Vaciclor

Valaciclovir

1. Name of the medicinal product

Vaciclor

2. Qualitative and quantitative composition

Each film-coated tablet contains 500 mg valaciclovir (as valaciclovir hydrochloride monohydrate 611.7 mg).
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet
500 mg tablets: Oval, white, biconvex, film-coated tablets, 17.6 x 8.8 mm with VC2 on one side

4. Clinical particulars

4.1 Therapeutic indications

Vaciclor is indicated for the treatment of herpes zoster (shingles). Vaciclor accelerates the resolution of pain; it reduces the duration of and the proportion of patients with zoster associated pain, which includes acute and post-herpetic neuralgia.
Vaciclor is indicated for the treatment of herpes simplex infection of the skin and mucous membranes, including initial and recurrent genital herpes.
Vaciclor can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.
Vaciclor is indicated for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes.
Consideration should be given to official guidance on the appropriate use of antiviral agents.

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). The tablet can be taken with or without food.

Adults
Herpes zoster infections
Treatment of zoster-associated pain:
- 1000 mg 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 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
Elderly
Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

Therapeutic indication	Creatinine clearance ml/min	Vaciclor dosage
Herpes zoster	15-30 less than 15	1 g twice a day 1 g once a day
Herpes simplex (treatment) (500 mg bd regimen)	less than 15	500 mg once a day
Herpes simplex prevention (suppression): - immunocompetent patients -immunocompromised patients	 less than 15 less than 15	 250 mg once a day 500 mg once a day
Reduction of transmission of genital herpes:	less than 15	250 mg once a day

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.
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.

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

Hypersensitivity to 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 reintroduction, the dosage must be reduced.

Hepatic impairment
There is no data available on the use of high doses (4 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).

Drug reaction with eosinophilia and systemic symptoms *(DRESS)*
DRESS, which can be life-threatening or fatal, has been reported in association with valaciclovir treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of *DRESS* appear, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed *DRESS* with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time.

4.5 Interaction 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 (4 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

Teratogenicity :
Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolized to aciclovir. Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats and rabbits. In additional studies in rats, foetal abnormalities were observed at subcutaneous doses that produced plasma levels of 100 mcg/ml and maternal toxicity.

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

Pregnancy : There are limited data on the use of Vaciclor in pregnancy. Vaciclor should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk. Pregnancy registries have documented the pregnancy the pregnancy outcomes in women exposed to 111 and 11246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. The findings of the aciclovir pregnancy registry have not shown an increase in the number of birth defects amongst acyclovir-exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Given the small number of women enrolled into the valaciclovir pregnancy registry, reliable and definitive conclusions could not be reached regarding the safety of valaciclovir in pregnancy. (See also 5.2 Pharmacokinetic Properties).

Lactation : Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. Following oral administration of a 500 mg dose of valaciclovir, peak acyclovir concentrations (Cmax) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2). The median acyclovir concentration in breast milk was 2.24 g/ml (9.95M). with a maternal valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral acyclovir dosage of about 0.61 mg/kg/day. The elimination half-life of acyclovir from breast milk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breast milk, or infant urine. Caution is advised if Vaciclor is to be as=dministered to a nursing woman. However, acyclovir is used to treat neonatal herpes simplex at intravenous doses of 30 mg/kg/day.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of Vaciclor should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of Vaciclor on driving performance or the ability to operate machinery. Further a detrimental on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

The adverse events are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:
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), not known (cannot be estimated form the available data).

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leucopoenia/neutropenia (mainly reported in immunocompromised patients).

Immune system disorders
Very rare: Anaphylaxis.

Psychiatric disorders
Rare: Confusion, hallucinations, altered consciousness.
Very rare: Agitation, psychotic symptoms.
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 (8 g daily) 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 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.

Under Post Marketing Data
Skin and subcutaneous tissue disorders
Drug reaction with eosinophilia and systemic symptoms *(DRESS)*

4.9 Overdose
Valaciclovir is rapidly and completely metabolised 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 acyclovir 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: J05AB11
Valaciclovir is the L-valine ester of aciclovir, the active antiviral. It is rapidly and completely metabolised 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, valaciclovir is well absorbed and rapidly and almost completely metabolized 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 mcmol/l (2.2 to 8.3 µg/ml) and are reached approximately 1 to 2 hours after dosing. The bioavailability of acyclovir 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 acyclovir after single and repeat doses is approximately 3 hours. In patients with end-stage renal disease, the average elimination halflife of aciclovir after valaciclovir administration is approximately 14 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is mainly eliminated as aciclovir and its metabolite, 9-(carboxymethoxymethyl)-guanine, in the urine.
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 halflife 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 was not teratogenic in rats or rabbits.

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

6. Pharmaceutical particulars

6.1 List of excipients
Tablet core
Cellulose microcrystalline, Povidone, Magnesium Stearate.

Tablet coating
Opadry White Y-5-7068: Hyromellose, Hydroxypropyl cellulose, Titanium dioxide (E171), Macrogol 400, Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer to cartons for shelf life information.

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
PVC/aluminium blister
Pack sizes (Blisters): 30, 42 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

Balkanpharma Dupnitsa AD
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Dupnitsa 2600
Bulgaria

8. Date of revision of the text

February 2023.