

VACLOVIR

Valaciclovir 250 mg, 500 mg, 1000 mg Tablets

Pharmaceutical Form

Film coated tablets.

Presentation

VACLOVIR 250 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets. Each tablet contains valaciclovir hydrochloride equivalent to 250 mg valaciclovir.

VACLOVIR 500 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir.

VACLOVIR 1000 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 1000 mg valaciclovir.

Do not halve VACLOVIR 250 mg tablet. Dose equivalence when the tablet is divided has not been established.

Uses

Actions

Refer Pharmacological Properties

Indications

VACLOVIR is indicated for the treatment of herpes zoster (shingles) and the reduction of zoster – associated pain, which includes acute and post herpetic neuralgia, when given to immunocompetent patients in infection of less than 72 hours duration.

VACLOVIR is indicated for the treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes in immunocompetent patients.

VACLOVIR can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.

VACLOVIR is indicated for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes in immunocompetent and immunocompromised patients.

VACLOVIR is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation. CMV prophylaxis with VACLOVIR reduces acute graft rejection (renal transplant patients), opportunistic infections and other herpes virus infections (HSV, VZV).

Dosage and Administration

Do not halve VACLOVIR 250 mg tablet. Dose equivalence when the tablet is divided has not been established.

Treatment of herpes zoster:

The dosage in adults is 1000 mg of VACLOVIR to be taken 3 times daily for 7 days.

Treatment of herpes simplex infections:

The dosage in adults is 500 mg of VACLOVIR to be taken twice daily.

For recurrent episodes, treatment should be for 5 days. For initial episodes, which can be more severe, treatment may have to be extended to 10 days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately the first signs or symptoms appear.

Prevention (suppression) of recurrences of herpes simplex infections:

In immunocompetent adult patients, 500 mg of VACLOVIR to be taken once daily.

Some patients with very frequent recurrences (e.g. 10 or more per year) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily).

For immunocompromised adult patients the dose is 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease

Dosage in adults and adolescents (from 12 years of age)

The dosage of VACLOVIR is 2 g four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see Dosage in renal impairment below).

The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.

Dosage in renal impairment:

Herpes zoster treatment and herpes simplex treatment and prevention (suppression)

The dosage of VACLOVIR should be reduced in patients with significantly impaired renal function as shown in the table below:

Indication	Creatinine clearance mL/min	VACLOVIR dosage
<i>Herpes zoster</i>	15-30	1 g twice a day
	less than 15	1 g once a day
<i>Herpes simplex (treatment)</i>	less than 15	500 mg once a day
<i>Herpes simplex prevention (suppression):</i>		
- immunocompetent patients	less than 15	250 mg once a day
- immunocompromised patients	less than 15	500 mg once a day

In patients on haemodialysis, the VACLOVIR dosage recommended for patients with a creatinine clearance of less than 15 mL/min should be used. This should be administered after the haemodialysis has been performed.

CMV prophylaxis

The dosage of VACLOVIR should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine clearance mL/min	VACLOVIR dosage
75 or greater	2 g four times daily
50 to less than 75	1.5 g four times a day
25 to less than 50	1.5 g three times a day
10 to less than 25	1.5 g twice a day
less than 10 or dialysis [◊]	1.5 g once a day

[◊]In patients on haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment. The VACLOVIR dosage should be adjusted accordingly.

Dosage in hepatic impairment:

Studies with a 1 g unit dose of valaciclovir show that dose modification is not required in patients with mild to moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis, (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment; however, clinical experience is limited. For higher doses recommended for CMV prophylaxis see Special Warnings and Precautions.

Dosage in children:

There are no data available on the use of valaciclovir in children.

Dosage in the elderly:

Dosage modification is not required unless renal function is significantly impaired (see Dosage in renal impairment above). Adequate hydration should be maintained.

Contraindications

VACLOVIR is contra-indicated in patients known to be hypersensitive to valaciclovir, aciclovir or any components of the formulations of VACLOVIR.

Warnings and Precautions

Thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome, in some cases resulting in death, has occurred in patients with advanced HIV disease who were treated with valaciclovir for prolonged periods and also in allogenic bone marrow transplant and renal transplant recipients who were treated with valaciclovir while participating in clinical trials at doses of 8 grams per day.

Similar signs have been observed in patients with the same underlying or concurrent conditions who were not treated with valaciclovir.

Use of valaciclovir at doses of 1000 mg/day in immunocompromised patients with CD4⁺ counts > 100x10⁶/L has not been associated with occurrences of thrombotic microangiopathy (TMA). However use in severely immunocompromised patients (CD4⁺ counts < 100x10⁶/L) has not been examined at this low dosage.

Hydration status:

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Use in renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see Dosage and Administration). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see Adverse Effects).

Use of high dose Valaciclovir in hepatic impairment and liver transplantation:

There are no data available on the use of high doses of valaciclovir (8 g/day) in patients with liver disease. Caution should therefore be exercised when administering high doses of valaciclovir to these patients. Specific studies of valaciclovir have not been conducted in liver transplantation; however high dose aciclovir prophylaxis has been shown to reduce CMV infection and disease

Interactions

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations following valaciclovir administration.

Following 1 g valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered.

Care is also required (with monitoring for changes in renal function) if administering high-dose valaciclovir with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

Pregnancy and Lactation

Teratogenicity:

Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolised to aciclovir. Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal

abnormalities were observed at subcutaneous doses that produced plasma levels of 100 mcg/mL and maternal toxicity.

Fertility:

Valaciclovir did not affect fertility in male or female rats dosed by the oral route.

Pregnancy:

There are limited data on the use of valaciclovir in pregnancy. VACLOVIR should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

In prospective aciclovir studies, there has not been an increased incidence of birth defects in approximately 550 women exposed to systemic aciclovir (most at oral doses up to 1000 mg per day) during the first trimester of pregnancy, as compared with the incidence in the general population. The reported defects show no uniqueness or pattern to suggest a common aetiology.

The daily aciclovir AUC (area under plasma concentration-time curve) following valaciclovir 1000 mg and 8000 mg daily would be approximately 2 to 9 times greater than that expected with oral aciclovir 1000 mg daily.

Lactation:

The principle metabolite of valaciclovir is aciclovir which is excreted in breast milk. Aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding aciclovir plasma concentrations. Following oral administration of 200 mg aciclovir five times a day, the mean steady state peak plasma concentration (C^{ss}_{max}) is 3.1 microM (0.7 mcg/mL). These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg/day. The elimination half-life of aciclovir from breast milk has been reported to be 2.8 hours, similar to that in plasma. Caution is therefore advised if VACLOVIR is to be administered to a nursing woman. However aciclovir is used to treat neonatal herpes simplex at intravenous doses of 30 mg/kg/day.

Effects on Ability to Drive and Use Machines

No special precautions necessary.

Adverse Effects

Adverse reactions are listed below by MedDRA body system organ class and by frequency.

The frequency categories used are:

very common	≥ 1 in 10,
common	≥ 1 in 100 and < 1 in 10,
uncommon	≥ 1 in 1,000 and < 1 in 100,
rare	≥ 1 in 10,000 and < 1 in 1,000,
very rare	< 1 in 10,000.

Clinical trial data have been used to assign frequency categories to adverse reactions if, in the trials, there was evidence of an association with valaciclovir (i.e. there was a statistically significant difference between the incidence in patients taking valaciclovir and placebo). For all other adverse events, spontaneous post-marketing data has been used as a basis for allocating frequency.

Clinical Trial Data

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Nausea

Post Marketing Data

Blood and lymphatic system disorders

Very rare: Leukopenia, thrombocytopenia

Leukopenia is mainly reported in immunocompromised patients.

Immune system disorders

Very rare: Anaphylaxis

Psychiatric and nervous system disorders

Rare: Dizziness, confusion, hallucinations, decreased consciousness.

Very rare: Agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma.

The above events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see Warnings and Precautions). In organ transplant patients receiving high doses (8 g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Gastrointestinal disorders

Rare: Abdominal discomfort, vomiting, diarrhoea

Hepato-biliary disorders

Very rare: Reversible increases in liver function tests

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders

Uncommon: Rashes including photosensitivity

Rare: Pruritus

Very rare: Urticaria, angioedema

Renal and urinary disorders

Rare: Renal impairment

Very rare: Acute renal failure, renal pain

Renal pain may be associated with renal failure.

Other:

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

Overdosage

Symptoms and signs:

There are at present limited data available on overdosage with valaciclovir. However patients have ingested single overdoses of up to 20 g of aciclovir, which is only partially absorbed in the gastrointestinal tract, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion). Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with intravenous overdosage.

Management:

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic group:

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue.

Mode of Action:

Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase.

Aciclovir is a specific inhibitor of the herpes viruses with *in vitro* activity against herpes simplex viruses (HSV) type 1 and type 2, varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of UL97. This requirement for activation of aciclovir by a virus specific enzyme largely explains its selectivity.

The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Extensive monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

Resistance is normally due to a thymidine kinase deficient phenotype which results in a virus which is profoundly disadvantaged in the natural host. Infrequently, reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine

kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Pharmacokinetic Properties

General characteristics:

After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as valaciclovir hydrolase.

The bioavailability of aciclovir from 1000 mg valaciclovir is 54%, and is not reduced by food. Mean peak aciclovir concentrations are 10-37 microM (2.2-8.3 mcg/mL) following single doses of 250-2000 mg valaciclovir to healthy subjects with normal renal function, and occur at a median time of 1.00-2.00 hours post dose.

Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occurring at a median time of 30 to 100 minutes post dose, and are at or below the limit of quantification 3 hours after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. Binding of valaciclovir to plasma proteins is very low (15%).

In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the known aciclovir metabolite, 9-(carboxymethoxy) methylguanine (CMMG).

Characteristics in patients:

Herpes zoster and herpes simplex do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir.

In patients with HIV infection, the disposition and pharmacokinetic characteristics of aciclovir after oral administration of single or multiple doses of 1000 mg or 2000 mg valaciclovir are unaltered compared with healthy subjects.

In transplant recipients receiving valaciclovir 2000 mg four times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Preclinical Safety Data

Mutagenicity:

The results of mutagenicity tests *in vitro* and *in vivo* indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity:

Valaciclovir was not carcinogenic in bio-assays performed in mice and rats.

Pharmaceutical Precautions

List of Excipients

VACLOVIR tablets contain microcrystalline cellulose and magnesium stearate in the tablet core and hypromellose, titanium dioxide and polyethylene glycol in the film coat.

Incompatibilities

No data.

Special Precautions for Storage

Store below 25°C.

Nature and Contents of Container

VACLOVIR 250 mg tablets are available in foil blister packs of 60 tablets.

VACLOVIR 500 mg tablets are available in foil blister packs of 2, 4, 6, 10, 20, 30, 42, 60, 80, 90, 100, 240 & 480 tablets and bottles of 100, 240, 480 & 500 tablets.

VACLOVIR 1000 mg tablets are available in foil blister packs of 3 & 21 tablets and bottles of 100 & 250 tablets.

Not all pack sizes may be marketed.

Instructions for Use/Handling

No special instructions for use.

Medicine Classification

Prescription Only Medicine

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