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.

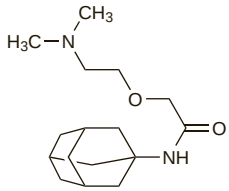
Тромантадина Гидрохлорид

$C_{16}H_{28}N_2O_2$,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.

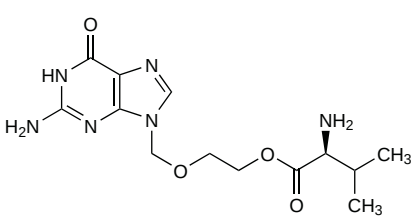
Валацикловира Гидрохлорид

$C_{13}H_{20}N_6O_4$,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 .

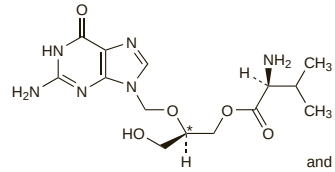
Вальганцикловира Гидрохлорид

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

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

ATC — J05AB14.

ATC Vet — QJ05AB14.



and epimer at C*

(valganciclovir)