Produktinformationen för Valaciclovir Docpharma 500 mg filmdragerad tablett, MTnr 25929, gäller vid det tillfälle då läkemedlet godkändes. Informationen kommer inte att uppdateras eftersom läkemedlet inte marknadsförs i Sverige. Av samma anledning finns inte någon svensk produktinformation.
Den engelska produktinformationen kommer dock att uppdateras för de produkter där Sverige är referensland.
Om läkemedelsnamnet i följande produktinformation inte stämmer med namnet på dokumentet, beror det på att läkemedlet i Sverige är godkänt under ett annat namn.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Valaciclovir 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg valaciclovir (as valaciclovir hydrochloride monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White coloured, oval shaped, biconvex film-coated tablet with a break line on one side and plain on the other side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- In immunocompetent patients :
    - Treatment of herpes zoster in patients aged over 50 years: valaciclovir reduces the duration of severe infection and accordingly the proportion of patients with zoster-associated pain.
    - Valaciclovir is indicated for the treatment of initial and recurrent genital herpes simplex infections.
    - Valaciclovir is indicated for the prevention of recurrent genital herpes simplex infections in patients with at least 6 recurrences per year.
- Valaciclovir is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, in particular after renal transplantation, except after lung transplantation.

4.2 Posology and method of administration

Route of administration
Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water), with or without food.

Adults

Herpes zoster infections

Prevention of zoster-associated pain:

- 1000 mg (two 500 mg tablets) of valaciclovir 3 times daily for 7 days

Treatment should be initiated as soon as possible after the beginning of the infection, within 72 hours of the appearance of skin lesions.

Herpes simplex infections

Treatment of genital herpes simplex infections in immunocompetent patients:

- 500 mg twice daily for 10 days for the initial episode
- 1000 mg (two 500 mg tablets) per day in one or two divided doses for 5 days for recurrent episodes

Treatment should be initiated as soon as possible in the course of infection, preferably at the prodromal stage or when lesions begin to appear.

Suppression of recurrent genital herpes simplex infections:

- 500 mg per day in one or two divided doses

(Better results have been obtained by dividing the daily dose into two, i.e. by administering 250 mg twice daily, when the administration of a single 500 mg dose per day failed, or if the recurrences were frequent or very symptomatic).
For this indication, the need for treatment must be re-evaluated after 6 to 12 months.

Adults and adolescents aged 12 years and above

Cytomegalovirus infections

Prophylaxis of infections and diseases caused by cytomegalovirus (CMV):

- 2000 mg of valaciclovir 4 times daily

Treatment should be initiated as soon as possible after the organ transplant.
The dose of valaciclovir should be adapted according to the creatinine clearance (see second table below).
The duration of treatment is usually 90 days, although longer treatment may be necessary in high risk patients.

Elderly

Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

Renal impairment

Prevention of zoster-associated pain, suppression and treatment of genital herpes simplex infections:

The dosage should be adjusted according to the creatinine clearance:

Creatinine-clearance ml/min	*Herpes Zoster*	*Herpes simplex*	
		Treatment	*Prophylaxis*
>50 ml/min	1 g 3 times daily (Normal dose)	500 mg twice daily (Normal dose)	500 mg once daily (Normal dose)
>30-50 ml/min	1 g twice daily	500 mg twice daily (Normal dose)	500 mg once daily (Normal dose)
10–30 ml/min	1 g once daily	500 mg once daily	250 mg once daily
<10 ml/min	500 mg once daily	500 mg once daily	250 mg once daily

Patients on haemodialysis should receive the same dose as patients with creatinine clearance <10 ml/min. On dialysis days, the dose should be given after dialysis.

Prophylaxis of infections and diseases caused by cytomegalovirus (CMV)

The dosage should be adjusted according to the creatinine clearance, which must be assessed frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment.

Creatinine clearance	Dosage
50-75 ml/min	1500 mg 4 times daily
25-50 ml/min	1500 mg 3 times daily
10-25 ml/min	1500 mg twice daily
< 10 ml/min	1500 mg daily

In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.

Hepatic impairment
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 the higher doses recommended for the prevention of infections and diseases caused by CMV, see section 4.4.

Children below the age of 12 years
Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

4.3 Contraindications

Known hypersensitivity to the active substance valaciclovir, aciclovir or to any of the excipients.

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 renal impairment and the elderly
The dose should be adapted according to the creatinine clearance (see section 4.2). The elderly and patients with a history of renal impairment are also at increased risk of developing neurological disorders (see section 4.8). If neurological disorders occur, the treatment must be stopped. Upon re-introduction, the dosage must be reduced.

Hepatic impairment or liver transplantation
There is no data available on the use of high doses (8 g per day) in patients with hepatic impairment. Therefore, caution should be exercised when administering high doses of valaciclovir to these patients.

Use in genital herpes
Therapy with valaciclovir 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 valaciclovir, it is recommended that patients use safer sex practices (particularly the use of condoms).

4.5 Interactions with other medicinal products and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products; in particular immunosuppressants like ciclosporin, tacrolimus, mycophenolate mofetil, must be taken into account, especially in case of impaired renal function, and warrants regular monitoring. This applies for aminoglycosides, organoplatins, iodinated contrast media, methotrexate, pentamidine, foscarnet as well.

Aciclovir is eliminated primarily unchanged in the urine via active tubular secretion. Any medicinal products administered concurrently that compete with this mechanism for elimination (e.g. cimetidine, probenecid or mycophenolate mofetil) may increase aciclovir plasma concentrations following valaciclovir administration. In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with these kinds of products. However, following 1 g valaciclovir, no dosage adjustment is necessary at this dose of 1 g because of the wide therapeutic index of aciclovir. Alternative products, which do not interact with other substances excreted primarily via the kidney, may be considered for the management of excess gastric acid production and urate-lowering therapy when administering high-dose valaciclovir.

4.6 Pregnancy and lactation

Pregnancy
Data on a large number of exposed pregnancies indicate no adverse effects of aciclovir, the active metabolite of valaciclovir, on pregnancy or on the health of the fetus/newborn child. However, only epidemiological studies would allow to substantiate the lack of harmfulness of the agent on pregnancy.
Studies in animals have not shown reproductive toxicity in a single species at high doses (see section 5.3)

Valaciclovir should not be used during pregnancy unless clearly necessary.

There is no data to justify the long-term use of valaciclovir in recurrent herpes in pregnant women, in particular at the end of pregnancy.

Lactation
Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk (see section 5.2).

If systemic treatment of the mother is necessary for a serious infection, breast-feeding should be discontinued owing to the risk of infection. Otherwise, local treatment should be used so breast-feeding can be continued.

4.7 Effects on ability to drive and use machines

Valaciclovir has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse events are ranked under headings of frequency, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
- Very rare: thrombocytopenia, leucopenia / neutropenia (especially in immunocompromised patients).

Immune system disorders
- Very rare: anaphylaxis.

Psychiatric disorders
- Rare: altered consciousness, confusion, hallucinations.
- Very rare: agitation, psychotic symptoms.

Nervous system disorders
- Common: headache.
- Rare: dizziness, somnolence, decreased consciousness.
- Very rare: tremor, ataxia, dysarthria, convulsions, encephalopathy, coma.

The above events are usually seen in patients with renal impairment receiving doses greater

than those recommended or in patients with other predisposing factors (especially the elderly, see section 4.4). These neurological disorders are common in transplant recipients receiving high doses of valaciclovir for the prophylaxis of infections and diseases caused by CMV.

Respiratory, thoracic and mediastinal disorders
- Uncommon: dyspnoea.

Gastrointestinal disorders
- Common: nausea.
- Rare: abdominal discomfort, vomiting, diarrhoea.

Hepato-biliary disorders
- Very rare: reversible increases of bilirubin and serum hepatic enzyme levels.

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders
- Uncommon: rash, including photosensitivity.
- Rare: pruritus.
- Very rare: urticaria, angioedema.

Renal and urinary disorders
- Rare: renal impairment.
- Very rare: increased blood urea and creatinine, acute renal failure, sometimes with crystal precipitation in the tubule lumen, in particular in elderly or renally impaired patients when the doses used exceed those recommended.

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced human immunodeficiency virus (HIV) disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

4.9 Overdose

Valaciclovir is rapidly and completely metabolized to aciclovir.

The intravenous administration of a high dose of aciclovir (80 mg/kg) corresponds to a valaciclovir dose of approximately 15 g.

Symptoms
Few cases of overdose have been reported with valaciclovir.

The oral administration of doses of aciclovir up to 20 g did not lead to adverse events.

The accidental and repeated oral administration of high doses of aciclovir over a period of several days led to gastrointestinal (nausea and vomiting) and neurological (headache and

confusion) disorders.

The intravenous administration of a high dose of aciclovir caused an increase in serum creatinine levels with renal impairment secondary to the precipitation of crystals in the tubule lumen. Neurological disorders (confusion, hallucinations, agitation, epilepsy and coma) have been described following intravenous overdose.

The use of doses unadapted to renal function in the renally impaired has been observed to cause altered consciousness, from confusion with hallucinations to coma.

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 excl. reverse transcriptase inhibitors
ATC code: J05A B11

Valaciclovir is the L-valine ester of aciclovir, the active antiviral. It is rapidly and completely metabolized to aciclovir by a 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.

The phosphorylation process is completed (conversion from mono- to di- and 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.

This dual selectivity ensures that aciclovir does not interfere with the metabolism of healthy cells.
Extensive monitoring of clinical 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. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency

virus (HIV).

Resistance is normally due to a thymidine kinase deficient phenotype, which results in a virus that 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.

5.2 Pharmacokinetic properties

After oral administration, valaciclocir is well absorbed and rapidly and almost completely metabolised to aciclovir by a marked first pass effect, which is mainly hepatic. After administration of single 250 mg and 2000 mg doses, the maximal aciclovir concentrations obtained are 10 and 37 µmol/l (2.2 to 8.3 µg/ml) and are reached approximately 1 to 2 hours after dosing. The bioavailability of aciclovir from valaciclovir is 54%; it is not affected by food intake. Maximum plasma valaciclovir concentrations are only 4% of those of aciclovir. Valaciclovir cannot be detected within 3 hours of administration. The plasma profiles of valaciclovir and aciclovir are similar after single and multiple dosing.

Binding of aciclovir and valaciclovir to plasma proteins is very low (approximately 15%). Aciclovir distributes rapidly into all tissues, especially the liver, kidneys, muscles, lungs. It also diffuses into vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

In patients with normal renal function, the elimination half-life of aciclovir after single and repeat doses is approximately 3 hours. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours. In patients with normal renal function, valaciclovir is eliminated principally as acyclovir (greater than 80% of the recovered dose), the 9-carboxymethoxymethylguanine (CMMG) (10-15% of the dose) and 8-hydroxiaciclovir (1% of the dose), in urine. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug.

The exposure to aciclovir and the metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated in 6 subjects with normal renal function (mean creatinine clearance 123 ml/min) and 3 subjects with severe renal impairment (mean creatinine clearance 26 ml/min) after administration of the recommended doses for valaciclovir in CMV profylaxis, i.e. 2000 mg 4 times daily at normal renal function and 1500 mg twice daily at severe renal impairment. In plasma as well as CSF, the concentration of acyclovir, CMMG and 8-OH-ACV was on average 2 times, 4 times and 5-6 times higher, respectively, in subjects with severe renal impairment compared with subjects with normal renal function. In both groups of subjects, the CSF concentrations of acyclovir and 8-OH-CV were on average 25% of those in plasma, and the CSF concentrations of CMMG were on average 2.5% of those in plasma. The concentrations of metabolites in CSF were less than 2.5% of the concentrations of acyclovir in CSF.

In elderly, cirrhotic and HIV-positive patients, the pharmacokinetic profile of aciclovir after administration of valaciclovir is not significantly different. In non-dialysed severely renally impaired patients, the maximum concentration of aciclovir is approximately doubled and its elimination half-life is increased by a factor of 5. In organ transplant recipients treated with

2000 mg of valaciclovir 4 times daily, the maximum plasma concentrations of aciclovir are similar or greater than those obtained in healthy volunteers receiving the same dose. The areas under the curve are appreciably greater. At the end of pregnancy, the area under the curve of the plasma concentration of aciclovir versus time for 1000 mg of valaciclovir is approximately twice greater than after administration of 1200 mg/day of aciclovir. Pregnancy does not modify the pharmacokinetic characteristics of valaciclovir.

With a maternal valaciclovir dosage of 500 mg twice daily, the amount of substance excreted in breast milk 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

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

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

Teratogenicity
Valaciclovir is not teratogenic in rats and rabbits.

Fertility
Orally administered valaciclovir did not modify the fertility of male or female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Film coating:
Opadry White 0Y-58900:

- Hypromellose (E464)
- Titanium dioxide (E171)
- Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

No special storage condition required.

6.5 Nature and contents of container

Opaque, metallic silver colored, oriented polyamide/Aluminium/PVC-Aluminium blister: 10, 30, 42 and 90 tablets
HDPE bottle with polypropylene screw cap: 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Docpharma NV
Ambachtenlaan 13H
3001 Heverlee
Belgium

8 MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT