Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valaciclovir Pfizer 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Valaciclovir 500 mg film-coated tablets
Each tablet contains valaciclovir hydrochloride (hydrated) equivalent to 500 mg valaciclovir.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Blue, film-coated, capsule shaped tablets with a partial score bar on both sides containing ‘F’ on one side and ‘9’ and ‘3’ on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Varicella zoster virus (VZV) infections – herpes zoster

Valaciclovir is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see section 4.4).

Valaciclovir 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
Valaciclovir 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 patients
  - recurrences of genital herpes in immunocompetent and immunocompromised patients
  - suppression of recurrent genital herpes in immunocompetent and immunocompromised patients

- Treatment and suppression of recurrent ocular HSV infections (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:
Valaciclovir 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
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 Valaciclovir 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. Valaciclovir 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 patients, 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. 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 Valaciclovir to be taken once daily. Some patients with very frequent recurrences (≥ 10/year in absence of therapy) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg 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.

Immunocompromised Adults
The dose is 500 mg of Valaciclovir 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 Valaciclovir 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 Valaciclovir 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 Valaciclovir to patients with impaired renal function. Adequate hydration should be maintained. The dose of Valaciclovir should be reduced in patients with impaired renal function as shown in Table 1 below.

In patients on intermittent haemodialysis, the Valaciclovir 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 Valaciclovir 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 Indications	Creatinine Clearance (mL/min)	Valaciclovir Dosage[a]
Varicella-Zoster Virus (VZV) Infections		
Treatment of herpes zoster (shingles) in immunocompetent and	≥ 50	1000 mg three times daily
	30 to 49	1000 mg twice

immunocompromised adults		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 adults and adolescents (alternative 1-fay regimen)	≥ 50	2000 mg twice in one day
	30 to 49	1000 mg twice in one day
	10 to 29	500 mg twice in one day
	< 10	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	15000 mg four times daily
	25 to <50	1500 mg three times daily
	10 to <25	1500 mg twice daily
	<10 or on dialysis	15000 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 aciclovir 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 patients and the adverse reaction profile of valaciclovir 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 valaciclovir 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 ≤1/1,000);
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.
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 (8g daily) of Valaciclovir 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 os 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 (8 g 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors,
ATC code: J05A B11

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 to aciclovir 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 host 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
Valaciclovir 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. Valaciclovir 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 co-infected patients. with a median CD4 count of > 100cells/mm3. 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)
Cmax	micrograms/mL	2.20 ± 0.38	3.37 ± 0.95	5.20 ± 1.92	8.30 ± 1.43
Tmax	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

Cmax = peak concentration; Tmax = time to peak concentration; AUC = area under the concentration-time curve. Values for Cmax and AUC denote mean ± standard deviation. Values for Tmax denote median and range.

Peak plasma concentrations of unchanged valaciclovir are only about 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

Core:
Cellulose, microcrystalline
Crospovidone (Type A)
Povidone K90
Magnesium stearate

Film-coating:
Opadry Blue 13B50578
(Hypromellose, Indigo carmine aluminium lake (E132), Titanium dioxide (E171), Macrogol 400, Polysorbate)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Clear PVC/PVdC Aluminium foil blister pack or in HDPE bottle with PP closure.

Blister pack:
500 mg: 5, 10, 21, 24, 30, 42, 50, 90 and 112 tablets

HDPE bottle pack:
500 mg 30 and 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 822/57/1

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