PACKAGE INSERT TEMPLATE FOR ACYCLOVIR POWDER FOR INTRAVENOUS INFUSION

Brand or Product Name

[Product name] Powder for IV Infusion 250mg

Name and Strength of Active Substance(s)

Acyclovir sodium ….mg equivalent to acyclovir 250mg

Product Description

[Visual description of the appearance of the product (eg colour, odour)
eg :A sterile, white freeze dried powder]

Pharmacodynamics

Acyclovir 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, varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir 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 acyclovir for HSV-1, HSV-2, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non- infected cells does not use acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Prolonged or repeated courses of acyclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued acyclovir treatment.

Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK however, strains with altered viral TK or DNA polymerase have also been reported. In vitro exposure of HSV isolates to acyclovir can also lead to the emergence of less sensitive strains. The relationship between the in-vitro determined sensitivity of HSV isolates and clinical response to acyclovir therapy is not clear. All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Pharmacokinetics

Absorption

In adults, mean steady state peak plasma concentrations (C^{ss}max) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 22.7 micromoles (5.1 micrograms/ml), 43.6 micromoles (9.8 micrograms/ml), 92 micromoles (20.7 micrograms/ml) and 105 micromoles (23.6 micrograms/ml), respectively. The corresponding trough levels (C^{ss}min) 7 h later were 2.2 micromoles (0.5 micrograms/ml), 3.1 micromoles (0.7 micrograms/ml), 10.2 micromoles (2.3 micrograms/ml) and 8.8 micromoles (2.0 micrograms/ml), respectively. In children over 1 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 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 h the C^{ss}max was found to be 61.2 micromoles (13.8 micrograms/ml) and the C^{ss}min to be 10.1 micromoles (2.3 micrograms/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 acyclovir levels dropped approximately 60% during dialysis. 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.

Indication

Acyclovir IV for Infusion is indicated for :
- the treatment of Herpes simplex infections
- the prophylaxis of Herpes simplex infections in immune-compromised patients.
- the treatment of Varicella zoster infections.
- the treatment of Herpes simplex infections in the neonate.

Recommended Dosage

Adults

Patients with herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given acyclovir i.v. for infusion in doses of 5 mg/kg bodyweight every eight hours.

Immunocompromised patients with Varicella zoster infections or patients with herpes encephalitis should be given Acyclovir IV in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired

Children

The dose of Acyyclovir IV for infusion for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children with herpes simplex (except herpes encephalitis) or varicella zoster infections should be given Acyclovir IV for infusion in doses of 250 mg per square metre body surface area every 8 hours.

In immune-compromised children with Varicella zoster infections or children with herpes encephalitis, Acyclovir IV for infusion should be given in doses of 500 mg per square metre body surface area every 8 hours if renal function is not impaired.

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Neonates

The dosage of Acyclovir IV for infusion in neonates is calculated on the basis of bodyweight. Neonates with herpes simplex infections should be given Acyclovir IV for infusion in doses of 10 mg/kg bodyweight every 8 hours.

Elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly. Adequate hydration should be maintained.

Renal Impairment

Caution is advised when administering Acyclovir IV for infusion to patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine Clearance	Dosage
25-50 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 12 hours.
10-25 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight) should be given 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 or 500 mg/m2) 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.

A course of treatment with Acyclovir IV for infusion usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis and neonatal herpes simplex infections usually lasts 10 days. The duration of prophylactic administration of Acyclovir IV for infusion is determined by the duration of the period at risk.

Mode of Administration
Intravenous infusion.
The required dose of Acyclovir IV should be administered by slow IV infusion over 1 hour period.

Contraindications
Contraindicated in patients known to be hypersensitive to acyclovir or valacyclovir.

Warnings and Precautions

In patients receiving Acyclovir IV 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 Acyclovir IV for infusion has a pH of approximately 11.0 and should not be administered by mouth.

Use in patients with renal impairment and in elderly patients
Acyclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment. 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.

Effect on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Interactions with Other Medicaments

No clinically significant interactions have been identified. Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increase the AUC of acyclovir by this mechanism, and reduce acyclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of acyclovir.

In patients receiving intravenous acyclovir, caution is required during concurrent administration with drugs which compete with acyclovir 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 acyclovir with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

Statement on Usage During Pregnancy and Lactation

Pregnancy
A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of acyclovir. The birth defects described amongst acyclovir exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

Lactation
Following oral administration of 200 mg five times a day, acyclovir 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 acyclovir dosages of up to 0.3 mg/kg body weight/day. Caution is therefore advised if acyclovir is to be administered to a nursing woman.

Fertility
There is no information on the effect of acyclovir on human female fertility. In a study of 20 male patients with normal sperm count, oral acyclovir 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.

Adverse Effects / Undesirable Effects

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, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.
The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors.

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, 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.
Rapid increases in blood urea and creatinine levels are believed to be related to the 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.
Adequate hydration 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.

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 Acyclovir IV for infusion has been inadvertantly infused into extracellular tissues.

Overdose and Treatment

Symptoms and Signs
Overdosage of intravenous acyclovir 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.

Incompatibilities
None known

Instruction for Use

Reconstitution

Acyclovir IV should be reconstituted using the following volumes of either Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v) to provide a solution containing 25 mg acyclovir per ml:

Formulation	Volume of fluid for reconstitution
250 mg vial	10 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.

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

- 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 4 ml reconstituted solution (100 mg acyclovir) 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 acyclovir 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 acyclovir (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, Acyclovir IV is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15°C to 25°C):
- 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).

Acyclovir IV when diluted in accordance with the above schedule will give an acyclovir 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.

Storage Conditions
Finished product - Store below ….°C
Reconstituted product (if applicable) - Store below ….°C for …. hours.
* If not, please include this statement - For single use only. Discard any unused portion after opening.
Reconstituted and diluted solutions should not be refrigerated.

Dosage Forms and Packaging Available
[Packaging type & pack size eg
5ml clear glass vial X 5/box]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]