Package leaflet: Information for the user
Aciclovir 250mg Powder for Solution for Infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Aciclovir 250mg Powder for Solution for Infusion. In the rest of this leaflet it is called Aciclovir for Infusion (Infusion is a slow injection).

What is in this leaflet

1. What Aciclovir for Infusion is and what it is used for

Aciclovir belongs to a group of medicines called antivirals. These medicines work by stopping viruses from spreading in the body.

Aciclovir for Infusion is used to treat a variety of infections caused by herpes viruses:
- herpes infections in newborn infants and babies up to 3 months of age
- herpes infections in patients with a low resistance to disease
- inflammation of the brain caused by herpes virus
- severe infections of the genitals caused by herpes virus
- chickenpox and shingles

Aciclovir for Infusion is also used to prevent herpes infections in people who have a low resistance to disease.

2. What you need to know before you use Aciclovir for Infusion

Do not take aciclovir for infusion:
- if you are allergic to aciclovir, valaciclovir or to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist or nurse before using Aciclovir for Infusion if you:
- have kidney problems as the dose may need to be modified according to how your kidneys are working.
- have a low resistance to disease (are immune compromised)
- are elderly
- are dehydrated (extremely thirsty)
- are on a low sodium diet (see 'Important information for patients on a controlled sodium diet' section below).

Other medicines and Aciclovir for Infusion

Taking another medicine while you are being given aciclovir for infusion can affect how it or the other medicine works.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, even those you may have bought yourself without a prescription.

Please check with your doctor if you are taking any of the following or any other medication:
- Probenecid, a drug used to prevent gout (arthritis in the joints).
- Cimetidine, an anti-stomach ulcer drug.
- Drugs used in transplant patients (i.e. mycophenolate mofetil, ciclosporin and tacrolimus).

Pregnancy and breast-feeding

It is not certain if the use of Aciclovir during pregnancy causes birth defects. You should let your doctor know if you think you may be pregnant or are trying for a baby.

Aciclovir can get into human breast milk. You should let your doctor know if you are breast-feeding or want to start breast-feeding while you are having treatment with aciclovir for infusion.

Driving and using machines

Aciclovir for Infusion can cause confusion, hallucinations (seeing or hearing things that are not there), agitation, tremor and drowsiness which may affect your ability to drive or use machines. If you are affected, do not drive or operate machinery.

Aciclovir for Infusion contains sodium

Each vial contains 26mg of sodium. You should tell your doctor or pharmacist if you are on a controlled sodium diet.

3. How to use Aciclovir for Infusion

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Do not take by mouth.

Your doctor or nurse will prepare your injection by diluting it with water or salt solution, either in the vial or in another container. The mixture is given by a slow injection into a vein (called an infusion) over an hour using a syringe-pump or with a drip.

It is important to drink plenty of water after you have been given aciclovir infusion.

For the treatment of herpes infections, chickenpox or 'shingles' in adults
- The recommended adult dose of Aciclovir for Infusion is 5mg per kg bodyweight every eight hours for five days.
- This dose is doubled to 10mg per kg every eight hours for:
  - patients with low resistance to disease who have chicken pox or shingles
  - patients with herpes inflammation of the brain (these patients may need ten days treatment).

Use in children and adolescents

For the treatment of herpes infections in newborn and babies up to 3 months old
- In the newborn and babies up to three months old, the dose is 20mg per kg of bodyweight every eight hours, usually for 14 days for skin, eye and mouth infections, or 21 days if the disease is widely spread or has affected the central nervous system.

For the treatment of chickenpox or herpes infections in children aged 3 months to 12 years
- For children aged 3 months to 12 years, the dose is 250mg per m^2 of body surface area, every eight hours, usually for five days.

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Aciclovir 250mg Powder for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 250mg of aciclovir as the sodium salt
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Powder for solution for infusion.
White powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
Aciclovir for infusion is indicated for the treatment of Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.
Aciclovir for infusion is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.
Aciclovir for infusion is indicated for the treatment of *Varicella zoster* infections.
Aciclovir for infusion is indicated for the treatment of herpes encephalitis.
Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in the neonate and infant up to three months of age.

4.2 Posology and method of administration
Route of administration: Slow intravenous infusion over one hour.
A course of treatment with aciclovir for infusion usually lasts five days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts ten days. Treatment for neonatal herpes usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for disseminated or central nervous system disease.
The duration of prophylactic administration of aciclovir for infusion is determined by the duration of the period at risk.

Posology
Dosage in adults:
Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 5mg/kg bodyweight every eight hours provided renal function is not impaired (see Dosage in renal impairment).
Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given aciclovir for infusion in doses of 10mg/kg bodyweight every eight hours provided renal function is not impaired (see Dosage in renal impairment).
In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.
Dosage in children:
The dose of aciclovir for infusion for children aged between three months and 12 years is calculated on the basis of body surface area.
Children three months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 250 mg per square metre of body surface area every eight hours if renal function is not impaired.
In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, aciclovir for infusion should be given in doses of 500 mg per square metre body surface area every eight hours if renal function is not impaired.
The dosage of aciclovir for infusion in neonates and infants up to three months of age is calculated on the basis of bodyweight.
The recommended regimen for infants treated for known or suspected neonatal herpes is aciclovir 20 mg/kg body weight IV every eight hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.
Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).
Dosage in the elderly:
The possibility of renal impairment in the elderly must be considered. 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.
Adequate hydration should be maintained.
Dosage in renal impairment:
Caution is advised when administering aciclovir for infusion to patients with impaired renal function. Adequate hydration should be maintained.
Dosage adjustment for patients with renal impairment is based on creatinine clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m^2 for infants and children less than 13 years of age. The following adjustments in dosage are suggested:

Dosage adjustments in adults and adolescents:

Creatinine Clearance	Dosage
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 24 hours.
0 (anuric) to 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommend above (5 or 10 mg/kg/bodyweight should have 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.

Dosage adjustments in infants and children:

Creatinine Clearance	Dosage
25 to 50 ml/min/ 1.73m^2	The dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min/ 1.73m^2	The dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be given every 24 hours.
0(anuric) to 10 ml/min/ 1.73m^2	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.

Method of 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 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.
For instructions on reconstitution and dilution of the medicinal *product before administration see section 6.6.*

4.3. Contraindications
Hypersensitivity to aciclovir and valaciclovir, or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use
Use in patients with renal impairment and in elderly patients:
Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).
Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment.
In patients receiving aciclovir for infusion at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.
Reconstituted aciclovir for infusion has a pH of approximately 11.0 and should not be administered by mouth.
Aciclovir for infusion contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.
This vial contains approximately 26mg of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

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 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 transplant patients, have been shown when the drugs are co-administered.
Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6. Fertility, pregnancy and lactation
Pregnancy
The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

Fertility
There is no information on the effect of aciclovir on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

Breast-feeding
Following oral administration of 200mg five times a day, aciclovir has been detected in human breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg bodyweight/day. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

4.7. Effects on ability to drive and use machines
Aciclovir for infusion is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant. There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. However, aciclovir can cause reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis and coma, which can all affect the ability to drive and use machinery.

4.8. Undesirable effects
The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events 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 ≥ 1/1,000 and <1/100, rare ≥ 1/10,000 and <1/1,000, very rare <1/10,000.

Blood and lymphatic system disorders
Uncommon: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Immune system disorders
Very rare: Anaphylaxis.

- This can be doubled to 500mg per m^2 of body surface area every eight hours for:
  - children with low resistance to disease who have chickenpox
  - children with herpes inflammation of the brain

Your dosage may need to be reduced if you have kidney problems, are obese or are elderly.
Your doctor will decide the dose which is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

If you use more aciclovir for infusion than you should
A doctor or a nurse will usually give you this medicine. If you are given too much Aciclovir for Infusion you may feel confused or agitated, or suffer from hallucinations (imagining things) or seizures. Too much Aciclovir for Infusion can also cause changes in blood chemicals, kidney failure and loss of consciousness. If you have been given too much medicine, you may be put on a kidney machine to reduce the amount of Aciclovir for Infusion in your blood.
If you think you may have received too much aciclovir for infusion, please tell your doctor or nurse at once.

If you forget to use aciclovir for infusion
A doctor or a nurse will usually give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following symptoms, tell your doctor or nurse immediately:
Very rare: may affect up to 1 in 10,000 people
- **severe allergy, breathing problems or swelling of the face**

Uncommon: may affect up to 1 in 100 people
- **a fall in the number of blood cells may cause unexplained bleeding or bruising, sore throats, mouth ulcers, or a low resistance to infections.**

Other side effects include:
Common: may affect up to 1 in 10 people
- nausea and vomiting
- allergic reactions such as rashes, sensitivity to light and itching
- swelling, redness and tenderness at the site of injection.

Uncommon: may affect up to 1 in 100 people
- anaemia

Very rare: may affect up to 1 in 10,000 people
- headache or feeling dizzy
- diarrhoea or stomach pains
- feeling tired
- fever
- drowsiness, confusion, hallucinations (imagining things), feeling agitated, difficulty in controlling movements, difficulty in speaking, personality changes and inability to concentrate, shaking, fits and loss of consciousness, particularly in patients with other medical problems
- severe local inflammation leading to a breakdown of the skin at the site of injection if aciclovir leaks out of the vein
- liver and kidney problems. These may cause increases in the levels of various chemicals in the blood and yellowing of the skin
- pain in your lower back, the kidney area of your back or just above your hip (renal pain).

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aciclovir for Infusion

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 carton and the label on the small glass container (vial). The expiry date refers to the last day of that month.
- Your doctor, nurse or pharmacist will be responsible for storing and preparing aciclovir before use and for checking that the vials have not passed their expiry date.
- Do not store above 25°C. The vials should be kept in their outer carton, in order to protect from light.
- Once the powder has been made into a solution the product should be used immediately. If this is not possible it would generally not be stored for more than 24 hours at 2-8°C.

Do not throw away 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 for Infusion contains
Each vial contains 250mg of the active ingredient, aciclovir (as the sodium salt), as a powder.
The other ingredient is sodium hydroxide.

What Aciclovir for Infusion looks like and contents of the pack
The white powder comes in a glass vial with a rubber cap and metal/plastic seal. It is available in packs of 1, 5 or 10 vials. Not all pack sizes may be marketed.

Other formats
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK Only)
Please be ready to give the following information:

Product name	Reference number
Aciclovir 250mg Powder for Solution for Infusion	29831/0320

This is a service provided by the Royal National Institute of Blind People.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
Manufacturer: CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

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Psychiatric and nervous system disorders
Very rare: Headache, dizziness, confusion, hallucinations, agitation, tremor, ataxia, dysarthria, somnolence, psychotic symptoms, encephalopathy, convulsions and coma.
The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see section 4.4).
Vascular disorders
Common: Phlebitis.
Respiratory, thoracic and mediastinal disorders
Very rare: Dyspnoea.
Gastrointestinal disorders
Common: Nausea, vomiting
Very rare: Diarrhoea, abdominal pain.
Hepato-biliary disorders
Common: Reversible increases in liver-related enzymes
Very rare: Reversible increases in bilirubin, hepatitis and jaundice.
Skin and subcutaneous tissue disorders
Common: Rashes including photosensitivity, urticaria, pruritus
Very rare: Angioedema.
Renal and urinary disorders
Common: Increases in blood urea and creatinine
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 developing during treatment with aciclovir for infusion 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.
Renal pain may be associated with renal failure and crystalluria.
General disorders and administration site conditions
Very rare: Fatigue, fever, local inflammatory reactions
Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when formulations of aciclovir for intravenous use have been inadvertently infused into extravascular tissues.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

Symptoms and Signs
Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage.
Treatment
Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of acyclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: J05A B01, Direct Acting Antiviral
Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including *Herpes simplex* virus (HSV) types 1 and 2 and *Varicella zoster* virus (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV, and CMV.
The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

5.2. Pharmacokinetic properties

In adults, the terminal plasma half-life of aciclovir after administration of aciclovir for infusion is 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 accounts for 10 to 15% of the dose excreted in the urine.
When aciclovir is given one hour after 1g of probenecid the terminal half-life and the area under the plasma concentration time curve, are extended by 18% and 40% respectively.
In adults, mean steady state peak plasma concentrations (Cmax,ss) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml), 43.6 micromolar (9.8 microgram/ml), and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough levels (Cmin,ss) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml) respectively. In children over one year of age similar mean peak (Cmax,s) and trough (Cmin,ss) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 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 Cmax,s was found to be 61.2 micromolar (13.8 microgram/ml) and the Cmin,ss.to be 10.1 micromolar (2.3 microgram/ml). A separate group of neonates treated with 15 mg/kg every eight hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml).
The terminal plasma half-life in these patients was 3.8 hours. In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.
In patients with chronic renal failure the mean terminal half-life was found to be 19.5 hours. The mean acyclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.
In a clinical study in which morbidly obese female patients (n=7) were dosed with intravenous aciclovir based on their actual body weight, plasma concentrations were found to be approximately twice that of normal weight patients (n=5), consistent with the difference in body weight between the two groups.
Cerebrospinal fluid levels 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.

5.3. Preclinical safety data

The results of a wide range of mutagenicity test *in vitro* and *in vivo* indicate that aciclovir is unlikely to pose a genetic risk to man.
Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice.
In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.
There is no experience of the effect of aciclovir for infusion on human fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium hydroxide

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Unopened - 3 years
For reconstituted solutions, chemical and physical in-use stability has been demonstrated for at least 24 hours at 25°C. From a microbiological point of view, once opened, 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.
Following dilution using the fluids detailed in section 6.6, chemical and physical in-use stability has been demonstrated for up to 12 hours at 25°C. From a microbiological point of view the diluted solution should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Unopened: Do not store above 25°C
Keep the vials in the outer carton.
After reconstitution: Do not store above 25°C (see 6.3 Shelf Life).

6.5. Nature and contents of container

Packs* of one, five or ten Type II colourless glass 10ml vials stoppered with a chlorobutyl stopper and an aluminium and polypropylene flip-off cap.
*Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling

Reconstitution:
Aciclovir 250mg for infusion should be reconstituted using 10ml of either Water for Injections PhEur or Sodium Chloride Intravenous Infusion BP (0.9% w/v) to provide a solution containing 25mg aciclovir per ml.
From the calculated dose, determine the appropriate number and strength of vials to be used. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.
The reconstituted solution appears light yellow and slightly opalescent.
After reconstitution aciclovir powder for solution for infusion 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:
For further dilution, add the required volume of reconstituted solution to the chosen infusion solution, as recommended below, and shake 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 on the basis of 4ml reconstituted solution (100mg aciclovir) added to 20 ml of infusion fluid.
For adults, it is recommended that infusion bags containing 100ml 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 250mg and 500mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 and 1000mg.
When diluted in accordance with the recommended schedules, aciclovir for infusion is known to be compatible with the following infusion fluids:
- sodium chloride intravenous infusion BP (0.45% and 0.9% w/v);
- sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion BP
- sodium chloride (0.45% w/v) and glucose (2.5% w/v) intravenous infusion BP
- compound sodium lactate intravenous infusion BP (Hartmann's Solution).

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

7. MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

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