Pharma code Ref. No. 7767

VALTREX™
VALACICLOVIR

QUALITATIVE AND QUANTITATIVE COMPOSITION
Film-coated tablets containing 250 mg, 500 mg or 1000 mg of valaciclovir.

PHARMACEUTICAL FORM
Film-coated tablets.

CLINICAL PARTICULARS
Indications
VALTREX is indicated for the treatment of herpes zoster (shingles).
VALTREX accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and post-herpetic neuralgia.
VALTREX is indicated for the treatment of herpes simplex infections of the skin and mucous membranes, including initial and recurrent genital herpes.
VALTREX is indicated for the treatment of herpes labialis (cold sores).
VALTREX is indicated for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes.
VALTREX can reduce transmission of genital herpes when taken as suppressive therapy and combined with safer sex practices.
VALTREX is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation. CMV prophylaxis with *VALTREX* reduces acute graft rejection (renal transplant patients), opportunistic infections and other herpes virus infections (herpes simplex virus (HSV), varicella zoster virus (VZV)).

Dosage and Administration
- **Adults**

Treatment of herpes zoster (shingles) including ophthalmic zoster
The dosage is 1000 mg of *VALTREX* to be taken three times daily for seven days.
Treatment of herpes simplex infections
Immunocompetent adults and adolescents (12 years and older)
The dosage is 500 mg of *VALTREX* to be taken twice daily.
For recurrent episodes, treatment should be for three or five days. For initial episodes, which can be more severe, treatment may have to be extended from five days 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 the first signs or symptoms appear. *VALTREX* can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.
Alternatively, for herpes labialis (cold sores), *VALTREX* 2 g twice-daily for one day is effective treatment. The second dose should be taken about 12 hours (no sooner than 6 hours) after the first dose. When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).
Prevention (suppression) of recurrences of herpes simplex infections
Immunocompetent adults and adolescents (12 years and older)
In immunocompetent patients, 500 mg of *VALTREX* 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).
Immunocompromised adults
For immunocompromised patients the dose is 500 mg twice daily.
Reduction of transmission of genital herpes
In immunocompetent heterosexual adults with 9 or fewer recurrences per year, 500 mg of *VALTREX* to be taken once daily by the infected partner.
There are no data on the reduction of transmission in other patient populations.
Prophylaxis of cytomegalovirus (CMV) infection and disease
The dosage of *VALTREX* in adults and adolescents (from 12 years of age) 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 Renal Impairment below*).
The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.
- **Children**

There are no data available on the use of *VALTREX* 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 *VALTREX* should be reduced in patients with significantly impaired renal function as shown in the table below:

Therapeutic indication	Creatinine clearance mL/min	*Valaciclovir dosage*
Herpes zoster (treatment) in immunocompetent and immunocompromised adults	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)		
- immunocompetent adults and adolescents	at least 30 less than 30	*500 mg twice a day* *500 mg once a day*
Herpes labialis (treatment) in immunocompetent adults and adolescents	at least 50 30 to 49 10 to 29 less than 10	*2 g twice in one day* *1 g twice in one day* *500 mg twice in one day* *500 mg once*
Herpes simplex prevention (suppression):		
- immunocompetent adults and adolescents	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*
Cytomegalovirus (prophylaxis) in adults and adolescents	at least 75 50 to less than 75 25 to less than 50 10 to less than 25 less than 10 or on dialysis	*2 g four times a day* *1.5 g four times a day* *1.5 g three times a day* *1.5 g twice a day* *1.5 g once a day*

In patients on intermittent haemodialysis, the *VALTREX* 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.

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

Studies with a 1 g unit dose of *VALTREX* 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
VALTREX is contra-indicated in patients known to be hypersensitive to valaciclovir, aciclovir or any components of formulations of *VALTREX*.

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*).
Use of higher doses of VALTREX in hepatic impairment and liver transplantation: There are no data available on the use of higher doses of *VALTREX* (4 g or more/day) in patients with liver disease. Caution should therefore be exercised when administering higher doses of *VALTREX* to these patients. Specific studies of *VALTREX* have not been conducted in liver transplantation; however high dose aciclovir prophylaxis has been shown to reduce CMV infection and disease.
Use in genital herpes: Suppressive therapy with *VALTREX* 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 *VALTREX*, it is recommended that patients use safer sex practices.

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 *VALTREX* 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 *VALTREX* (4 g or more/day), 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 oral aciclovir and mycophenolate mofetil are co-administered.
Care is also required (with monitoring for changes in renal function) if administering higher doses of *VALTREX* (4 g or more/day) with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

Pregnancy and Lactation
Fertility
In animal studies, VALTREX did not affect fertility. However, high parenteral doses of aciclovir caused testicular effects in rats and dogs (see Preclinical Safety Data).
No human fertility studies were performed with VALTREX, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 mg to 1 g aciclovir.
Pregnancy
There are limited data on the use of *VALTREX* in pregnancy. *VALTREX* 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 *VALTREX* or to any formulation of *ZOVIRAX*™ (aciclovir, the active metabolite of *VALTREX*); 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 *VALTREX* in pregnancy (*see Pharmacokinetics*).
Lactation
Aciclovir, the principle metabolite of *VALTREX*, is excreted in breast milk. Following oral administration of a 500 mg dose of *VALTREX*, 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 *VALTREX* 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 *VALTREX* is to be administered to a nursing woman. However, *ZOVIRAX* is used to treat neonatal herpes simplex at intravenous doses of 30 mg/kg/day.

Effects on Ability to Drive and Use Machines
The clinical status of the patient and the adverse event profile of *VALTREX* 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 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 *VALTREX* (i.e. there was a statistically

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significant difference between the incidence in patients taking *VALTREX* and placebo). For all other adverse events, spontaneous post-marketing data have 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 *VALTREX* 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.

Hepatobiliary 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 *VALTREX* for prolonged periods in clinical trials. These findings have been observed in patients not treated with *VALTREX* who have the same underlying or concurrent conditions.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

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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

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. VALTREX 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%). CSF penetration, determined by CSF/plasma AUC ratio, is about 25% for aciclovir and the metabolite 8-hydroxy-aciclovir (8-OH-ACV), and about 2.5% for the metabolite 9-(carboxymethoxy)methylguanine (CMMG) (see Pharmacokinetics: Special Patient Populations).

Metabolism

After oral administration, VALTREX 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 VALTREX nor aciclovir is metabolised by cytochrome P450 enzymes.

Elimination

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).

Special Patient Populations

Renal impairment

The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after VALTREX administration is approximately 14 hours, compared with about 3 hours for normal renal function (see Dosing and Administration).

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose VALTREX administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, in severe renal impairment compared with normal renal function. There was no difference in extent of CSF penetration (as determined by CSF/plasma AUC ratio) for aciclovir, CMMG or 8-OH-aciclovir between the two populations (see Pharmacokinetics: Distribution).

Hepatic impairment

Pharmacokinetic data indicate that hepatic impairment decreases the rate of conversion of VALTREX to aciclovir but not the extent of conversion. Aciclovir half-life is not affected.

Pregnant women

In a study of the pharmacokinetics of VALTREX and aciclovir during late pregnancy, the steady-state daily aciclovir AUC following VALTREX 1000 mg daily was approximately 2 times greater than that observed with oral aciclovir at 1200 mg daily.

For information on transfer into breast milk see Lactation section.

HIV infection

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.

Organ transplantation

In transplant recipients receiving VALTREX 2000 mg 4 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

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

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

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

At high parenteral doses of aciclovir testicular atrophy and aspermatogenesis have been observed in rats and dogs.

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 micrograms/mL and maternal toxicity.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core	Film coat
Microcrystalline cellulose	Hydroxypropylmethylcellulose
Crospovidone	Titanium dioxide
Povidone	Polyethylene glycol
Magnesium stearate	Polysorbate 80 (500 and 1000 mg tablets only)
Colloidal silicon dioxide	Purified water
Purified water	Carnauba wax

Incompatibilities

No data.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store below 30°C.

Nature and Contents of Container

Tablets are packed into blister packs prepared from unplasticised polyvinyl chloride and aluminium foil.

Instructions for Use/Handling

No special instructions for use.

Not all presentations are available in every country.

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