PACKAGE LEAFLET

Package leaflet: Information for the patient

Aciclovir 500 mg powder for solution for infusion

aciclovir

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aciclovir is and what it is used for

Aciclovir contains the active substance aciclovir. This medicine is a direct-acting antiviral agent (it destroys or stops the growth of viruses that cause shingles or herpes).
It is used to treat certain infections due to the herpes virus and certain forms of chickenpox and shingles (a viral disease characterised by a painful rash, for example, in the eye).

2. What you need to know before you are given Aciclovir

You must not be given Aciclovir
- if you are allergic to aciclovir or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before being given Aciclovir.
- if you have kidney problems (impaired kidney function)
- if you experience back pain around the kidney area, this could be a sign of kidney problems (impaired kidney function); discontinuation of treatment may be considered
- if you are receiving intravenous aciclovir or taking high doses of oral aciclovir, you should also keep yourself hydrated regularly.

Other medicines and Aciclovir
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without prescription.
- if Aciclovir is used at the same time as other medicines that are toxic to the kidneys, it can increase the risk of kidney problems. Caution is required when administering aciclovir IV with other nephrotoxic medicines.
- avoid combined intravenous treatment (injection of several medicines at the same time into the same tubing set and, similarly, mixing them in the same infusion. This medicine may crystallise when combined with certain medicines.
- if you are given lithium (medicine used to regulate mood) at the same time as high doses of intravenous aciclovir, lithium levels in your blood should be closely monitored due to the risk of lithium toxicity.
- if aciclovir is administered at the same time as theophylline (medicine used to treat asthma and some respiratory diseases), your doctor may ask for tests to measure theophylline levels in your

blood.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before receiving this medicine.

You should not take this medicine during pregnancy unless clearly indicated by your doctor.
If you find out that you are pregnant during treatment, tell your doctor because only he/she can decide if you need to continue it.

Avoid breast-feeding during your treatment with aciclovir as it can be excreted into human milk.

Driving and using machines
Your doctor will assess your ability to drive vehicles and use machines, depending on your state of health and certain side effects, particularly on the nervous system, which may occur during treatment (see Section 4: Possible side effects).

Aciclovir contains sodium
500 mg vial:
This medicine contains 52.2 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.6 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Aciclovir is given

You will never be expected to give yourself this medicine. It will always be given to you by a person who is trained to do so.

Dosage
The dosage is determined according to the condition being treated and the patient's age and weight.
- **in adults:** 5-10 mg/kg every 8 hours,
- **in children over 3 months of age:** the dosage should be calculated according to body weight, 10 to 20mg/kg every 8 hours with a maximum dose of 400 mg to 800 mg every 8 hours, respectively,
- **in newborn children:** 20 mg/kg every 8 hours.

Use in patients with kidney problems
Caution is advised when administering aciclovir by infusion to patients with impaired kidney function.
- If you have kidney problems, your doctor will need to adjust your dose of this medicine.
- If you are elderly, your doctor will adjust the dose, as kidney function in elderly people may be reduced.
- In over-weight patients and particularly in those with kidney problems and elderly people the dose should be adjusted.
- In infants and children with kidney problems, the dose should be properly adjusted depending on the extent of kidney problems.
- In all events, it is important that you keep yourself sufficiently hydrated throughout treatment to reduce the risk of impaired kidney function.

Method of administration
This medicine will be administered to you by a healthcare professional, who will inject it into a vein (strict intravenous (IV) use).

Duration of treatment
The duration of treatment is usually 5-10 days. It must be adjusted to the patient's condition and his/her response to treatment. In the case of neonatal herpes and depending on the indication, this duration may be 14 or 21 days.

If you are given more Aciclovir than you should

Consult your doctor immediately.
In some situations (for example, if you have kidney problems), neurological disorders may occur (see section 4: Possible side effects).

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
These side effects are ranked from the most commonly to the most rarely observed.

Common: (may affect up to 1 in 10 people)
- **Gastrointestinal problems:**
  - nausea,
  - vomiting,
  - diarrhoea,
  - abdominal pain.
- **Liver problems:** increases in serum bilirubin and hepatic enzymes (substances produced by the liver).

These effects usually disappear upon discontinuation of treatment.
- **Skin reactions:**
  - pruritus (itching),
  - skin rash,
  - hives (rash identical to that caused by nettle stings).
- **Kidney problems:** increase in urea and creatinine in the blood (sign of kidney function problems).
- **General problems:** inflammatory skin lesions or phlebitis (formation of a blood clot in a vein) at the site where the medicine was injected, which can lead to necrosis (destruction of cells) in exceptional cases of extravasation (where the medicine leaks from the vein into which it is injected) or insufficient dilution of the solution. These inflammatory lesions are related to the alkaline pH of this medicine.

Not known: (frequency cannot be estimated from the available data)
- **Blood problems:**
  - thrombocytopenia (decrease in platelets – cells that enable blood clotting)
  - leukopenia (decrease in white blood cells).
- **Neuropsychiatric problems**:
  - Headache, feeling giddy.
  - Balance problems, ataxia (problems walking and lack of coordination) and dysarthria (slowness of speech and articulation problems), which may be observed together or in isolation and are evidence of a cerebellar syndrome (collection of signs and symptoms characteristic of rather serious damage to the cerebellum, a part of the brain used in balance).
  - Neurological problems**,** sometimes severe, which may indicate encephalopathy (brain disease) and include confusion, agitation, tremors, myoclonus (involuntary muscle contractions), convulsions, hallucinations, psychosis (personality problems), drowsiness and coma. These neurological signs are usually observed in patients with kidney problems who have received doses above the recommended dosage or in elderly patients (see "Warnings and precautions"). These effects usually disappear upon discontinuation of treatment. The presence of these symptoms may be due to an overdose; talk to your doctor about it as soon as possible.
- **Liver problems:** acute liver injury.
- **Respiratory problems:** dyspnoea (difficulty breathing).
- **Immune system problems:** anaphylactic reactions (generalised allergic reaction).

- **Skin reactions:** angioedema (sudden swelling of the face and neck).
- **Kidney problems:** acute kidney failure, especially in elderly people or those with kidney problems if the dosage is exceeded, back pain around the kidney area, which may be associated with kidney problems (see also "Warnings and precautions").
  The risk of acute kidney failure is caused by an overdose and/or dehydration, or by combination with medicines that are toxic to the kidneys.
  These risk factors should be checked, regardless of the patient's age. The risk of kidney problems can be avoided by respecting the dosage, the precautions for use (especially maintenance of adequate hydration) and a slow rate of administration.

Other side effects
Not known: (frequency cannot be estimated from the available data)
- fatigue,
- fever.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www. hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aciclovir

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 vial and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

After reconstitution for 500 mg:
Chemical and physical in-use stability has been demonstrated for 24 hours at 23-27ºC under artificial light and at 2-8ºC when dissolved in 20 ml of water for injections or *sodium chloride 9 mg/mL (0.9 %) solution for injection.*

After dilution for 500 mg:
Chemical and physical in-use stability has been demonstrated for 12 hours at 23-27°C at a concentration of Aciclovir 5.0 mg/ml after dilution with the compatible solutions mentioned mentioned in section Information for healthcare professionals, Preparation and handling.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC or than the times stated above for the chemical and physical in-use stability, whichever is the shorter unless opening/reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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 Aciclovir contains
- The active substance is aciclovir. Each 500 mg powder for solution for infusion contains 500 mg of aciclovir (as sodium salt).

- The other excipient is sodium hydroxide.

What Aciclovir looks like and contents of the pack
Aciclovir powder for solution for infusion, is supplied in clear type-I glass vials, with capacity of 20 ml, containing a white to off white powder, closed with bromobutyl closures 20 mm and sealed with 20 mm aluminum seals, with turn-off coloured (yellow) plastic caps.

Pack sizes: 1, 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Noridem Enterprises Limited
Evagorou & Makariou
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1065 Nicosia, Cyprus

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This medicinal product is authorised in the Member States of the European Economic Area under the following names:

Germany:	Aciclovir Noridem 500 mg Pulver zur Herstellung einer Infusionslösung
Czech Republic:	Aciclovir Noridem
Romania:	Aciclovir Noridem 500 mg Pulbere pentru soluţie perfuzabilă
Croatia:	Aciklovir Noridem 500 mg prašak za otopinu za infuziju
France:	Aciclovir Noridem 500 mg Poudre pour solution pour perfusion
Italy:	Aciclovir Noridem
Poland:	Aciclovir Noridem
Slovakia:	Aciclovir Noridem 500 mg Prášok na infúzny roztok
Spain:	Aciclovir Noridem 500 mg polvo para solución para perfusion
Portugal:	Aciclovir Noridem
Austria:	Aciclovir Noridem 500 mg Pulver zur Herstellung einer Infusionslösung
Netherlands:	Aciclovir Noridem 500 mg Poeder voor oplossing voor infusie
Hungary:	Aciclovir Noridem 500 mg Por oldatos infúzióhoz
Slovenia:	Aciklovir Noridem 500 mg prašek za raztopino za infundiranje
Belgium:	Aciclovir Noridem 500 mg poudre pour solution pour perfusion / pulver zur Herstellung einer Infusionslösung / poeder voor oplossing voor infusie
Cyprus:	Aciclovir Noridem 500 mg κόνις για διάλυμα προς έγχυση
Denmark:	Aciclovir Noridem
Finland:	Aciclovir Noridem 500 mg infuusiokuiva-aine, liuosta varten
Norway:	Aciclovir Noridem
Sweden:	Aciclovir Noridem
Ireland:	Aciclovir 500 mg powder for solution for infusion

This leaflet was last revised in

The following information is intended for healthcare professionals only:

Preparation and handling

Should be prepared immediately prior to use. Any unused solution must be discarded.

Reconstitution:
Aciclovir should be reconstituted using the following volumes of either water for injections or *sodium chloride 9 mg/mL (0.9 %) solution for injection* to provide a solution containing 25 mg aciclovir per ml:

Formulation	volume of fluid for reconstitution
250 mg vial	10 ml
500 mg vial	20 ml

From the calculated dose, the appropriate number and strength of vials to be used should be determined. To reconstitute each vial the recommended volume of infusion fluid is to be added and shaked gently until the contents of the vial have dissolved completely.

Administration
The required dose of Aciclovir should be administered by slow intravenous infusion over a one-hour period.

After reconstitution Aciclovir may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

The required volume of reconstituted solution to the chosen infusion solution should be added, as recommended below, and shaked well to ensure adequate mixing occurs.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is based on 4 ml reconstituted solution (100 mg aciclovir) added to 20 ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus, one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 mg and 1000 mg.
When diluted in accordance with the recommended schedules, Aciclovir is known to be compatible with the following infusion fluids:

- Sodium chloride 9 mg/mL (0.9 %) solution for injection
- Sodium Chloride Intravenous Infusion (0.45% w/v)
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion
- Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution).

Aciclovir when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.
The reconstituted or diluted solutions should not be refrigerated.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local

requirements.

Incompatibilities

This medicinal product should not be mixed with other medicinal products except those mentioned in section Administration.

Posology and method of administration

Posology

Dosage for patients with normal kidney function is given below. In patients with abnormal kidney function, dosage must be adapted according to the level of renal impairment (see paragraph, Patients with renal impairment).
Regarding recommendations for the duration of treatment, see paragraph, Duration of treatment.

Dosage in patients with normal renal function

Adults and adolescents (>12 years of age)

- *Varicella zoster* virus (VZV) infections: 10 mg/kg every 8 hours; 10-15 mg/kg every 8 hours in pregnant women;
- *Herpes simplex* virus (HSV) (except meningoencephalitis): 5 mg/kg every 8 hours.
- Herpetic meningoencephalitis: 10 mg/kg every 8 hours

Obese patients must be given the recommended dose for adults based on ideal body weight rather than actual body weight.

Paediatric population

In children over 3 months of age

In children between 3 months and 12 years of age, the dosage must be calculated according to body weight.
- HSV infection (except meningoencephalitis) or VZV infections: 10 mg/kg every 8 hours, with a maximum dose of 400 mg every 8 hours.
- HSV meningoencephalitis or VZV infection in immunosuppressed children: 20 mg/kg every 8 hours, with a maximum dose of 800 mg every 8 hours.

Neonates

In neonates and infants up to 3 months of age, the dosage is calculated according to body weight.
- Known or suspected neonatal herpes, the recommended regimen is 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease confined to the skin and mucous membranes.

Dosage in patients with renal impairment

The interval between two doses and the dosage should be adjusted according to creatinine clearance in mL/min for adults and adolescents and in mL/min/1.73 m^2 for infants and children under 13 years of age. Caution is advised when administering aciclovir by infusion to patients with impaired renal function. In such patients, special care should be taken to ensure adequate fluid intake.

The following dosage adjustments are proposed.

Dosage adjustment recommended in adults and adolescents > 12 years with impaired renal function:

Creatinine clearance	Recommended dose unit and dosing frequency according to indication	
	HSV or VZV infections (*except meningoencephalitis*)	**VZV infections in immunocompromised children or herpetic meningoencephalitis**
25-50 mL/min	5 mg/kg body weight every 12 hours	10 mg/kg body weight every 12 hours
10-25 mL/min	5 mg/kg body weight every 24 hours	10 mg/kg body weight every 24 hours
0 (anuria) to 10 mL/min	2.5 mg/kg body weight every 24 hours	5 mg/kg body weight every 24 hours
Patients on haemodialysis	2.5 mg/kg body weight every 24 hours and after haemodialysis	5 mg/kg body weight every 24 hours and after haemodialysis

Dosage adjustment in children ≤ 12 years, infants and neonates with impaired renal function:

Creatinine clearance (mL/min/1.73 m^2)	**Recommended dose unit and dosing frequency by indication**	
	In infants and children aged 3 months or older	
	HSV or VZV infections (except meningoencephalitis) VZV infection	**VZV infections in immunocompromised patients or with herpetic meningoencephalitis**
25-50 mL/min/1.73 m^2	10 mg/kg of body weight twice a day	20 mg/kg of body weight twice a day
10-25 mL/min/1.73 m^2	5 mg/kg of body weight twice a day	10 mg/kg of body weight twice a day
0 (anuria) to 10 mL/min/1.73 m^2	2.5 mg/kg of body weight twice a day	5 mg/kg of body weight twice a day
Patients on haemodialysis	2.5 mg/kg of body weight twice a day after hemodialysis	5 mg/kg of body weight twice a day after hemodialysis

Elderly
The possibility of renal impairment in elderly patients must be taken into account and the dosage should be adjusted according to creatinine clearance (see section "Dosage in patients with renal impairment".
Adequate fluid intake must be ensured.

Duration of treatment

The duration of treatment is generally 5 days, but it can be adjusted depending on the patient's condition and response to treatment. The duration is:
- 8-10 days for infections with the *Varicella zoster* virus
- 10 days for the treatment of herpetic meningoencephalitis; it must be adjusted according to the patient's condition and his/her response to treatment
- 5-10 days for other infections with the *Herpes simplex* virus
- 14 days for the treatment of neonatal herpes for mucocutaneous infections (skin/eye/mouth)
- 21 days for the treatment of neonatal herpes for disseminated disease or disease of the central nervous system.

The duration of prophylactic treatment with Aciclovir is determined by the length of the risk period.

Method of administration

Strictly intravenous use:

Each dose should be injected slowly intravenously (by pump or infusion) **over at least one hour.** For instructions on reconstitution of the medicinal product before administration, see section Preparation and handling.

Overdose

Signs and symptoms

Overdose of intravenous aciclovir has led to an increase in serum creatinine, blood urea and subsequent renal impairment. Neurological effects such as confusion, hallucinations, agitation, convulsions and coma have been described in association with overdose.

Management

Patients must be closely monitored to detect any signs of toxicity.
Haemodialysis significantly increases the elimination of aciclovir from the bloodstream and may therefore be considered as a management option in cases of symptomatic overdose.