Packaging Insert

Vaxcel®

ACYCLOVIR 25mg/ml

IV INFUSION

MAL11060004AZ

COMPOSITION:

Each ml contains

Acyclovir 25mg

PRESENTATION:

Acyclovir Intravenous Infusion is a clear colourless or almost colourless sterile solution containing the equivalent of 25mg/ml of Acyclovir in Water for Injection.

INDICATIONS:

Acyclovir Intravenous Infusion is indicated:

1. For the treatment of Herpes simplex infections.
2. For the prophylaxis of Herpes simplex infections in immune-compromised patients.
3. In the treatment of Varicella zoster infections.

PHARMACODYNAMICS:

Microbiology:

Acyclovir is an antiviral agent which is active in vitro against Herpes simples (HSV) types I & II and Varicella zoster virus (VZV). However, the relationship between in vitro sensitivity of herpes viruses to Acyclovir and clinical response to therapy has yet to be established. Acyclovir needs to be phosphorylated to the active compound acyclovir triphosphate, in order to become active against the virus. Such conversion is very limited in normal cells and in addition, cellular DNA polymerase is not very sensitive to the active compound. However, in infected cells, HSV or VZV coded thymidine kinase facilitates the conversion of Acyclovir to Acyclovir Monophosphate which is then converted to Acyclovir triphosphate by cellular enzymes. Acyclovir Triphophate acts as an inhibitor of, and substrate for, the herpes specified DNA polymerase preventing further viral DNA synthesis.

Animal studies indicate that at high doses Acyclovir is cytotoxic.

PHARMACOKINETICS:

In adults, mean steady state peak plasma concentrations ($C^{ss}max$) following a one-hour infusion of 2.5mg/kg, 5mg/kg, 10mg/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/m^2 was substituted for 5mg/kg and a dose of 500mg/m^2 was substituted for 10mg/kg. In neonates (0 to 3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8h 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). Distribution 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 is not anticipated.

Elimination in adults the terminal plasma half life of Acyclovir after administration of Acyclovir i.v. for infusion is about 2.9h. Most of the drug is excreted unchanged by the kidney. Renal clearance of Acyclovir is substantially greater than creatinine clearance indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug. 9-carboxymethoxy-methylguanine is the only significant metabolite of Acyclovir and accounts for approximately 10 to 15% of the dose excreted in the urine. When Acyclovir is given one hour after 1 gram of probenecid the terminal half life and the area under the plasma concentration time curve is extended by 18% and 40% respectively.

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 terminal plasma half life was 3.8h. Special Patient Populations In patients with chronic renal failure the mean terminal half life was found to be 19.5h. The mean Acyclovir half life during haemodialysis was 5.7h. Plasma Acyclovir levels dropped approximately 60% during dialysis. In the elderly total body clearance falls with increasing age, associated with decreases in creatinine clearance, although there is little change in the terminal plasma half life.

DOSAGE AND ADMINISTRATION:

A course of treatment with Acyclovir Intravenous 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 Intravenous Infusion is determined by the duration of the period at risk.

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Acyclovir Intravenous Infusion in doses of 5mg/kg body weight every 8 hours.

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Acyclovir Intravenous Infusion in doses of 10mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

In obese patients dosed with intravenous Acyclovir based on their actual body weight, higher plasma concentrations may be obtained (see 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 Acyclovir Intravenous 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 Intravenous Infusion in doses of 250mg per square metre of body surface area every 8 hours.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, Acyclovir Intravenous Infusion should be given in doses of 500mg per square meter 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.

The dosage of Acyclovir Intravenous Infusion in neonates and infants up to 3 months of age is calculated on the basis of body weight.

Neonates and infants up to 3 months of age with Herpes simplex infections should be given Acyclovir Intravenous Infusion in doses of 10mg/kg body weight every 8 hours. Treatment for neonatal *Herpes simplex* infections usually lasts 10 days.

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly (see *Dosage in renal impairment* below).

Adequate hydration should be maintained.

Dosage in renal impairment:

Caution is advised when administering Acyclovir Intravenous Infusion to patients with impaired renal function. Adequate hydration should be maintained.

The following adjustments in dosage are suggested:

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

ROUTE OF ADMINISTRATION:

Each dose must be administered by slow intravenous infusion over a period of at least one hour to avoid renal tubular damage.

Acyclovir Intravenous Infusion may be injected directly into a vein over one hour by a controlled rate infusion pump or be diluted for administration by infusion.

For intravenous injection by a controlled rate infusion pump, a solution containing acyclovir 25mg/ml is used.

For intravenous infusion, each vial of Acyclovir Intravenous Infusion should be added to and mixed with at least 50ml of infusion solution and a maximum of 500mg of acyclovir may be added to 100ml of infusion solution. After addition of Acyclovir Intravenous Infusion to an infusion solution, the mixture should be shaken to ensure thorough mixing. Acyclovir Intravenous Infusion when diluted in accordance with the above schedule with give an acyclovir concentration not greater than 0.5% w/v (5mg/ml).

Acyclovir Intravenous Infusion is known to be compatible with the following infusion fluids and stable for up to 24 hours at room temperature (25^{o}C): Sodium Chloride Intravenous Infusion BP (0.9% w/v), Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP, Sodium Chloride (0.9% w/v) and Glucose (5% w/v) Intravenous Infusion BP and Compound Sodium Lactate Intravenous Infusion BP (Lactated Ringers Solution).

Acyclovir Intravenous Infusion contains no preservative. Dilutions should therefore be carried out immediately before use and any unused solution should be discarded. Should visible turbidity or crystallization appear in the solution before or during infusion, the preparation should be discarded.

THIS SOLUTION SHOULD NOT BE REFRIGERATED as this causes precipitation of crystals. These crystals usually do not redissolve when solution temperature is brought to room temperature.

CONTRAINDICATIONS:

Acyclovir Intravenous Infusion is contraindicated in patients known to be hypersensitive to acyclovir, valacyclovir or any component of the Vaxcel Acyclovir Intravenous Infusion.

WARNING & PRECAUTIONS:

In patients receiving Acyclovir Intravenous 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. Acyclovir Intravenous 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.

Use in pregnancy:
Acyclovir was found not to be teratogenic. Acyclovir can be excreted in breast milk. Hence Acyclovir should not be used in pregnancy or nursing mothers unless the potential benefit justifies the potential risk to the fetus and nursing infant.

INTERACTION WITH OTHER MEDICAMENTS:

Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism or affect renal physiology may increase Acyclovir plasma concentrations.
Probenecid and cimetidine increase the AUC of Acyclovir by this mechanism, and reduce Acyclovir renal clearance.
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 Acyclovir and of the inactive metabolite of mycoophenolate 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 which affect other aspects of renal physiology (e.g. cyclosporine, tacrolimus). There are reports of additive nephrotoxicity when both Acyclovir and cyclosporine are administered concomitantly.

Incompatibilities: None known

SIDE EFFECTS:

The following table of incidence of reactions is based on clinical studies in patients who received Acyclovir:

System	Estimated overall incidence >1%	Estimated overall incidence <1%
Body as a whole	Local inflammation at injection site (approximately 9%)	Fever Headache
Cardiovascular	Injection site phlebitis (approximately 9%)	Hypotension
Gastrointestinal	Nausea and vomiting (approximately 7%)	Anorexia
Genitourinary		Abnormal urinalysis (characterized by an increase in formed elements in urine sediment) Anuria Dysuria Haematuria
Haemotological		Anaemia Neutropenia Thrombocytopenia
Metabolic and nutritional	Elevation of transaminases (1 to 2%) Rapid increases in serum Urea nitrogen and creatinine (5 to 10%)*	Oedema Thirst
Nervous		Encephalopathic chantes characterized by one or more of the following: lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizure, and coma (approximately 1%) Dizziness
Skin and appendages	Hives (approximately 2%) Itching (approximately 2%) Rashes (approximately 2%)	Diaphoresis

* These increases are usually reversible but progression to acute renal failure can occur in rare cases. The risk of renal damage is increased by bolus injection, dehydration, concomitant use of other nephrotoxic drugs and pre-existing renal disease.

Other reaction has been reported with a frequency of less than 1% in patients receiving Acyclovir, but a causal relationship between acyclovir and the reaction could not be determined. These include:
- abdominal pain, chest pain, chills, ischaemia of digits
- purpura fulminans
- haemoglobinemia, leukocytosis, neutrophilia, thrombocytosis
- hypokalemia
- pulmonary oedema with cardiac tamponade
- pressure on urination

The following adverse reactions have been reported during clinical practice with Acyclovir :
- Anaphylaxis, fever, angioedema, pain; local necrosis and inflammation may occur due to extravasation at the site of injection.
- Increases in liver related enzymes, nausea. Hepatitis and jaundice have been reported on very rare occasions.
- Decreases in haemotological indices have been reported during clinical practice, leucopenia. Disseminate intravascular coagulation has also been noted.
- Elevated serum urea nitrogen and creatinine.
- Agitation, coma, confusion, convulsions, delirium, hallucination, lethargy, obtundation, psychosis, somnolence and tremor.
- Dyspnoea
- Rash (including photosensitivity), urticaria and pruritus. Stevens-Johnson syndrome and toxic epidermal necrolysis has also been reported.
- Renal failure

SYMPTOMS AND TREATMENT OF OVERDOSE:

There are little experience concerning overdosage with Acyclovir. Effect from overdosage may be expected to be similar in nature but more severe effects to those as stated in Side Effects.
Overdosage has been reported following administration of bolus injections, or inappropriately high doses and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in serum urea and creatinine and subsequent renal failure. Lethargy, convulsions and coma have been reported rarely.
Acyclovir can be removed from the circulation by haemodialysis: a 6 hour haemodialysis results in a 60% decrease in plasma acyclovir concentration.

STORAGE:

Store below 30°C. Do not refrigerate.
For single use only. Discard any remaining solution.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:

Available in glass vials of 10ml, 20ml and 50ml. Single vial per box for 50ml; 10 vials per box for 10ml & 20ml.

Further information can be obtained from pharmacist, physician or the manufacturer.

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