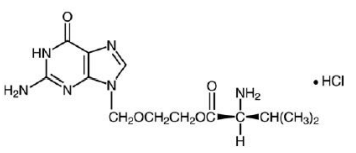
For the use of a Registered Medical Practitioner only or a Hospital or a Laboratory

℞ Valacyclovir Tablets 500 mg

Composition:
Each tablet contains 556 mg of Valacyclovir hydrochloride equivalent to 500 mg Valacyclovir.

Description:
Valacyclovir tablets are white to off white, film coated, and caplet shaped tablets, debossed with 'V' on one side and '500' on the other side. The inactive ingredients are crospovidone, Cellulose microcrystalline, povidone, magnesium stearate, Opadry white YS-1-7003 (Titanium dioxide, Hypromellose, Macrogol/PEG and Polysorbate 80).

The chemical name of valacyclovir hydrochloride is L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It has the following structural formula:



Valacyclovir hydrochloride is a white to off-white powder with the molecular formula $C_{13}H_{20}N_6O_4HCl$ and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The pKas for valacyclovir hydrochloride are 1.90, 7.47, and 9.43

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

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 result in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects
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.

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).

PHARMACOKINETICS
Absorption
In a study of the pharmacokinetics of valaciclovir and aciclovir during late pregnancy, the steady-state daily aciclovir AUC (area under plasma concentration-time curve) following valaciclovir 1000 mg was approximately 2 times greater than that observed with oral aciclovir at 1200 mg daily.

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 Valtrex are unaltered compared with healthy subjects.

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. Valacyclovir pharmacokinetics are not dose-proportional. The rate and extent of absorption decrease with increasing dose, resulting in a less than proportional increase in C_{max} over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Mean peak aciclovir concentrations are 10 to 37 micromoles (2.2 to 8.3 micrograms/mL) following single doses of 250 to 2000 mg valaciclovir to healthy subjects with normal renal function, and occur at a median time of 1 to 2 h post dose.

Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occur at a median time of 30 to 100 min post dose, and are at or below the limit of quantification 3 h after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing.

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

Distribution
Binding of valaciclovir to plasma proteins is very low (15%).

Metabolism
After oral administration, Valacyclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9-(carboxymethoxy) methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase.

Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither Valacyclovir nor aciclovir is metabolised by cytochrome P450 enzymes.

Elimination
In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours.

In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 h. 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).

INDICATIONS
Treatment of shingles (herpes zoster) infection.

Herpes simplex infections of the skin and mucous membranes, including initial and recurrent genital herpes.

Prophylaxis of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes.

DOSAGE AND ADMINISTRATION
Treatment of shingles (herpes zoster)

The dosage in adults is 1000 mg three times a day for 7 days.

Treatment of herpes simplex infections
The dosage in adults is 500 mg of Valacyclovir twice daily.

For recurrent infections, treatment should be maintained 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 as soon as the first signs appear.

Prophylaxis of recurrences of herpes simplex infections

Immunocompetent patients should take 500 mg of Valacyclovir once daily.

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

There are no data on the reduction of transmission in other patient populations.

- **Children**

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

- **Elderly**

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Renal impairment below).

Adequate hydration should be maintained.

- **Renal impairment**

Caution is advised when administering valaciclovir to patients with impaired renal function. Adequate hydration should be maintained.

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

Therapeutic indication	**Creatinine clearance mL/min**	***Valaciclovir dosage***
Herpes zoster (treatment)	at least 50 30 to 49 10 to 29 less than 10	1 g three times a day 1 g twice a day 1 g once a day 500 mg once a day
Herpes simplex (treatment)	at least 30 less than 30	500 mg twice a day 500 mg once a day
Herpes simplex prevention (suppression) - immunocompetent adults	at least 30 less than 30	500 mg once a day 250 mg once a day
- immunocompromised adults	at least 30 less than 30	500 mg twice a day 500 mg once a day
Reduction of transmission of genital herpes	at least 30 less than 30	500 mg once a day 250 mg once a day

In patients on intermittent haemodialysis, the Valaciclovir 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, the Valaciclovir dosage should be adjusted accordingly.

Hepatic impairment
Studies with a 1 g unit dose of Valaciclovir show that dose modification is not required in patients with mild or 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 (4 g or more/day), see *Warnings and Precautions*.

CONTRAINDICATIONS
Hypersensitivity to Valacyclovir, acyclovir or any of the excipients.

WARNINGS/PRECAUTIONS
Hydration status: Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Use in patients with 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 Reactions).

Use of higher doses of Valaciclovir in hepatic impairment: There are no data available on the use of higher doses of Valaciclovir (4 g or more/day) in patients with liver disease.

Caution should therefore be exercised when administering higher doses of Valaciclovir to these patients. Specific studies of Valaciclovir have not been conducted in liver transplantation.

Use in genital herpes: Suppressive therapy with Valaciclovir reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with Valaciclovir, it is recommended that patients use safer sex practices.

Drug reaction with eosinophilia and systemic symptoms (DRESS)
DRESS, which can be life-threatening or fatal, has been reported in association with valaciclovir treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed DRESS with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time.

Pregnancy and Lactation
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. Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Pregnancy registries have documented the pregnancy outcomes in women exposed to Valaciclovir or to any formulation of Aciclovir (aciclovir, the active metabolite of Valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. The findings of the aciclovir pregnancy registry have not shown an increase in the number of birth defects amongst aciclovir-exposed subjects compared with the general

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60 GSM Maplitho paper
Single colour (Pantone Black C)

population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Given the small number of women enrolled into the valaciclovir pregnancy registry, reliable and definitive conclusions could not be reached regarding the safety of Valaciclovir in pregnancy (*see Pharmacokinetics*).

Lactation
Aciclovir, the principle metabolite of Valaciclovir, is excreted in breast milk. Following oral administration of a 500 mg dose of Valaciclovir, peak aciclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal aciclovir serum concentrations. The aciclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2). The median aciclovir concentration in breast milk was 2.24 micrograms/mL (9.95 micromoles). With a maternal Valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral aciclovir dosage of about 0.61 mg/kg/day. The elimination half-life of aciclovir from breast milk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breast milk, or infant urine.

Caution is advised if Valaciclovir 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.

NON-CLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Carcinogenicity:
Valacyclovir was not carcinogenic in studies performed in mice and rats.

Teratogenicity:
Valacyclovir was not teratogenic in rats and rabbits. Valacyclovir is almost completely metabolised to acyclovir. Experiments with subcutaneous administration of acyclovir did not produce teratogenic effects in rats and rabbits. In additional studies in rats, foetal abnormalities were observed at subcutaneous doses that produced plasma levels of 100 mcg/ml and maternal toxicity.

DRUG INTERACTIONS
No clinically significant interactions have been identified.

Acyclovir is excreted primarily unchanged in the urine via active renal tubular secretion. Any medicinal products administered concurrently that are excreted the same way may increase acyclovir blood concentrations following Valacyclovir administration.

Following administration of 1 g of Valacyclovir, cimetidine and probenecid increase the AUC of acyclovir by this mechanism, and reduce acyclovir urine excretion. However, no dosage adjustment is necessary at this dose because of the high therapeutic index of acyclovir.

In patients receiving higher doses of Valacyclovir (8 g /day) as cytomegalovirus prophylaxis, caution is required during concurrent administration with medicinal products which compete with acyclovir for elimination, because of the potential for increased blood levels of one or both products. Increases in AUCs of acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been seen when the medicinal products are co-administered.

Caution is also required (with monitoring for changes in renal function) if administering high doses of Valacyclovir with medicinal products which affect other aspects of renal function (e.g. ciclosporin, tacrolimus).

SIDE 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 have been used as a basis for allocating frequency

Nervous system disorders
Common: Headache.

Gastrointestinal disorders
Common: Nausea.

Post Marketing Data
Skin and subcutaneous tissue disorders
Drug reaction with eosinophilia and systemic symptoms (DRESS)

Blood and lymphatic system disorders
Luekopenia is mainly reported in immunocompromised patients.

Very rare: Thrombocytopenia, leukopenia

Immune system disorders
Very rare: Anaphylaxis.

Psychiatric and nervous system disorders

Very Rare: Agitation and Psychotic symptoms

Rare: Dizziness, confusion, hallucinations, decreased consciousness.

Very rare: Tremor, ataxia, dysarthria, convulsions, encephalopathy, coma.

The above events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors.

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.

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, which are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Rashes including photosensitivity.
Rare: Pruritus.
Very rare: Urticaria, angioedema.

Renal and urinary disorders
Renal pain may be associated with renal failure .
Rare: Renal impairment.
Very rare: Renal pain.

OVERDOSE:
There is limited data available on overdosage with Valacyclovir.

However patients have ingested single overdoses of up to 20 g of acyclovir, which is only partially absorbed in the gastrointestinal tract, usually without toxic effects. Accidental, repeated overdoses of oral acyclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion). Overdosage of intravenous acyclovir 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.

STORAGE:
Store below 30°C and protect from moisture.

SHELF LIFE:
Observe "Expiry date" (month / year) imprinted on outer pack.

PRESENTATION:
3 x 10's (30 Tablets) Blister Alu-PVC, Alu-PVC/PVdC and Alu-PVC/PE/PVdC pack.

Product Owner:
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