Zovirax* I.V.

for Infusion

To the Medical and Pharmaceutical Professions

Presentations

Zovirax 250mg

A sterile, white to off-white, freeze-dried powder in vials containing 250mg Acyclovir as the Sodium salt.

The sodium ion content is approximately 26mg per vial.

Zovirax 500mg

A sterile, white to off-white, freeze-dried powder in vials containing 500mg Acyclovir as the Sodium salt.

The sodium ion content is approximately 52mg per vial.

When reconstituted as directed, Zovirax I.V. for Infusion has a pH of approximrely 11.

Indications

Zovirax I.V. for Infusion is indicated for the treatment of *Herpes simplex* infections. Zovirax LV. for Infusion is indicated for the prophylaxis of *Herpes simplex infections* in immune-compromised patients.

Zovirax LV. for Infusion is indicated in the treatment of *Varicella* zoster infections. Zovirax I.V. for Infusion is indicated for the treatment of *Herpes simplex infections* in the neonate.

Dosage, reconstitution and administration

Dosage

Dosage in Adults

Patients with *Herpes simplex (*except herpes encephalitis) or *Varicella zoster* infections should be given Zovirax LV. for Infusion in doses of 5mg/kg bodyweight every 8 hours.

Immune-compromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Zovirax I.V. for Infusion in doses of 10mg/kg bodyweight every 8 hours provided renal function is not impaired.

Dosage in Children

The dose of Zovirax I.V. 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 Zovirax I.V. for Infusion in doses of 250mg per square metre body surface area every 8 hours.

In immune-compromised children with *Varicella zoster* infections or children with herpes encephalitis, Zovirax I.V. for Infusion should be given in doses of 500mg 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.

Dosage in Neonates

The dosage of Zovirax I.V. for Infusion in neonates is calculated on the basis of bodyweight.

Neonates with *Herpes simplex* infections should be given Zovirax I.V. for Infusion in doses of 10mg/kg bodyweight every 8 hours.

Dosage in the Elderly

In the elderly, total acyclovir 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

Caution is advised when administering Zovirax I.V. 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 10mg/kg bodyweight) should be given every 12 hours.
10-25 ml/min	The dose recommended above (5 or 10mg/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 10mg/kg bodyweight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10mg/kg bodyweight) should be halved and administered every 24 hours and after dialysis.

A course of treatment with Zovirax I.V. 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 Zovirax I.V. for Infusion is determined by the duration of the period at risk.

Reconstitution

Zovirax I.V. for Infusion 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 25mg acyclovir per ml:

Formulation	Volume of fluid for reconstitution
250mg vial	10 ml
500mg vial	20ml

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

The required dose of Zovirax I.V. for Infusion should be administered by slow intravenous infusion over a one-hour period.

After reconstitution Zovirax I.V. for Infusion 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 5mg/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 an the basis of 4m1 reconstituted solution (100mg acyclovir) added to 20ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100ml of infusion fluid are used, even when this would give an acyclovir concentration substantially below 0.5% w/v. Thus one 100ml infusion bag may be used far any dose between 250mg and 500mg acyclovir (10 and 20ml of reconstituted solution), but a second bag must be used for doses between 500 and 1000mg.

When diluted in accordance with the recommended schedules, Zovirax I.V. for Infusion is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15° 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).

Zovirax I.V. for Infusion 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.

Mode of action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in viva* inhibitory activity against human herpes viruses, including *Herpes* simplex virus types 1 and 2, *Varicella zostervirus* (VZV), *Epstein Barrvirus* (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-l, HSV-2, VZV and EBV is highly selective. The enzyme

thymidine kinase (TK) of normal, uninfected 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 viral 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
In adults, the terminal plasma half life of acyclovir after administration of Zovirax I.V. for Infusion is about 2.9 hours. 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-carboxymethoxymethylguanine is the only significant metabolite of acyclovir and accounts for approximately 10-15% 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 adults, mean steady state peak plasma concentrations (C^{ss}max) following a one-hour infusion of 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7 µM (5.1µg/ml) 43.6µM (9.8µg/ml) and 92µM (20.7 µg/ml), respectively. The corresponding trough levels (C^{ss}min) 7 hours later were 2.2µM (0.5µg/ml), 3.1 µM (0.7 µg/ml) and 10.2µM (2.3µg/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 250mg/m^2 was substituted for 5mg/kg and a dose of 500mg/m^2 was substituted for 10mg/kg. In neonates (0-3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours, the C^{ss}max was found to be 61.2µM (13.8µg/ml) and the C^{ss}min to be 10.1 µM (2.3µg/ml). The terminal plasma half life in these patients was 3.8 hours. 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.
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.

Contra-indications
Zovirax I.V. for Infusion is contra-indicated in patients known to be previously hypersensitive to acyclovir.

Precautions/warnings
The dose of Zovirax I.V. for Infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of acyclovir in the body (see Dosage in renal impairment).
In patients receiving Zovirax I.V. 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 Zovirax I.V. for Infusion has a pH of approximately 11.0 and should not be administered by mouth.

Mutagenicity
The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that acyclovir does not pose a genetic risk to man.

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

Teratogenicity
Systemic administration of acyclovir 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.

Fertility
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of (orally administered) acyclovir on fertility.
There is no experience of the effect of Zovirax LV. for Infusion on human fertility. Zovirax Tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

Pregnancy
Limited data are available on the use of acyclovir during pregnancy. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

Lactation
Following oral administration of 200mg 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 0.3mglkg bodyweight/day. Caution is therefore advised if Zovirax is to be administered to a nursing woman.

Drug interactions
Probenecid increases the acyclovir mean half life and area under the plasma concentration-time curve. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of acyclovir. However, clinical experience has not identified other drug interactions with acyclovir.

Adverse reactions
Rapid increases in blood urea and creatinine levels may occasionally occur in patients given Zovirax I.V. for Infusion. This is 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. Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with Zovirax I.V. 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. Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when Zovirax I.V. for Infusion has been inadvertently infused into extravascular tissues.
Reversible neurological reactions, such as confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with Zovirax I.V. for Infusion therapy, usually in medically complicated cases.
Nausea and vomiting have been reported in patients receiving therapy with Zovirax LV. for Infusion.
Other events reported in patients receiving Zovirax I.V. for Infusion include increases in liver-related enzymes, rashes, fevers and decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Overdosage
Single doses of Zovirax I.V. for Infusion up to 80mg/kg bodyweight have been inadvertently administered without adverse effects.
Acyclovir is dialysable.

Storage precautions
Keep at temperatures not exceeding 25°C.

Pharmaceutical precautions
Zovirax I.V. for Infusion contains no antimicrobial preservative. Reconstitution or dilution should therefore be carried out either under full aseptic conditions or immediately before use and any unused solution discarded.
Reconstituted or diluted solutions should not be refrigerated.

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