

ERPIZON
Aciclovir 250 mg/vial
Lyophilisate for Solution for Intravenous Infusion

1. DESCRIPTION OF THE MEDICINAL PRODUCT

1.1 Name: ERPIZON 250 mg/vial

1.2 Qualitative composition: *Active substance:* Aciclovir. *Excipients:* Sodium Hydroxide.

1.3 Pharmaceutical form: Lyophilisate for Solution for Intravenous Infusion.

1.4 Content: Each vial contains 250 mg of aciclovir.

1.5 Description-Package: Glass vial with a rubber stopper, sealed with a plastic-aluminium "flip-off" cap containing 250 mg of lyophilisate. Pack of 1 vial or pack of 5 vials.

1.6 Pharmacotherapeutic category: Antivirus agent.

1.7 Marketing Authorisation Holder - Manufacturer: DEMO S.A., 21st Km National Road Athens-Lamia, 14568 Kryoneri, Greece, Tel.: + 30 210 8161802, Fax: + 30 210 8161587.

2. WHAT YOU SHOULD KNOW ABOUT THE MEDICINE THAT YOUR DOCTOR HAS PRESCRIBED TO YOU

2.1 General information

Aciclovir is an antiviral agent extremely active in vitro against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity for mammal host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active substance aciclovir triphosphate. The first step in this process depends on the presence of viral-coded thymidine kinase. Aciclovir triphosphate acts as inhibitor or substrate for herpes specific DNA polymerase preventing further viral DNA synthesis without affecting normal cell functions.

2.2 Therapeutic indications

For the treatment of herpes simplex virus infections. For the treatment of severe primary genital herpes. For the treatment of recurrent varicella-zoster virus infection in immunocompetent patients. For the treatment of primary and recurrent varicella-zoster virus infection in immunocompromised patients. For the treatment of herpes simplex infections in neonates and infants up to three months of age.

2.3 Contraindications

It is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

2.4 Special warnings and precautions for use

2.4.1 General: The dose of ERPIZON intravenous infusion should be adjusted in patients with impaired renal function in order to avoid the accumulation of aciclovir in the body (refer to posology). Special care must be taken regarding the renal function of patients receiving ERPIZON by intravenous infusion at higher doses (e.g. for herpes encephalitis), particularly when patients are dehydrated or have any renal impairment. The reconstituted solution of ERPIZON for intravenous infusion has a pH of approximately 11.0 and should not be administered orally.

2.4.2 Elderly: Refer to posology and method of administration.

2.4.3 Pregnancy: A post-marketing aciclovir pregnancy registry has provided data regarding the exposure of pregnant women to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst women exposed to aciclovir compared to the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Experience in humans is limited so the intravenous use of ERPIZON which should be considered only when the potential benefits outweigh the possibility of unknown risks.

2.4.4 Lactation: There is some evidence that aciclovir is excreted in breast milk. Therefore caution is advised when it has to be administered to a nursing mother.

2.4.5 Children: Refer to posology and method of administration.

2.4.6 Effects on ability to drive and use machines: Aciclovir infusion is generally used in a hospitalized patient population, and information on the effect it may have on the ability to drive or operate machinery is usually not applicable. There have been no studies to investigate the effect of aciclovir on the ability to drive or operate machinery.

2.4.7 Special warnings about excipients: Not mentioned.

2.5 Interaction with other medicinal products and other kinds of interaction

No clinically significant interaction has been identified. Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the area under the plasma concentration curve (AUC) of aciclovir by this mechanism, and reduce aciclovir renal clearance. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir. In patients receiving intravenous ERPIZON, caution is required during concurrent administration with drugs that compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in patients who have undergone transplantation, have been shown when the two drugs are co-administered. Care is also required (with monitoring for changes in renal function) when administering intravenous ERPIZON with drugs which affect other aspects of renal physiology (e.g. cyclosporine, tacrolimus).

2.6 Posology and method of administration

Method of administration: The required dose of ERPIZON for infusion should be administered by slow intravenous infusion over one hour. ERPIZON for intravenous drip infusion contains no antimicrobial preservative. Therefore, reconstitution or dilution must be done in either fully aseptic conditions, or immediately prior to administration and the remainder of the solution should be discarded. The reconstituted or diluted solutions should not be stored in the refrigerator.

Dosage in adults: In obese patients the adult dose should be used and calculated for the ideal and not the actual body weight of the patient. In patients infected with the herpes simplex virus (except herpes encephalitis) ERPIZON should be given in doses of 5mg/kg every 8 hours. In patients with herpes encephalitis, ERPIZON for intravenous infusion should be administered in doses of 10mg/kg every 8 hours, provided that renal function is not impaired.

Dosage in children: The calculation of the dose of ERPIZON for intravenous infusion in children aged between 3 months and 12 years, is based on the body surface area. In children with herpes simplex virus infection (except herpes encephalitis) ERPIZON for intravenous infusion should be administered at a dose of 250mg per square meter of body surface area, every 8 hours. In children with herpes encephalitis, ERPIZON for intravenous infusion should be administered at a dose of 500mg per square meter of body surface area every 8 hours, provided that renal function is not impaired. In children with impaired renal function an appropriately modified dose is required, depending on the degree of impairment.

Dosage in neonates and infants up to 3 months: The dosage of injectable ERPIZON for intravenous infusion in neonates is calculated based on body weight. In newborns infected with herpes simplex, ERPIZON for intravenous infusion should be given in doses of 10mg/kg of body weight every 8 hours, for 7 to 21 days, depending on the type and severity of the infection.

Dosage in elderly: In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired renal creatinine clearance.

Dosage in patients with renal impairment: In patients with impaired renal function, ERPIZON for intravenous infusion should be administered with caution. In these cases we recommend the following dosage adjustments:

Creatinine clearance	Dosage
25 – 50 ml/min	5 or 10 mg/kg of body weight every 12 hours
10 – 25 ml/min	5 or 10 mg/kg of body weight every 24 hours
0 (anuria) – 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD), the dose recommended above (5 or 10 mg/kg) should be halved and administered every 24 hours. In patients receiving haemodialysis, the dose recommended above (5 or 10 mg/kg) should be halved and administered every 24 hours and after dialysis.

Treatment with ERPIZON usually lasts 5 days, but this can be adjusted depending on patient condition and response to treatment. Treatment for herpes encephalitis usually lasts 10 days.

Reconstitution of solution for infusion: The reconstitution of each vial of ERPIZON 250 mg/vial for infusion is done by adding 10ml of Water for Injection or Sodium Chloride for Intravenous Infusion (0.9% w/v). The solutions obtained, contain 25 mg/ml of aciclovir.

Depending on the calculated dose, the required number and the strength of the vials that are going to be used, are determined. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the powder is completely dissolved.

Administration: The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period. After reconstitution, ERPIZON for infusion, with an aciclovir concentration of 25mg/ml, may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give a solution of aciclovir with a concentration not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

For dilution, the required volume of reconstituted solution is added to the chosen solution for infusion, according to the instructions below, and shake well to ensure adequate mixing. In the case of children and infants, where it is advisable to keep the volume of infusion fluid to a minimum, dilution based on the addition of the necessary quantity, according to the case, of the reconstituted solution in 20ml of infusion liquid, is recommended.

For adults, it is recommended to use infusion bags of a volume of 100ml of infusion fluid even if the resulting concentration of aciclovir is substantially less than 0.5% w/v. Thus, an infusion bag of a volume of 100ml may be used for any dose between 250 and 500 mg of acyclovir (10 and 20ml of reconstituted solution) but a second bag will be needed for doses between 500-1000mg. When ERPIZON is dissolved in accordance with the instructions above, then it is compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15°C -25°C):

- Sodium chloride solution for intravenous infusion (0.45% and 0.9% w/v)
- Sodium chloride solution (0.18% w/v) and glucose (4.0% w/v) for intravenous infusion
- Compound sodium lactate for intravenous infusion (Hartmann's Solution)

When ERPIZON is diluted according to the above schedule, the concentration of aciclovir in the solution does not exceed 0.5% w/v.

2.7 Overdose - Management

Exceeding the intravenous dose could cause crystalluria. Overdose of intravenous aciclovir had resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological reactions including confusion, hallucinations, agitation, seizures and coma have been associated with overdose. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

Poison Centre Call Number: +30 210 7793777

2.8 Undesirable effects

The frequency categories associated with the adverse reactions below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse reactions may vary in their incidence depending on the indication. The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10000 and <1/1000), very rare (<1/10000).

Blood and lymphatic system disorders:

Uncommon: Decreases in haematological indices (anemia, thrombocytopenia, leukopenia).

Immune system disorders:

Very rare: Anaphylaxis

Psychiatric and nervous system disorders:

Very rare: Headache, dizziness, restlessness, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.

The above reversible effects usually appear in medically complex cases.

Vascular disorders:

Common: Phlebitis

Respiratory, thoracic and mediastinal disorders:

Very rare: Dyspnoea

Gastrointestinal disorders:

Common: Nausea, vomiting

Very rare: Diarrhoea, abdominal pain

Hepatobiliary disorders:

Common: Reversible increases in liver enzymes

Very rare: Reversible increases in bilirubin, jaundice, hepatitis

Skin and subcutaneous tissue disorders:

Common: Pruritus, urticaria rashes (including photosensitivity)

Very rare: Angioedema

Renal and urinary disorders:

Common: Increases in blood urea and creatinine levels

Rapid increases in blood urea and creatinine levels are believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one-hour period.

Very rare: Renal impairment, acute renal failure, renal pain.

Adequate hydration of the patient should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

The renal pain may be associated with renal insufficiency.

General disorders and conditions of route of administration:

Very rare: Fatigue, fever, local inflammatory reactions

Serious local inflammatory reactions, sometimes leading to ulceration, have occurred after inadvertent extravasation of aciclovir I.V.

2.9 What you need to know if you forget to take a dose

If you miss a dose, do not worry. Just take it as soon as you remember and then continue as before. **Do not double the doses.**

2.10 Expiry date of product

It is stated on the outer and inner packaging. If expired, do not use the drug.

2.11 Special precautions for storage

Store below 25°C. After reconstitution, store below 25°C for up to 12 hours.

2.12 Date of last revision of the leaflet: April 2011

3. INFORMATION FOR THE RATIONAL USE OF MEDICINES

- Your doctor prescribed this medicine only for your particular medical problem. You should not give it to others or use it for another medical problem, without first consulting your doctor.

- If during treatment any problem with the medication occurs, please immediately inform your doctor or pharmacist.

- If you have any questions about your medical problem, do not hesitate to request information from your doctor or pharmacist.

- In order for the medicine administered to you to be effective and safe, it should be taken according to the instructions given to you.

- For your safety and health, you must carefully read all the information regarding the medicine given to you.

- Do not keep medicines in bathroom cabinets as heat and humidity can change their composition and make it harmful to your health.

- Do not keep medicines that are no longer needed or have already expired.
- Keep all medicines out of the sight and reach of children.

4. PRESCRIPTION METHOD

Only for hospital use.