PACKAGE LEAFLET: INFORMATION FOR THE USER

Erpizon
Lyophilisate for solution for infusion 250 mg/vial
Aciclovir

1. DESCRIPTION OF THE MEDICINAL PRODUCT

1.1 Name: ERPIZON 250 mg/vial

1.2 Qualitative composition: Active substance: Aciclovir Sodium Excipients: Sodium hydroxide

1.3 Pharmaceutical form: Powder for solution for infusion

1.4 Content: Each vial contains 250 mg of aciclovir

1.5 Description-Package: Glass vial with a rubber stopper, sealed with an aluminum cap containing a plastic "flip-off" cap and contains 250 mg lyophilized powder. Pack of 5 vials.

1.6 Pharmacotherapeutic category: Antivirus agent.

1.7 Marketing Authorisation Holder - Manufacturer: DEMO S.A. Pharmaceutical Industry, 21st Km National Road Athens-Lamia, 14568 Athens, 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 in 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 virus specific DNA polymerase preventing further synthesis of viral DNA 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

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 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 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 approximately pH 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 for 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 with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.Intravenous use of aciclovir 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: See dosage 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 effect on 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 applicable.

2.5 Interaction with other medicinal products and other kinds of interaction
No clinically significant interactions have 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 administered 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.

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

Posology 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 virus infection herpes simplex (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 herpetic encephalitis, ERPIZON for intravenous infusion should be administered at a dose of 500mg per square meter of body surface area every 8 hours, if renal function is not impaired. In children with impaired renal function an appropriately modified dose is required, depending on the degree of impairment.

Posology in neonates and infants up to 3 months: The dosage of injectable ERPIZON for 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.

Posology 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 creatinine clearance.

Posology 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	**POSOLOGY**
25 – 50 ml/min	5 or 10 mg/kg of body weigh every 12 hours.
10 – 25 ml/min	5 or 10 mg/kg of body weigh every 24 hours.
0 (anuric) – 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours and after dialysis

The duration of aciclovir treatment is usually 5 days, but this can be adjusted depending on patient condition and response to treatment. Treatment of herpetic encephalitis is usually for 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 contents of the vial have dissolved completely.

Administration: The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period. After reconstitution, aciclovir for infusion, aciclovir concentration 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 concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.
For dilution, the required volume of reconstituted solution to the chosen solution for infusion, is added according to the instructions below, and shake well to ensure adequate mixing occurs.
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, of each case, of the reconstituted solution in 20ml liquid infusion, is recommended.

For adults, it is recommended the use of infusion bags of volume of 100ml fluid infusion even if the resulting concentration of aciclovir is substantially less than 0.5% w/v. Thus, an infusion bag of 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 for doses between 500-1000mg will be needed. 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 -25ºC):

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

When ERPIZON for infusion is diluted according to the above schedule, the concentration of aciclovir in 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.

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 (>1/10,000 and <1/1000), very rare (<1/10,000).

Blood and lymphatic system
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 rises in liver enzymes
Very rare: Reversible elevations in bilirubin, jaundice, hepatitis

Skin and subcutaneous tissue:
Common: Pruritus, urticaria rashes (including photosensitivity)
Very rare: Angioedema

Renal and urinary disorders:
Common: Elevations 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 failure, 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 ERPIZON.

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 take a double dose**.

2.10 Expiry date of product
Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

2.11 Special precautions for storage
Keep this medicine out of the sight and reach of children. Do not store above 25°C. After reconstitution, store for 12 hours at temperature not above 25°C.

2.12 Date of last revision of the leaflet: September 2012.

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 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.
- To be effective and safe the medicine given to you, it should be taken according to the instructions given to you.
- For your safety and health, you must carefully read all information regarding the medicine given to you.
- Do not keep medicines in bathroom cabinets as heat and humidity can change the composition of medicine and make it harmful to your health.
- Do not keep medicines that are no longer needed or have been already expired.

4. PRESCRIPTION METHOD

By limited medicinal prescription: The treatment begins in the hospital and can be continued outside the hospital by the doctor's supervision.