VALTREX® Tablets

1. NAME OF THE MEDICINAL PRODUCT

Valtrex 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

500 mg tablet
White, biconvex, elongated tablet with a white to off-white core, branded “GX CF1”.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 section 4.4).

Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression (see section 4.4).

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 in immunocompetent adults and adolescents and in immunocompromised adults (see section 4.4)

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

Cytomegalovirus (CMV) infections:
Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (see section 4.4)

4.2 Posology and method of 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.

Herpes labialis

For herpes labialis (cold sores), valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose. This dose should be reduced according to creatinine clearance (see Renal impairment below). 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).

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. The use for suppression of HSV in immunocompetent adults and adolescents with CrCl < 30ml/min is not recommended. 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 infection (CMV) 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. 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 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
Treatment of herpes labialis (cold sores) in immunocompetent adults and adolescents (alternative 1-day regimen)	≥50 30 to 49 10 to 29 <10	2000mg twice in one day 1000 mg twice in one day 500 mg twice in one day 500 mg single dose
Suppression of HSV infections		
- immunocompetent adults and adolescents	≥ 30 < 30	500 mg once daily The use for suppression of HSV in immunocompetent adults and adolescents with CrCl < 30ml/min is not recommended.
- 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.

4.3 Contraindications

Hypersensitivity to valaciclovir or aciclovir or any of the excipients listed in 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 mofetil, 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 principal 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 aspermatogenesis 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 event 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: Leukopenia, thrombocytopenia

Leukopenia 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

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
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 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Antivirals for systemic use

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB11.

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 results 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 disadvantaged in the natural host. 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.

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 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).

Clinical studies

Varicella Zoster Virus Infection

Valtrex accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and, in patients older than 50 years, also post-herpetic neuralgia. Valtrex reduces the risk of ocular complications of ophthalmic zoster.

Intravenous therapy generally is considered standard for zoster treatment in immunocompromised patients; however, limited data indicate a clinical benefit of valaciclovir in the treatment of VZV infection (herpes zoster) in certain immunocompromised patients, including those with solid organ cancer, HIV, autoimmune diseases, lymphoma, leukaemia and stem cell transplants.

Herpes Simplex Virus Infection

Valaciclovir for ocular HSV infections should be given according to applicable treatment guidelines.

Studies of valaciclovir treatment and suppression for genital herpes were performed in HIV/HSV coinfected patients with a median CD4 count of > 100cells/mm^3. Valaciclovir 500 mg twice daily was superior to 1000 mg once daily for suppression of symptomatic recurrences. Valaciclovir 1000 mg twice daily for treatment of recurrences was comparable to oral aciclovir 200 mg five times daily on herpes episode duration. Valaciclovir has not been studied in patients with severe immune deficiency.

The efficacy of valaciclovir for the treatment of other HSV skin infections has been documented. Valaciclovir has shown efficacy in the treatment of herpes labialis (cold sores), mucositis due to chemotherapy or radiotherapy, HSV reactivation from facial resurfacing, and herpes gladiatorum. Based on historical aciclovir experience, valaciclovir appears to be as effective as aciclovir for the treatment of erythema multiforme, eczema herpeticum and herpetic whitlow.

Valaciclovir has been proven to reduce the risk of transmission of genital herpes in immunocompetent adults when taken as suppressive therapy and combined with safer sex practices. A double blind, placebo controlled study was conducted in 1,484 heterosexual, immunocompetent adult couples discordant for HSV-2 infection. Results showed significant reductions in risk of transmission: 75 % (symptomatic HSV-2 acquisition), 50 % (HSV-2 seroconversion), and 48 % (overall HSV-2 acquisition) for valaciclovir compared to placebo. Among subjects participating in a viral shedding sub-study, valaciclovir significantly reduced shedding by 73 % compared to placebo (see section 4.4 for additional information on transmission reduction).

Cytomegalovirus Infection (see section 4.4)
CMV prophylaxis with valaciclovir in subjects receiving solid organ transplantation (kidney, heart) reduces the occurrence of acute graft rejection, opportunistic infections and other herpes virus infections (HSV, VZV). There is no direct comparative study versus valganciclovir to define the optimal therapeutic management of solid organ transplant patients.

5.2 Pharmacokinetic properties

Absorption

Valaciclovir is a prodrug of aciclovir. The bioavailability of aciclovir from valaciclovir is about 3.3 to 5.5-fold greater than that historically observed for oral aciclovir. 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. Valaciclovir pharmacokinetics is not dose-proportional. The rate and extent of absorption decreases with increasing dose, resulting in a less than proportional increase in Cmax over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Aciclovir pharmacokinetic (PK) parameter estimates following single doses of 250 to 2000 mg valaciclovir to healthy subjects with normal renal function are shown below.

Aciclovir PK Parameter		250 mg (N=15)	500 mg (N=15)	1000 mg (N=15)	2000 mg (N=8)
C_{max}	micrograms/mL	2.20 ± 0.38	3.37 ± 0.95	5.20 ± 1.92	8.30 ± 1.43
T_{max}	hours (h)	0.75 (0.75–1.5)	1.0 (0.75–2.5)	2.0 (0.75–3.0)	2.0 (1.5–3.0)
AUC	h.micrograms/mL	5.50 ± 0.82	11.1 ± 1.75	18.9 ± 4.51	29.5 ± 6.36

C_{max} = peak concentration; T_{max} = time to peak concentration; AUC = area under the concentration-time curve. Values for C_{max} and AUC denote mean ± standard deviation. Values for T_{max} denote median and range.

Peak plasma concentrations of unchanged valaciclovir are only 4% of peak 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, herpes simplex and HIV infection do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir compared with healthy adults. In transplant recipients receiving valaciclovir 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.

Distribution

Binding of valaciclovir to plasma proteins is very low (15%). CSF penetration, determined by CSF/plasma AUC ratio, is independent of renal function and was about 25% for aciclovir and the metabolite 8-OH-ACV, and about 2.5% for the metabolite CMMG.

Biotransformation

After oral administration, valaciclovir 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 valaciclovir nor aciclovir is metabolized by cytochrome P450 enzymes.

Elimination

Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the aciclovir metabolite CMMG (about 14% of the recovered dose). The metabolite 8-OH-ACV is detected only in small amounts in urine (< 2% of the recovered dose). Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. 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.

Special 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 valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).

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 valaciclovir 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, at severe renal impairment compared with normal renal function.

Hepatic impairment

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

Pregnant women

A study of the pharmacokinetics of valaciclovir and aciclovir during late pregnancy indicates that pregnancy does not affect the pharmacokinetics of valaciclovir.

Transfer into 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 times the corresponding maternal aciclovir serum concentrations. 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

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

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

and maternal toxicity were observed at subcutaneous doses that produced plasma aciclovir levels of 100 micrograms/mL (>10-fold higher than 2000 mg single dose valaciclovir in humans with normal renal function).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Crospovidone
Povidone
Magnesium stearate
Colloidal anhydrous silica

Film coat
Hydroxypropylmethylcellulose
Titanium dioxide
Polyethylene glycol 400
Polysorbate 80
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

The storage condition is indicated on the packaging.

6.5 Special precautions for disposal

No special requirements for disposal

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VALTREX® Tablets - Patient Information Leaflet

1. What Valtrex is and what it is used for

Valtrex belongs to a group of medicines called antivirals. It works by killing or stopping the growth of viruses called herpes simplex (HSV), varicella zoster (VZV) and cytomegalovirus (CMV).

Valtrex can be used to:

- treat shingles (in adults)
- treat HSV infections of the skin and genital herpes (in adults and adolescents over 12 years old) It is also used to help prevent these infections from returning
- treat cold sores (in adults and adolescents over 12 years old)
- prevent infection with CMV after organ transplants (in adults and adolescents over 12 years old)
- treat and prevent HSV infections of the eye that continue to come back (in adults and adolescents over 12 years old)

2. What you need to know before you take Valtrex

Don't take Valtrex

- if you are allergic to valaciclovir or aciclovir or any of the other ingredients of this medicine (listed in Section 6)

Don't take Valtrex if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Valtrex.

Warnings and precautions

Check with your doctor or pharmacist before taking Valtrex if:

- **you have kidney problems**
- **you have liver problems**
- **you are over 65 years of age**
- **your immune system is weak**

If you are not sure if the above apply to you, talk to your doctor or pharmacist before taking Valtrex.

<u>Prevent passing genital herpes on to others</u>

If you are taking Valtrex to treat or prevent genital herpes, or you have had genital herpes in the past, you should still practise safe sex, including the use of condoms. This is important to prevent you passing the infection on to others. You should not have sex if you have genital sores or blisters.

Other medicines and Valtrex

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Tell your doctor or pharmacist if you are taking any other medicines that affect the kidneys. These include: aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, tacrolimus, cimetidine and probenecid.

Always tell your doctor or pharmacist about other medicines if you are taking Valtrex for treatment of shingles or after having an organ transplant.

Pregnancy and breast-feeding

Valtrex is not usually recommended for use during pregnancy. If you are pregnant, or think you could be, or if you are planning to become pregnant, don't take Valtrex without checking with your doctor. Your doctor will weigh up the benefit to you against the risk to your baby of taking Valtrex while you're pregnant or breastfeeding.

Driving or using machines
Valtrex can cause side effects that affect your ability to drive.
Don't drive or use machines unless you are sure you're not affected.

3. How to take Valtrex

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The dose that you should take will depend on why your doctor has prescribed Valtrex for you. Your doctor will discuss this with you.

Treatment of shingles
- The usual dose is 1000 mg (two 500 mg tablets) three times a day.
- You should take Valtrex for seven days.

Treatment of cold sores
- The usual dose is 2000 mg (four 500 mg tablets) twice a day.
- The second dose should be taken 12 hours (no sooner than 6 hours) after the first dose
- You should take Valtrex for one day (two doses) only.

Treatment of HSV infections of the skin and genital herpes
- The usual dose is 500 mg (one 500 mg tablet) twice a day.
- For the first infection you should take Valtrex for five days or for up to ten days if your doctor tells you to. For recurrent infection the duration of treatment is normally three to five days.

Helping to prevent HSV infections from returning after you have had them
- The usual dose is one 500 mg tablet once a day.
- You should take Valtrex until your doctor tells you to stop.

To stop you being infected with CMV (*Cytomegalovirus*)
- The usual dose is 2000 mg (four 500 mg tablets) four times a day.
- You should take each dose about 6 hours apart.
- You will usually start taking Valtrex as soon as possible after your surgery.
- You should take Valtrex for around 90 days after your surgery, until your doctor tells you to stop.

Your doctor may adjust the dose of Valtrex if:
- you are over 65 years of age
- you have a weak immune system
- you have kidney problems.

Talk to your doctor before taking Valtrex if any of the above apply.

Taking this medicine
- Take this medicine by mouth.
- Swallow the tablets whole with a drink of water.
- Take Valtrex at the same time each day.
- Take Valtrex according to instructions from your doctor or pharmacist.

People over 65 years of age or with kidney problems
It is very important while you are taking Valtrex that you drink water regularly during the day. This will help to reduce side effects that can affect the kidney or nervous system. Your doctor will closely monitor you for signs of these. Nervous system side effects might include feeling confused or agitated, or feeling unusually sleepy or drowsy.

If you take more Valtrex than you should
Valtrex is not usually harmful, unless you take too much over several days. If you take too many tablets you may feel sick, vomit, get kidney problems, may be confused, agitated, feel less aware, see things that aren't there, or become unconscious. Talk to your doctor or pharmacist if you take too much Valtrex. Take the medicine pack with you.

If you forget to take Valtrex
- If you forget to take Valtrex, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose.
- Don't take a double dose to make up for a forgotten dose.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Conditions you need to look out for
- severe allergic reactions (*anaphylaxis*)

These are rare in people taking Valtrex. Rapid development of symptoms including:
- flushing, itchy skin rash
- swelling of the lips, face, neck and throat, causing difficulty in breathing (*angiodema*)
- fall in blood pressure leading to collapse.

If you have an allergic reaction, stop taking Valtrex and see a doctor straight away.

Very Common (may affect more than 1 in 10 people):
- headache

Common (may affect up to 1 in 10 people)
- feeling sick
- dizziness
- vomiting
- diarrhoea
- skin reaction after exposure to sunlight (*photosensitivity*)
- rash
- itching (*pruritus*)

Uncommon (may affect up to 1 in 100 people)
- feeling confused
- seeing or hearing things that aren't there (*hallucinations*)
- feeling very drowsy
- tremors
- feeling agitated

These nervous system side effects usually occur in people with kidney problems, the elderly or in organ transplant patients taking high doses of 8 grams of Valtrex a day. They usually get better when Valtrex is stopped or the dose reduced.

Other uncommon side effects:
- shortness of breath (*dyspnoea*)
- stomach discomfort
- rash, sometimes itchy, hive-like rash (*urticaria*)
- low back pain (*kidney pain*)
- blood in urine *(haematuria)*

Uncommon side effects that may show up in blood tests:

- reduction in the number of white blood cells (*leukopenia*)
- reduction in the number of *blood platelets* which are cells that help blood to clot (*thrombocytopenia*)
- increase in substances produced by the liver

Rare (may affect up to 1 in 1,000 people)

- unsteadiness when walking and lack of coordination (*ataxia*)
- slow, slurred speech (*dysarthria*)
- fits (*convulsions*)
- altered brain function (*encephalopathy*)
- unconsciousness (*coma*)
- confused or disturbed thoughts *(delirium)*

These nervous system side effects usually occur in people with kidney problems, the elderly or in organ transplant patients taking high doses of 8 grams of Valtrex a day. They usually get better when Valtrex is stopped or the dose reduced.

Other rare side effects:

- kidney problems where you pass little or no urine.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet

5. How to store Valtrex

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton.
- Store as stated on the packaging.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Valtrex contains

- The active substance is valaciclovir. Each tablet contains 500 mg of valaciclovir (as valaciclovir hydrochloride).

The other ingredients are:
Tablet core
Microcrystalline cellulose
Crospovidone
Povidone
Magnesium stearate
Colloidal anhydrous silica

Film coat
Hyproxypropylmethylcellulose
Titanium dioxide
Polyethylene glycol 400
Polysorbate 80
Carnauba wax

What Valtrex tablets look like

Valtrex Tablets 500 mg are white and marked with “GX CF1” on one side.
Version number: HK022017 (GDS22/emc20140414)
VALTREX is a registered trade mark of the GSK group of companies.

Valtrex®藥片——患者須知

1. Valtrex 是什麼及有何用途

Valtrex 是一種抗病毒藥物。它的作用是殺滅或阻止單純疱疹病毒（HSV）、水痘帶狀疱疹病毒（VZV）和巨細胞病毒（CMV）的生長。

Valtrex 可用於：

- 治療帶狀疱疹（成人）
- 治療皮膚單純疱疹病毒感染和生殖器疱疹（成人和年滿 12 歲的青少年），及用於防治這些感染復發
- 治療唇疱疹（成人和年滿 12 歲的青少年）
- 防止進行器官移植後出現巨細胞病毒感染（成人和年滿 12 歲的青少年）
- 治療及預防不斷復發的眼部單純疱疹病毒感染（成人和年滿 12 歲的青少年）

2. 在服用 Valtrex 前，您需要了解哪些資訊

如有以下情況，請勿服用 Valtrex

- 如果您對 valaciclovir 或 aciclovir 或本藥物任何其他成份（在*第 6 部分*列出）過敏

如果任何上述情況適用於您，請勿服用 Valtrex。假如您無法確定，請在服用 Valtrex 前諮詢您的醫生或藥劑師。

警告和注意事項

如果您有以下情況，請在服用 Valtrex 前諮詢您的醫生或藥劑師：

- **您有腎臟問題**
- **您有肝臟問題**
- **您的年齡超過 65 歲**
- **您的免疫系統較弱**

如果您無法確定上述任何情況是否適用於您，請在服用 Valtrex 前諮詢您的醫生或藥劑師。

避免將生殖器疱疹傳染給他人

如果您正在服用 Valtrex 治療生殖器疱疹或預防其復發，或您曾患過生殖器疱疹，您仍然需要進行安全的性行為，包括使用安全套。這對防止您將感染傳染給他人十分重要。如果您的生殖器上有瘡或水疱，切勿發生性行為。

其他藥物與 Valtrex

如果您正在服用或最近服用過任何其他藥物，請告知您的醫生或藥劑師。這包括未經處方獲得的藥物，包括中草藥。

如果您正在服用任何其他會影響腎臟的藥物，請告知您的醫生或藥劑師。這些藥物包括：aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, tacrolimus, cimetidine 及 probenecid。

如果您正在服用 Valtrex 治療帶狀疱疹或接受了器官移植，請務必告知您的醫生或藥劑師有關您服用其他藥物的情況。

懷孕和哺乳

通常不建議在懷孕期間服用 Valtrex。如果您已經懷孕，或認為自己可能懷孕，或正在計劃懷孕，切勿在未得醫生確認的情況下服用 Valtrex。如果您正在懷孕或哺乳，您的醫生會權衡服用 Valtrex 對您的益處及對您嬰兒的風險。

駕駛或使用機器

Valtrex 引起的副作用可能會影響您的駕駛能力。

除非您肯定自己沒有受到藥物影響，否則切勿駕駛或使用機器。

3. 如何服用 Valtrex

請遵從醫生指示服用。如果您有不確定的地方，請諮詢您的醫生或藥劑師。

您服藥的劑量取決於您醫生為您處方 Valtrex 的原因。您的醫生會就此與您討論。

治療帶狀疱疹

- 常用劑量為一日三次，每次 1000 毫克（兩片 500 毫克的藥片）。
- 您應服用 Valtrex 七天。

治療唇疱疹

- 常用劑量為一日兩次，每次 2000 毫克（四片 500 毫克的藥片）。
- 第二次服藥時間應與第一次服藥時間相隔 12 小時（不可少於 6 小時）。
- 您應只需服用 Valtrex 一天（兩個劑量）。

治療皮膚單純疱疹病毒感染和生殖器疱疹

- 常用劑量為一日兩次，每次 500 毫克（一片 500 毫克的藥片）。
- 對於首次感染，您應服用 Valtrex 五天，或如果醫生建議，可服用最多十天。至於復發性的感染，其治療週期通常為三至五天。

預防單純疱疹病毒感染復發

- 常用劑量為一日一次，每次一片 500 毫克的藥片。
- 您應一直服用 Valtrex 直到醫生吩咐您停藥為止。

預防您被巨細胞病毒感染

- 常規劑量為一日四次，每次 2000 毫克（四片 500 毫克的藥片）。
- 每次服藥之間應相隔約 6 小時。
- 通常在接受手術後，您會儘快開始服用 Valtrex。
- 您應在手術後服用 Valtrex 90 天左右，直到醫生吩咐您停藥為止。

您的醫生可能會調整 Valtrex 的劑量，如果：

- 您的年齡超過 65 歲
- 您的免疫系統較弱
- 您有腎臟問題

如果上述任何情況適用於您，請在服用 Valtrex 前諮詢您的醫生。

服用本藥物

- 本藥物為口服藥物。
- 以水吞服整片藥片。
- 每天請定時服用 Valtrex。
- 請根據醫生或藥劑師指示服用 Valtrex。

65 歲以上或有腎臟問題的患者

在服用 Valtrex 期間，每天定時飲水尤為重要。這有助減少影響腎臟或神經系統的副作用。您的醫生會密切監察您有沒有出現這些情況的跡象。神經系統副作用可能包括感到意識不清或焦慮不安，或感到不尋常的困倦或嗜睡。

如果服用了過量的 Valtrex

Valtrex 通常沒有危害性，除非您在幾天之內過量服用。如果您服用了過量藥片，您可能會感到噁心、嘔吐、腎臟出現問題，可能會感到意識不清、焦慮不安、意識模糊、看見不存在的事物或失去知覺。如果您服用了過量的 Valtrex，請諮詢您的醫生或藥劑師，同時帶上您的藥物包裝。

如果您忘記服用 Valtrex

- 如果您忘記服用 Valtrex，請在記起時立即服用。如果此時已經接近您下一次的服藥時間，請忽略錯過的劑量。
- 請勿因為忘記服藥而一次服用雙倍劑量。

4. 可能出現的副作用

和所有藥物一樣，本藥物可能會引發一些副作用，儘管並非所有人都會有。本藥物可能會產生以下副作用：

您需要注意的情況

- 嚴重的過敏性反應（*過敏反應*）

這些情況在服用 Valtrex 的患者中較為罕見。快速出現的症狀包括：

- 面紅、發癢皮疹
- 嘴唇、面部、頸部和咽喉腫大，造成呼吸困難（*血管性水腫*）
- 血壓下降導致虛脫。

如果您出現過敏性反應，請停止服用 Valtrex 並立即就醫。

十分常見（每 10 個人中有多於 1 人可能會受此影響）：

- 頭痛

常見（每 10 個人中最多有 1 人可能會受此影響）：

- 感到噁心
- 眩暈
- 嘔吐
- 腹瀉
- 在陽光照射後皮膚出現反應（*光敏反應*）
- 皮疹
- 痕癢（*瘙癢症*）

不常見（每 100 個人中最多有 1 人可能會受此影響）：

- 感到意識不清
- 看見或聽到不存在的事物（*幻覺*）
- 感到十分嗜睡
- 震顫
- 感到焦慮不安

這些神經系統的副作用通常會出現在有腎臟問題的患者、老年人或每日服食 8 克高劑量 Valtrex 的器官移植患者身上。他們的情況一般會在停止服用 Valtrex 或減少劑量後有所好轉。

其他不常見的副作用：

- 呼吸急促（*呼吸困難*）
- 胃部不適
- 皮疹，有時發癢，類似蜂巢狀的皮疹（*蕁麻疹*）
- 下背疼痛（*腎痛*）
- 尿液有血（*血尿症*）

在血液測試中可能出現的不常見副作用有：

- 白血球數量減少（*白血球減少症*）
- 血小板 – 幫助血液凝固的細胞數量減少（*血小板減少症*）
- 某些由肝臟產生的物質的數量增加

罕見（每 1,000 個人中最多有 1 人可能會受此影響）

- 走路時身體不穩定，缺乏協調性（*運動失調*）
- 說話緩慢含糊（*構音障礙*）
- 抽搐（*痙攣*）
- 腦部功能改變（*腦病*）
- 失去意識（*昏迷*）
- 感到意識不清或思維混亂（*神智失常*）

這些神經系統的副作用通常會出現在有腎臟問題的患者、老年人或每日服食 8 克高劑量 Valtrex 的器官移植患者身上。他們的情況一般會在停止服用 Valtrex 或減少劑量後有所好轉。

其他罕見的副作用
- 腎臟問題令患者少尿或無尿。

副作用報告
如果您出現了任何副作用，請諮詢您的醫生或藥劑師，包括未在本單張中列出的任何可能出現的副作用。

5. 如何存放 Valtrex
- 請將本藥物放在兒童無法看見及觸及的地方。
- 如果藥物過了包裝盒上印刷的到期日，請勿服用。
- 請按照包裝上的說明存放。
- 切勿通過廢水或家庭垃圾丟棄任何藥物。請諮詢您的藥劑師如何丟棄不用的藥物。這些措施有助於保護環境。

6. 包裝內容和其他資訊
Valtrex 包含哪些成份
- 活性成份為 Valaciclovir。每藥片含 500 毫克 Valaciclovir（作為 Valaciclovir hydrochloride）。

其他成份為：
片芯
Microcrystalline cellulose
Crospovidone
Povidone
Magnesium stearate
Colloidal anhydrous silica

薄膜衣
Hydroxypropylmethylcellulose
Titanium dioxide
Polyethylene glycol 400
Polysorbate 80
Carnauba wax

Valtrex 藥片的外觀
Valtrex 500 毫克藥片是白色的，其中一面印有「GX CF1」字樣。

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