SUMMARY OF PRODUCT CHARACTERISITICS

1. NAME OF THE MEDICINAL PRODUCT

ERPIZON, Lyophilisate for solution for infusion 250 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250mg of aciclovir.

3. PHARMACEUTICAL FORM

Lyophilisate for solution for infusion

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Route of administration: Intravenous drip infusion.

Posology

Dosage 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.

Dosage in children:

The calculation of the dose of aciclovir 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, aciclovir 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.

Dosage in neonates and infants up to 3 months:

The dosage of injectable aciclovir for infusion in neonates is calculated based on body weight.
In newborns infected with herpes simplex, aciclovir for intravenous infusion should be given in doses of 10mg/kg of body weight every 8 hours, for 7 to 21 days. (The duration of treatment, depends on the type and severity of the infection). The same dosage regimen should be followed in the case of herpes encephalitis, but with treatment duration from 14 to 21 days.

In severe infections doses of 15-20 mg/kg body weight have also been tried, again given every 8 hours. In general, in such infections (especially in encephalitis) dosing regimens are individualized both in terms of increased dosage and prolonged treatment duration.
Studies are in progress to determine optimal dosing regimens and ascertain the efficacy of intravenous aciclovir administration in recurrent neonatal herpes infections.

Dosage in the 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.

Dosage in renal impairment:
In patients with impaired renal function, aciclovir 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 aciclovir for injection 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 aciclovir (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 (15-25ºC):

- 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.

4.3 Contraindications

Aciclovir for infusion is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

4.4 Special warnings and precautions for use

The dose of aciclovir for intravenous infusion should be adjusted in patients with impaired renal function in order to avoid the accumulation of aciclovir in the body (see paragraph 4.2.).
Specific care regarding renal function should be taken in patients receiving aciclovir for intravenous infusion at higher doses (e.g. for herpes encephalitis), particularly when patients are dehydrated or have any renal impairment.
The reconstituted solution of aciclovir for intravenous infusion has a pH of approximately 11.0 and should not be administered orally.

4.5 Interaction with other medicinal products and other forms 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 aciclovir, caution is required during concurrent administration with drugs which 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 aciclovir with drugs which affect other aspects of renal physiology (e.g. cyclosporine, tacrolimus).

4.6 Fertility, pregnancy and lactation

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.

Teratogenesis

Systemic administration of aciclovir in internationally accepted standard trials did not cause embryotoxic or teratogenic effects in rabbits, rats, or mice. In a non-standard trial in rats serious development disorders were observed, but only after subcutaneous administration of doses so high that they probably caused maternal toxicity. Clinical significance is uncertain.

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.

4.7 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.

4.8 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 disorders

Uncommon: Decreases in haematological indices (anaemia, 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 disorders:

Common: Pruritus, urticaria rashes (including photosensitivity)
Very rare: Angioedema

Renal and urinary disorders:

Common: Elevations in blood urea and blood 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 administration site conditions:
Very rare: Fatigue, fever, local inflammatory reactions

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

4.9 Overdose
Exceeding the intravenous dose could cause crystalluria. Overdose of intravenous aciclovir has 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Direct Acting Antiviral, ATC code: J05A B01.

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.

5.2 Pharmacokinetic properties
From studies with intravenous aciclovir, the half-life in plasma was determined in about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug.
9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir and corresponds to 10-15% of the dose excreted in urine.
In patients with chronic renal insufficiency, the mean half-life was found to be 19.5 hours. The average half-life of aciclovir during haemodialysis was 5.7 hours. Plasma aciclovir levels drop approximately 60% during dialysis. In the elderly, total body clearance falls with increasing age and is accompanied by decreases in creatinine clearance although there is little change in the terminal plasma half-life.
Mean peak plasma concentrations of aciclovir in steady state (C^{ss} max) after one-hour infusion of 5 or 10mg/kg aciclovir were 9.8 and 20.7 micrograms/ml, respectively. Respective mean minimum levels measured 7 hours later were 0.7 and 2.3 micrograms/ml respectively. In children over one year of age similar mean peak (C^{ss} max) and trough (C^{ss} min) levels were observed when a dose of 250 mg/m² was substituted for 5 mg/kg and a dose of 500 mg/m² was substituted for 10 mg/kg.
In neonates (0 to three months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours, the maximum plasma concentration at steady state (C^{ss} max) was found to be 13,8 micrograms/ml, while the minimum corresponding (C^{ss} min) to be 2.3 micrograms / ml.
The terminal plasma half-life in these patients was 3.8 hours. The levels of the drug in cerebrospinal fluid are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.

Clinical studies
There is no data on the effect of oral or intravenously infused aciclovir on human female fertility. In a study of 20 male patients with normal sperm counts, oral administration of aciclovir in doses up to 1g daily and for up to 6 months did not appear to have clinically significant effects on sperm count, motility or morphology.

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.

Carcinogenesis
Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Fertility
Largely reversible adverse effects on spermatogenesis in combination with genetic toxicity in rats and dogs have been reported only at doses of aciclovir greatly exceeding those used therapeutically. Studies in two generations of mice did not reveal any effect of aciclovir on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide for pH adjustment.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Lyophilisate: 24 months
After reconstitution: 12 hours at temperature not above 25°C.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each box contains a glass vial.

6.6 Special precautions for disposal and other handling

Administration:
The required dose of aciclovir for infusion should be administered by slow intravenous infusion over one hour. Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution should be discarded.
The reconstituted and diluted solutions should not be stored in a refrigerator.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

40080/12/18-02-2013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ERPIZON 250 mg/vial: 28-10-2008 (first authorisation)
ERPIZON 250 mg/vial: 18-02-2013 (renewal)

10. DATE OF REVISION OF THE TEXT

September 2012

*Based on the circular 91106/30-12-2009 issued by the **National Organisation** for **Medicines** (**EOF**) and on the current QRD template version 3.0, 04/2013*