Valaciclovir

Core Safety Profile

4.2 Posology and method of administration

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. For higher doses (4000 mg or more per day), see section 4.4.

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	1000 mg three times daily
	30 to 49	1000 mg twice daily
	10 to 29	1000 mg once daily
	10	500 mg once daily
Herpes Simplex Virus (HSV) Infections		
Treatment of HSV infections		
- immunocompetent adults and adolescents	≥ 30	500 mg twice daily
	< 30	500 mg once daily
- immunocompromised adults	≥ 30	1000 mg twice daily
	< 30	1000 mg once daily
Treatment of herpes labialis (cold sores) in immunocompetent adultsand adolescents	≥ 50	2000mg twice in one day
	30 to 49	1000 mg twice in one day
	10 to 29	500 mg twice in one day
	<10	
(alternative 1-day regimen)		500 mg single dose
Suppression of HSV infections		
- immunocompetent adults and adolescents	≥ 30	500 mg once daily [b]
	< 30	250 mg once daily
- immunocompromised adults	≥ 30	500 mg twice daily
	< 30	500 mg once daily
Cytomegalovirus (CMV) Infections		
CMV prophylaxis in solid organ transplant recipients in adults and adolescents	≥ 75	2000 mg four times daily
	50 to <75	1500 mg four times daily
	25 to <50	1500 mg three times daily
	10 to <25	1500 mg twice daily

	<10 or on dialysis	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.

4.3 Contraindications

Hypersensitivity to valaciclovir or acyclovir or any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

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 section 4.2). 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 section 4.8).

Use of higher doses of valaciclovir in hepatic impairment and liver transplantation

There are no data available on the use of higher doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg to these patients.

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular

complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible. Therefore, in addition to therapy with valaciclovir, it is recommended that patients use safer sex practices.

Use in ocular HSV infections

Clinical response should be closely monitored in these patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is unlikely to be sufficient.

Use in CMV infections

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV-positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that valaciclovir should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Following 1000 mg valaciclovir, cimetidine and probenecid reduce aciclovir renal clearance and increase the AUC of aciclovir by about 25% and 45%, respectively, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65%. Other medicinal products (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase aciclovir concentrations by this mechanism. Similarly,

valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving higher aciclovir exposures from valaciclovir (e.g., at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with drugs which inhibit active renal tubular secretion.

Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate motefil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

4.6 Fertility, pregnancy and lactation

Pregnancy

A limited amount of data on the use of valaciclovir and a moderate amount of data on the use of aciclovir in pregnancy is available from pregnancy registries (which have documented the pregnancy outcomes in women exposed to valaciclovir or to oral or intravenous aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy, respectively) and postmarketing experience indicate no malformative or foeto/neonatal toxicity. Animal studies do not show reproductive toxicity for valaciclovir (see section 5.3). Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Breastfeeding

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. However, at therapeutic doses of valaciclovir, no effects on the breastfed newborns/infants are anticipated since the dose ingested by the child is less than 2% of the therapeutic dose of intravenous aciclovir for treatment of neonatal herpes (see Section 5.2). Valaciclovir should be used with caution during breast feeding and only when clinically indicated.

Fertility

Valaciclovir did not affect fertility in rats dosed by the oral route. At high parenteral doses of aciclovir testicular atrophy and a spermatogenesis have been observed in rats and dogs. No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 to 1000 mg aciclovir.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Valtrex should be borne in mind when considering the patient`s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

The most common adverse reactions (ARs) reported in at least one indication by patients treated with Valtrex in clinical trials were headache and nausea. More serious ARs such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure and neurological disorders are discussed in greater detail in other sections of the label.

Undesirable effects are listed below by body system organ class and by frequency.

The following frequency categories are used for classification of adverse effects:

Very common ≥1/10,

Common ≥1/100 to<1/10,

Uncommon ≥ 1/1,000 to < 1/100,

Rare ≥ 1/10,000 to < 1/1000,

Very rare < 1/10,000

Clinical trial data have been used to assign frequency categories to ARs if, in the trials, there was evidence of an association with valaciclovir.

For ARs identified from postmarketing experience, but not observed in clinical trials, the most conservative value of point estimate (“rule of three”) has been used to assign the AR frequency category. For ARs identified as associated with valaciclovir from post -marketing experience, and observed in clinical trials, study incidence has been used to assign the AR frequency category. The clinical trial safety database is based on 5855 subjects exposed to valaciclovir in clinical trials covering multiple indications (treatment of herpes zoster, treatment/suppression of genital herpes & treatment of cold sores).

Clinical Trial Data

Nervous system disorders

Very common: Headache

Gastrointestinal disorders

Common: Nausea

Post Marketing Data

Blood and lymphatic system disorders

Uncommon: Leucopenia, thrombocytopenia

Leucopenia is mainly reported in immunocompromised patients.

Immune system disorders

Rare: Anaphylaxis

Psychiatric and nervous system disorders

Common: Dizziness

Uncommon: Confusion, hallucinations, decreased consciousness, tremor, agitation

Rare: Ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms, delirium.

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8000 mg daily) of Valtrex for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Gastrointestinal disorders

Common: Vomiting, diarrhoea.

Uncommon: Abdominal discomfort

Hepato-biliary disorders

Uncommon: Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).

Skin and subcutaneous tissue disorders

Common: Rashes including photosensitivity, pruritus.

Uncommon: Urticaria

Rare: Angioedema

Renal and urinary disorders

Uncommon: Renal pain

Uncommon: Haematuria (often associated with other renal events).

Rare: Renal impairment, acute renal failure (especially in elderly patients or in patients

with renal impairment receiving higher than the recommended doses).

Renal pain may be associated with renal failure.

Intratubular precipitation of aciclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see section 4.4).

Additional information on special populations

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 (8000 mg daily) of valaciclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

4.9 Overdose

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.