of supplemental vitamin E.

Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy.

Interactions

Tipranavir is both an inducer and an inhibitor of the cytochrome P450 isoenzyme CYP3A4 although when given with low-dose ritonavir there is a net inhibition of CYP3A4; there is therefore the potential for complex interactions with other drugs metabolised by this enzyme. Ritonavir-boosted tipranavir is also a net inducer of P-glycoprotein.

Tipranavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, metoprolol, propafenone, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of tipranavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Tipranavir is a non-peptide HIV-protease inhibitor. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. HIV isolates resistant to tipranavir have been reported and viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Tipranavir is absorbed to a limited extent after oral doses. Food improves the tolerability and bioavailability is increased with a high fat meal. Peak plasma concentrations are reached within 1 to 5 hours and steady state is usually reached after 7 to 10 days of treatment. Tipranavir is about 99.9% bound to plasma proteins. It is metabolised by the cytochrome P450 system (predominantly the isoenzyme CYP3A4), although when given with ritonavir metabolism is minimal with the majority of tipranavir being excreted unchanged in the faeces. The mean elimination half-life of tipranavir is 4.8 to 6 hours.

Uses and Administration

Tipranavir is a non-peptide HIV-protease inhibitor with antiviral activity against HIV. It is used for the treatment of HIV infection and AIDS (p.856) in treatment-experienced patients or in those with multidrug-resistant HIV infection. Viral resistance emerges rapidly when tipranavir is used alone, and it is therefore used with other antiretrovirals.

It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer (ritonavir-boosted tipranavir). The dose is tipranavir 500 mg (with ritonavir 200 mg) twice daily with food.

For details of doses in children see below.

No dose adjustment is required for patients with renal impairment or mild liver disease. Tipranavir should not be given to patients with moderate to severe liver disease.

◊ Reviews.

1. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; **65:** 1669–77.
2. Dong BJ, Cocohoba JM. Tipranavir: a protease inhibitor for HIV salvage therapy. *Ann Pharmacother* 2006; **40:** 1311–21.
3. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. *Clin Pharmacokinet* 2006; **45:** 665–82.
4. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of drug-resistant HIV infection. *Clin Infect Dis* 2007; **45:** 761–9.
5. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. *Drugs* 2008; **68:** 1435–63.

Administration in children. For the treatment of HIV infection in children, tipranavir is given orally with other antiretroviral drugs. It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer. US licensed product information permits the use of oral tipranavir in children from 2 years of age. Doses are based on body-weight or body-surface and should not exceed the maximum adult dose (see above).

- The usual recommended dose in children is: tipranavir 14 mg/kg (with ritonavir 6 mg/kg) twice daily *or* tipranavir 375 mg/m^2 (with ritonavir 150 mg/m^2) twice daily
- children who are intolerant or develop toxicities to the usual dose may take a reduced dose: tipranavir 12 mg/kg (with ritonavir 5 mg/kg) twice daily *or* tipranavir 290 mg/m^2 (with ritonavir 115 mg/m^2) twice daily

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aptivus; ***Belg.:*** Aptivus; ***Cz.:*** Aptivus; ***Fin.:*** Aptivus; ***Fr.:*** Aptivus; ***Gr.:*** Aptivus; ***Hung.:*** Aptivus; ***Irl.:*** Aptivus; ***Ital.:*** Aptivus; ***Mex.:*** Aptivus; ***Pol.:*** Aptivus; ***Port.:*** Aptivus; ***Swed.:*** Aptivus; ***UK:*** Aptivus; ***USA:*** Aptivus.

Trichosanthin

Compound Q; GLQ-223 (a purified form of trichosanthin); Tricosantina.

CAS — 60318-52-7 (trichosanthins); 116899-30-0 (Trichosanthes kirilowii); 160185-58-0 (Trichosanthes kirilowii root); 120947-28-6 (GLQ-223).

Profile

Trichosanthin is a polypeptide extracted from the tuber of the Chinese cucumber, *Trichosanthes kirilowii* (Cucurbitaceae). It has been investigated in the treatment of HIV infection and is used in China as an abortifacient.

HIV infection and AIDS. Trichosanthin has been given to patients with AIDS, AIDS-related complex, or HIV infection.[1,2] It has generally been given by intravenous injection, the use of the intramuscular route having been abandoned due to the occurrence of pain and necrosis at the injection site.[1] A common adverse effect with intravenous use was a flu-like syndrome with headache, myalgias, fever, and arthralgia and was generally mild to moderate,[3] although neurological effects progressing to coma with fatalities have been reported.[1,2] Improvements in surrogate markers for HIV infection have been reported including increases in CD4+ T lymphocyte counts in patients with moderate disease[3] and in patients failing to respond to reverse transcriptase inhibitors.[4]

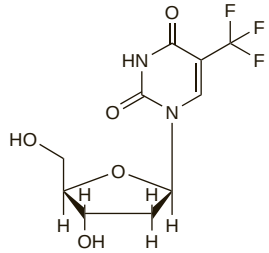
1. Byers VS, *et al.* A phase I/II study of trichosanthin treatment of HIV disease. *AIDS* 1990; **4:** 1189–96.
2. Kahn JO, *et al.* The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. *AIDS* 1990; **4:** 1197–1204.
3. Kahn JO, *et al.* Safety, activity, and pharmacokinetics of GLQ223 in patients with AIDS and AIDS-related complex. *Antimicrob Agents Chemother* 1994; **38:** 260–7.
4. Byers VS, *et al.* A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. *AIDS Res Hum Retroviruses* 1994; **10:** 413–20.

Trifluridine *(USAN, rINN)*

F_3T; F_3TDR; NSC-75520; Trifluorothymidine; Trifluorothymidinum; Trifluorotymidiini; Trifluorotymidin; Trifluridiini; Trifluridin; Trifluridina; Trifluridinum. ααα-Trifluorothymidine; 2′-Deoxy-5-trifluoromethyluridine.

Трифлуридин

$C_{10}H_{11}F_3N_2O_5$ = 296.2.
CAS — 70-00-8.
ATC — S01AD02.
ATC Vet — QS01AD02.



Pharmacopoeias. In *US.*
USP 31 (Trifluridine). A white, odourless powder, appearing under the microscope as rod-like crystals. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects occurring after the use of trifluridine in the eyes are similar to those for idoxuridine (p.881) but have been reported to occur less frequently.

◊ References.

1. Udell IJ. Trifluridine-associated conjunctival cicatrization. *Am J Ophthalmol* 1985; **99:** 363–4.

Antiviral Action

Trifluridine acts similarly to idoxuridine to interfere with viral DNA synthesis after phosphorylation. It is reported to be active against herpes simplex viruses, some adenoviruses, vaccinia viruses, and CMV. Like idoxuridine it is incorporated into mammalian DNA.

Pharmacokinetics

Trifluridine is absorbed through the cornea after application to the eye and penetration may be increased in the presence of damage or inflammation. Systemic absorption does not appear to follow ocular administration.

Uses and Administration

Trifluridine is a pyrimidine nucleoside structurally related to thymidine. It is used in the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses (p.854). One drop of a 1% ophthalmic solution is instilled into the eye every 2 hours up to a maximum of 9 times daily until complete re-epithelialisation has occurred. Treatment is then reduced to one drop every 4 hours to a minimum of 5 drops daily for a further 7 days. Treatment should not be continued for more than a total of 21 days.

Trifluridine, alone or as a combined formulation with a thymidine phosphorylase inhibitor to reduce its metabolism (TAS-102), has been investigated in the treatment of malignant neoplasms.

◊ Reviews.

1. Heidelberger C, King DH. Trifluorothymidine. *Pharmacol Ther* 1979; **6:** 427–42.
2. Carmine AA, *et al.* Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. *Drugs* 1982; **23:** 329–53.
3. Temmink OH, *et al.* Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. *Cancer Sci* 2007; **98:** 779–89.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Viroptic; ***Cz.:*** Triherpine†; ***Fr.:*** Virophta; ***Ger.:*** Triflumann; ***Gr.:*** Thilol; ***Hong Kong:*** Triherpine†; ***Hung.:*** Triherpine†; ***Ital.:*** Triherpine; ***Neth.:*** TFT Ophtiole; ***Port.:*** Adrocil†; Viridin; ***S.Afr.:*** TFT; ***Spain:*** Viromidin; ***Switz.:*** Triherpine†; ***Thai.:*** Triherpine; ***Turk.:*** TFT-Thilo; ***USA:*** Viroptic.

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.

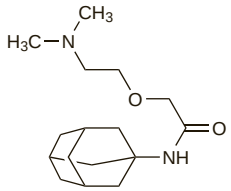
Тромантадина Гидрохлорид

$C_{16}H_{28}N_2O_2$,HCl = 316.9.

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

ATC — D06BB02; J05AC03.

ATC Vet — QD06BB02; QJ05AC03.



(tromantadine)

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.

1. Fanta D, Mischer P. Contact dermatitis from tromantadine hydrochloride. *Contact Dermatitis* 1976; **2:** 282–4.
2. Lembo G, *et al.* Allergic dermatitis from Viruserol ointment probably due to tromantadine hydrochloride. *Contact Dermatitis* 1984; **10:** 317.
3. 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.:*** Herpex; ***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; ***Ital.:*** Viruserol†; ***Malaysia:*** Viru-Merz; ***Mex.:*** Viru-Serol; ***Neth.:*** Viru-Merz†; ***Philipp.:*** Viru-Merz; ***Pol.:*** Viru-Merz; ***Port.:*** Viru-Merz; ***Rus.:*** Viru-Merz Serol (Виру-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; Valacyclovir Hydrochloride *(USAN)*. L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine hydrochloride.

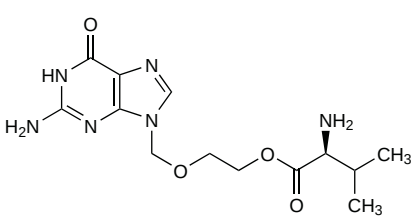
Валацикловира Гидрохлорид

$C_{13}H_{20}N_6O_4$,HCl = 360.8.

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

ATC — J05AB11.

ATC Vet — QJ05AB11.



(valaciclovir)

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 reported[1] 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.

1. Pary LF, *et al.* Vasculitic mononeuritis multiplex induced by valacyclovir. *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.

1. 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.
2. 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.
3. Bras AP, *et al.* Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol* 2001; **8:** 207–11.
4. Nadal D, *et al.* An investigation of the steady-state pharmacokinetics of oral valacyclovir in immunocompromised children. *J Infect Dis* 2002; **186** (suppl 1): S123–S130.
5. 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 recipients; 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.

1. 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.
2. Ormrod D, Goa K. Valaciclovir: a review of its use in the management of herpes zoster. *Drugs* 2000; **59:** 1317–40.
3. Tyring SK, *et al.* Valacyclovir 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.
4. Corey L, *et al.* Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350:** 11–20.
5. Brantley JS, *et al.* Valacyclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4:** 367–76.
6. Fife KH, *et al.* Effect of valacyclovir 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; ***Canad.:*** Valtrex; ***Chile:*** Pervioral; Vadiral; Valtrex; Virmax†; ***Cz.:*** Valtrex; ***Denm.:*** Zelitrex; ***Fin.:*** Valavir; Valtrex; ***Fr.:*** Zelitrex; ***Ger.:*** Valtrex; ***Gr.:*** Valtrex; ***Hong Kong:*** Valtrex; ***India:*** Valcivir; ***Indon.:*** Herclov; Valtrex; Valvir; ***Irl.:*** Valtrex; ***Israel:*** Valtrex; ***Ital.:*** Talavir; Zelitrex; ***Malaysia:*** Valtrex; ***Mex.:*** Rapivir; ***Neth.:*** Zelitrex; ***Norw.:*** Valtrex; ***Philipp.:*** Valtrex; ***Port.:*** Valavir; Valtrex; ***Rus.:*** Valtrex (Валтрекс); ***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 .

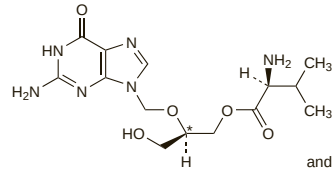
Вальганцикловира Гидрохлорид

$C_{14}H_{22}N_6O_5$,HCl = 390.8.

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

ATC — J05AB14.

ATC Vet — QJ05AB14.



and epimer at C*

(valganciclovir)