

PACKAGE LEAFLET
for medical use of a medicinal product

ACICLOVIR-DARNITSA

Qualitative and quantitative composition:

active substance: aciclovir;

1 tablet contains 200 mg of aciclovir.

list of excipients: potato starch, povidone, sodium croscarmellose, calcium stearate.

Pharmaceutical form. Tablets.

Main physical and chemical properties: white or almost white tablets with a bevel and a scoreline.

Pharmacotherapeutic group: Antiviral agents for systemic use.

ATC code J05A B01.

Pharmacological properties.

Pharmacodynamics properties.

Aciclovir is a synthetic purine nucleoside analogue with inhibitory activity *in vivo* and *in vitro* against human herpes virus, including herpes simplex virus type I and II, chickenpox and shingles virus, Epstein-Barr virus and cytomegalovirus. In a cell culture aciclovir is the most active against herpes simplex virus type I and further, in decreasing activity, against herpes simplex virus type II, chickenpox and herpes zoster virus, Epstein-Barr virus and cytomegalovirus.

The inhibitory activity of aciclovir against the above viruses is highly selective. The enzyme thymidine kinase in a normal uninfected cell does not use aciclovir as a substrate, hence the toxic effect on host cells is minimal. However, thymidine kinase, encoded in herpes simplex, chickenpox, herpes zoster and Epstein-Barr virus, converts aciclovir to aciclovir monophosphate – a nucleoside analogue, that is then converted sequentially to diphosphate and triphosphate using cell enzymes. Following the incorporation of aciclovir into viral DNA, triphosphate interacts with viral DNA polymerase, resulting in the cessation of viral DNA chain synthesis.

Prolonged or repeated courses of treatment in severely immunocompromised patients may reduce the susceptibility of certain strains of the virus, that do not always respond to aciclovir treatment. Most clinical cases of non-susceptibility are associated with viral thymidine kinase deficiency, although viral thymidine kinase and DNA damage have been reported. *In vitro* interaction of individual herpes simplex viruses with aciclovir may also lead to the formation of less sensitive strains. The relationship between the susceptibility of individual herpes simplex viruses *in vitro* and the clinical outcomes of aciclovir treatment is not fully understood.

Pharmacokinetic properties.

Aciclovir is only partially absorbed in the gastrointestinal tract (approximately 20% of the dose). Simultaneous intake of food does not reduce absorption. The maximum concentration is reached in 1.5 – 2 hours.

The level of its binding to plasma proteins is relatively low (from 9% to 33%) and does not change when interacting with other medicinal products.

Aciclovir penetrates the placental barrier, cerebrospinal fluid (50% of the corresponding plasma concentration), and breast milk.

Most of the medicinal product (85 – 90%) is excreted unchanged by kidneys and only a small part (10 – 15%) as a metabolite (9-carboxymethoxymethylguanine). Renal clearance of aciclovir is significantly higher than creatinine clearance, indicating that renal excretion is performed not only by glomerular filtration, but also by tubular secretion.

The terminal half-life of aciclovir following the intravenous administration is approximately 2.9 hours, in patients with chronic renal failure is 19.5 hours, during hemodialysis is 5.7 hours. Aciclovir levels in blood plasma are reduced approximately by 60% during dialysis.

Clinical particulars.***Therapeutic indications.***

- Treatment of infections of skin and mucous membranes caused by *Herpes simplex* virus, including primary and recurrent genital herpes.
- Prevention of relapse of infections caused by *Herpes simplex* virus in patients with normal immunity.
- Prevention of infections caused by *Herpes simplex* virus in immunodeficient patients.
- Treatment of infections caused by *Varicella zoster* virus (chickenpox, herpes zoster).

Contraindications.

Hypersensitivity to aciclovir, valaciclovir or any ingredient of the medicinal product.

Interaction with other medicinal products and other forms of interaction.

Aciclovir is excreted mainly unchanged by the kidneys by tubular secretion, so any medicinal products, that have a similar mechanism of excretion may increase the concentration of aciclovir in blood plasma. In case of simultaneous use of medicinal product with other medicines, the following is possible:

with probenecid, cimetidine – prolongation of the half-life of aciclovir and the area under the curve;

with immunosuppressants in patients after organ transplantation – increased level of aciclovir and inactive metabolite of immunosuppressive medicinal product (mycophenolate mofetil) in blood plasma; no dose adjustment is required due to the broad therapeutic index of aciclovir.

An experimental study of 5 men indicates that concomitant aciclovir therapy increases the AUC of fully administered theophylline by approximately 50%. It is recommended to measure the concentration in blood plasma during concomitant therapy with aciclovir.

No clinically relevant interactions of aciclovir with other medications were detected.

Special warnings and precautions for use.

When using high doses of the medicinal product, an adequate level of hydration should be maintained. ACICLOVIR-DARNITSA should be used with caution in patients with impaired renal function, as aciclovir is excreted mainly by renal clearance. Dose adjustment should be performed (see section «Posology and method of administration»).

ACICLOVIR-DARNITSA should be used with caution in elderly patients, as this group of patients is more likely to have impaired renal function. If necessary, dose adjustment should be performed (see section «Posology and method of administration»).

Both of these groups (patients with impaired renal function and elderly patients) are at risk for neurological disorders, and therefore should be closely monitored for these adverse reactions. According to the data obtained, such reactions are generally reversible in case of discontinuation of treatment with the medicinal product (see section "Undesirable effects").

The risk of kidney damage increases when used in combination with other nephrotoxic medications.

Prolonged or repeated courses of aciclovir treatment in immunocompromised individuals may result in the release of susceptible viral strains, that may not respond to long-term treatment with aciclovir.

The available clinical trial data are not sufficient to conclude that aciclovir treatment reduces the incidence of chickenpox-related complications in immunocompetent patients.

Fertility, pregnancy and lactation.

The results of the use of various pharmaceutical forms of aciclovir by pregnant women are documented in the post-authorization register of pregnancy supervision. There was no increase in the number of birth defects in children, whose mothers used aciclovir during pregnancy compared with the general population.

When aciclovir administered orally at a dose of 200 mg 5 times a day, it passes into breast milk in concentrations of 0.6-4.1% of the corresponding level of aciclovir in blood plasma. Potentially, a child can absorb aciclovir at a dose of up to 0.3 mg/kg body weight per day.

During pregnancy or breastfeeding, the medicinal product should be used when its potential benefit to the mother outweighs the possible risk to the fetus.

There is no information on the effect of aciclovir on female fertility.

In a study of 20 male patients with normal sperm counts when administered orally at a dose of up to 1 g per day for 6 months, no clinically significant effect on sperm count, motility or morphology was observed.

Effects on ability to drive and use machines.

Clinical studies of the effect of aciclovir on the speed of reaction when driving a car or working with other mechanisms have not been conducted. The pharmacology of aciclovir does not provide basis to expect any adverse effects. The clinical status of the patient and the adverse reaction profile of the medicinal product should be taken into account when deciding on the possibility of driving a car and other mechanisms.

Posology and method of administration.

The tablet should be taken whole with water. When using high doses of the medicinal product, an adequate level of hydration should be maintained.

Adults.

Treatment of infections caused by Herpes simplex virus.

ACICLOVIR-DARNITSA should be used at a dose of 200 mg 5 times per day with an interval of approximately 4 hours, except at night. The duration of treatment is 5 days, but in case of severe primary infection it can be extended.

If necessary, in patients with severe immunodeficiency (e.g. after bone marrow transplantation) or with reduced intestinal absorption, a single dose may be doubled to 400 mg or used the appropriate dose for intravenous administration.

Treatment should be started as early as possible after the onset of infection. In case of recurrent herpes, it is the best to start treatment in the prodromal period or after the first signs of skin lesions.

Prevention of relapse of infections caused by Herpes simplex virus in patients with normal immunity.

ACICLOVIR-DARNITSA should be used in a dose of 200 mg 4 times per day with a 6-hour interval (or for convenience, in a dose of 400 mg 2 times per day with a 12-hour interval).

Treatment will be effective even after reducing the dose of the medicinal product to 200 mg 3 times per day with an 8-hour interval or even 2 times per day with a 12-hour interval.

In some cases, a radical improvement is observed after administering a daily dose of 800 mg.

To monitor possible changes in the natural course of the disease, medication therapy should be interrupted periodically at intervals of 6 – 12 months.

Prevention of infections caused by Herpes simplex virus in immunodeficient patients.

ACICLOVIR-DARNITSA should be used at a dose of 200 mg 4 times a day with a 6-hour interval.

If necessary, in patients with severe immunodeficiency or with reduced intestinal absorption, a single dose may be doubled to 400 mg or the appropriate dose for intravenous administration should be used.

The duration of prevention depends on the length of the risk period.

Treatment of infections caused by Herpes simplex virus.

ACICLOVIR-DARNITSA should be used at a dose of 800 mg 5 times per day with an interval of approximately 4 hours, except at night. Duration of treatment – 7 days.

Treatment should be started as early as possible after the onset of the disease; the result will be better if therapy is started immediately after the appearance of the rash.

In patients with severe immunodeficiency (e.g. after bone marrow transplantation) or with reduced intestinal absorption, it is preferable to use intravenous administration of medicinal product.

Children under the age of 2 years.

Posology and prevention of infections caused by Herpes simplex virus in immunodeficient children.

ACICLOVIR-DARNITSA should be used in same doses as for adults.

Treatment of chickenpox.

ACICLOVIR-DARNITSA should be used in the following dose: children 2 to 6 years of age: 400 mg 4 times per day, children under the age of 6 years: 800 mg 4 times per day.

More precisely, the dose of the medicinal product can be calculated per the child's body weight, which is 20 mg/kg of body weight per day, divided into 4 doses. The maximum daily dose is 800 mg. Duration of treatment is 5 days.

There are no specific data on the use of aciclovir for the prevention of herpes simplex virus infections or for the treatment of herpes zoster virus infections in children with normal immunity.

Patients with renal impairment.

ACICLOVIR-DARNITSA should be used with caution. It is necessary to maintain an adequate level of hydration of body.

In the prevention and treatment of *Herpes simplex* infections in patients with renal insufficiency, the recommended oral doses do not result in the accumulation of aciclovir, which would exceed the safe level established for intravenous administration. However, in patients with severe renal insufficiency (creatinine clearance less than 10 mL/min) it is recommended to use ACICLOVIR-DARNITSA at a dose of 200 mg 2 times per day with an interval of approximately 12 hours.

In the treatment of infections caused by *Varicella zoster* virus, patients with significantly reduced immunity are recommended to use ACICLOVIR-DARNITSA in a dose of: in severe renal insufficiency (creatinine clearance less than 10 mL/min) – 800 mg 2 times per day with an interval of approximately 12 hours, in moderate renal insufficiency (creatinine clearance in the range of 10 – 25 mL/min) – 800 mg 3 times per day with an interval of approximately 8 hours.

Use in elderly patients.

ACICLOVIR-DARNITSA should be used with caution. It is necessary to maintain an adequate level of hydration of the body.

The possibility of renal impairment in elderly patients should be considered, and the dose of medicinal product for them should be changed accordingly.

Children.

ACICLOVIR-DARNITSA is used for children starting from 2 years.

Overdose.

Symptoms. Aciclovir is only partially absorbed from the digestive tract. Accidental administration of up to 20 g of aciclovir without toxic effects has been reported.

In case of accidental overdose of oral aciclovir for several days, the following symptoms occur: gastroenterological (nausea, vomiting) and neurological (headache, confusion).

Intravenous aciclovir overdose increases serum creatinine and, hence, the renal failure occurs. Neurological manifestations of overdose may include confusion, hallucinations, agitation, convulsions, and coma.

Treatment: symptoms of intoxication, symptomatic therapy, in severe cases, hemodialysis should be examined for.

Undesirable effects.

Adverse events have been ranked under headings of frequency using the following convention: *Very common* ($\geq 1/10$); *common* ($\geq 1/100$, $< 1/10$); *uncommon* ($\geq 1/1000$, $< 1/100$); *rare* ($\geq 1/10000$, $< 1/1000$); *very rare* ($< 1/10000$).

Respiratory, thoracic and mediastinal disorders: rare - shortness of breath.

Gastrointestinal disorders: rare - nausea, vomiting, diarrhea, abdominal pain, loss of appetite, gastritis, dysphagia.

Hepatobiliary disorders: rare - transient increase of liver enzymes and bilirubin levels; very rare - jaundice, hepatitis.

Renal and urinary disorders: rare - increased concentrations of urea and creatinine in the blood; very rare - acute renal failure, perirenal pain.

Renal pain may be associated with renal failure and crystalluria.

Nervous system disorders: common - headache, dizziness; very rare - psychomotoric agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, drowsiness, encephalopathy, coma.

The above mentioned symptoms are in most cases reversible and occur mainly in patients with renal insufficiency or other predisposing factors (see section "Special warnings and precautions for use").

Cardiac disorders: rare - palpitations, chest pain.

Blood and lymphatic system disorders: very rare - anemia, leukopenia, thrombocytopenia.

Immune system disorders: rare - hypersensitivity reactions, including angioneurotic edema, anaphylactic reactions.

Skin and subcutaneous tissue disorders: common - rash, itching, photosensitization; uncommon - hyperemia, urticaria, alopecia.

Because hair loss can be associated with a large number of diseases and medications, no clear association has been found with aciclovir.

General disorders and administration site conditions: common - fatigue, fever.

Shelf life.

3 years.

Special precautions for storage.

Store in the original package at a temperature below 25°C.

Keep out of the reach of children.

Nature and contents of container.

10 tablets in a blister container; 2 blister containers in a package.

Category of release.

Prescription only medicine.

Manufacturer.

PrJSC “Pharmaceutical firm “Darnitsa”.

The manufacturer's location and address of the place of business.

Ukraine, 02093, Kyiv, 13, Boryspilska Street.

Date of last reversion.

21.03.2019