VALTREX™ 500 mg

VALACICLOVIR

Qualitative and Quantitative Compostion
Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir
Pharmaceutical Form
Film-coated tablet
White, biconvex, elongated tablet with a white to off-white core, engraved "GX CF1" on one side.
Indications
Varicella zoster virus (VZV) infections – herpes zoster
Valtrex is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (*see Warnings and Precautions*).
Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression (*see Warnings and Precautions*).
Herpes simplex virus (HSV) infections
Valtrex is indicated

- for the treatment and suppression of HSV infections of the skin and mucous membranes including
  - treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults
  - treatment of recurrences of genital herpes in immunocompetent adults and adolescents, and in immunocompromised adults
  - suppression of recurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults
- Treatment and suppression of recurrent ocular HSV infections (*see Warnings and Precautions*).

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection.
Cytomegalovirus (CMV) infections:
Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (*see Warnings and Precautions*).
Dosage and Administration
Varicella zoster virus (VZV) infections – herpes zoster and ophthalmic zoster
Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.
Immunocompetent Adults
The dose in immunocompetent patients is 1000 mg three times daily for seven days (3000 mg total daily dose). This dose should be reduced according to creatinine clearance *(see Renal impairment below).*
Immunocompromised Adults
The dose in immunocompromised patients is 1000 mg three times daily for at least seven days (3000 mg total daily dose) and for 2 days following crusting of lesions. This dose should be reduced according to creatinine clearance (*see Renal impairment below).*
In immunocompromised patients, antiviral treatment is suggested for patients presenting within one week of vesicle formation or at any time before full crusting of lesions.
Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)
Immunocompetent Adults and Adolescents (≥12 years)
The dose is 500 mg of Valtrex to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance *(see Renal impairment below).*
For recurrent episodes, treatment should be for three to five days. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms. Valtrex can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.
Immunocompromised Adults
For the treatment of HSV in immunocompromised adults, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. This dose should be reduced according to creatinine clearance *(see Renal impairment below).* For maximum clinical benefit, the treatment should be started within 48 hours. A strict monitoring of the evolution of lesions is advised.
Suppression of recurrences of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)
Immunocompetent Adults and Adolescents (≥12 years)
The dose is 500 mg of Valtrex to be taken once daily. This dose should be reduced according to creatinine clearance *(see Renal impairment below).*Treatment should be re-evaluated after 6 to 12 months of therapy.
Immunocompromised Adults
The dose is 500 mg of Valtrex twice daily. This dose should be reduced according to creatinine clearance *(see Renal impairment below*). Treatment should be re-evaluated after 6 to 12 months of therapy.
Prophylaxis of cytomegalovirus (CMV) infection and disease in adults and adolescents (≥12 years)
The dosage of Valtrex is 2000 mg four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance *(see Renal impairment below).*
The duration of treatment will usually be 90 days, but may need to be extended in high-risk patients.
Special populations
Children
The efficacy of Valtrex in children below the age of 12 years has not been evaluated.
Elderly
The possibility of renal impairment in the elderly must be considered and the dose should be adjusted accordingly *(see Renal impairment below*). Adequate hydration should be maintained.
Renal impairment
Caution is advised when administering Valtrex to patients with impaired renal function. Adequate hydration should be maintained. The dose of Valtrex should be reduced in patients with impaired renal function as shown in Table 1 below.
In patients on intermittent haemodialysis, the Valtrex dose 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 renal transplantation or engraftment. The Valtrex dosage should be adjusted accordingly.
Hepatic impairment
Studies with a 1000 mg dose of valaciclovir in adult patients show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in adult patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dose adjustment; however, clinical experience is limited.
Table 1: DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

Therapeutic Indication	Creatinine Clearance (mL/min)	Valaciclovir Dosage [a]
Varicella-Zoster Virus (VZV) Infections		
Treatment of herpes zoster (shingles) in immunocompetent and immunocompromised adults	≥ 50 30 to 49 10 to 29 < 10	1000 mg three times daily 1000 mg twice daily 1000 mg once daily 500 mg once daily
Herpes Simplex Virus (HSV) Infections		
Treatment of HSV infections		
- immunocompetent adults and adolescents	≥ 30 < 30	500 mg twice daily 500 mg once daily
- immunocompromised adults	≥ 30 < 30	1000 mg twice daily 1000 mg once daily
Suppression of HSV infections		
- immunocompetent adults and adolescents	≥ 30 < 30	500 mg once daily [b] 250 mg once daily
- immunocompromised adults	≥ 30 < 30	500 mg twice daily 500 mg once daily
Cytomegalovirus (CMV) Infections		
CMV prophylaxis in solid organ transplant recipients in adults and adolescents	≥75 50 to <75 25 to <50 10 to <25 <10 or on dialysis	2000 mg four times daily 1500 mg four times daily 1500 mg three times daily 1500 mg twice daily 1500 mg once daily

[a] For patients on intermittent haemodialysis, the dose should be given after dialysis on dialysis days.
[b] For HSV suppression in immunocompetent subjects with a history of ≥10 recurrences/year, better results may be obtained with 250 mg twice daily.
Contraindications
Valtrex is contraindicated in patients known to be hypersensitive to valaciclovir, aciclovir or any of the excipients.
Warnings and 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).*
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 1g 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 higher-doses of valaciclovir (4 g or more per 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 higher-doses of valaciclovir (4g or more/day) with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).
Pregnancy and Lactation
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 (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 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.
Lactation
Aciclovir, the principal metabolite of valaciclovir, is excreted in breast milk. *Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (Cmax) 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/L). 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 i.v. doses of 30 mg/kg/day.
Ability to perform tasks that require judgement, motor or cognitive skills
The clinical status of the patient and the adverse event profile of valaciclovir should be borne in mind when considering the patient`s ability to drive or operate machinery. There have been no studies to investigate the effect of valaciclovir on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.
Adverse Reactions
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 < 1,000,
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 adult patients receiving high doses (8g 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 adult patients, particularly those with advanced HIV disease, receiving high doses (8g 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
Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.
Treatment
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.
List of excipients

Tablet Core	Film coat
Microcrystalline cellulose	**Hypromellose**
Crospovidone	**Titanium dioxide**
Povidone K90	**Polyethylene glycol 400**
Magnesium stearate	**Polysorbate 80**
Colloidal Anhydrous Silica	**Carnauba wax**

Shelf Life
As indicated on the outer packaging.
Special precautions for storage
Do not store above 30 °C
Nature and contents of container
Polyvinyl chloride / aluminium foil blister packs. Packs of 10 or 42 tablets
Not all pack sizes may be marketed.
Manufactured by:
GlaxoWellcome, S.A.*, Aranda de Duero, Spain
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Version number: GDS 21
Version Date: 12 October 2011

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

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