

DATA SHEETS

ZOVIRAX[®] I.V. for Infusion.

Aciclovir 250mg injection for intravenous infusion

Presentation

Freeze dried powder for Injection.

ZOVIRAX IV 250mg: a sterile, white to off-white, freeze-dried powder in vials containing 250mg aciclovir as the sodium salt. The sodium ion content is approximately 26mg per vial. When reconstituted as directed ZOVIRAX I.V. has a pH of approximately 11.

Uses

Actions

Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including Herpes simplex virus types 1 and 2, 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.

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. 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 aciclovir 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 aciclovir

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 aciclovir 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 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-carboxymethoxy- methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10-15% of the dose excreted in the urine. When aciclovir 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_{ssmax}) following a one-hour infusion of 2.5mg/kg, 5mg/kg, 10mg/kg and 15mg/kg were 22.7mcM (5.1mcg/mL), 43.6mcM (9.8mcg/mL), 92mcM (20.7mcg/mL) and 105mcM (23.6mcg/mL), respectively. The corresponding trough levels (C_{ssmin}) 7 hours later were 2.2mcM (0.5mcg/mL), 3.1mcM (0.7mcg/mL), 10.2mcM (2.3mcg/mL) and 8.8mcM (2.0mcg/mL), respectively. In children over 1 year of age similar mean peak (C_{ssmax}) and trough (C_{ssmin}) levels were observed when a dose of 250mg/m² was substituted for 5mg/kg and a dose of 500mg/m² 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_{ssmax} was found to be 61.2mcM (13.8mcg/mL) and the C_{ssmin} to be 10.1mcM (2.3mcg/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 aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir 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.

Indications

ZOVIRAX I.V. for Infusion is indicated for the treatment of Herpes simplex infections.

ZOVIRAX I.V. for Infusion is indicated for the prophylaxis of Herpes simplex infections in immune-compromised patients.

ZOVIRAX I.V. 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.

ZOVIRAX I.V. for Infusion formulations are indicated for prophylaxis of CMV infection in bone marrow transplant recipients. It has been shown that high dose intravenous ZOVIRAX reduces the incidence and delays the onset of CMV infection. When high dose intravenous ZOVIRAX is followed by 6 months treatment with high dose oral ZOVIRAX (see prescribing information for oral ZOVIRAX) mortality and the incidence of viraemia are also reduced.

Dosage and Administration

Dosage

Dosage in adults:-

Obese patients should be dosed at the recommended adult dose using ideal body weight, rather than actual body weight.

Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given ZOVIRAX I.V. 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.

For prophylaxis of CMV infection in bone marrow transplant recipients 500mg/m² ZOVIRAX should be given intravenously 3 times daily at approximately 8 hourly intervals. The duration of treatment recommended in bone marrow transplant recipients is from 5 days before up to 30 days after transplant.

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.

Limited data suggest that for the prophylaxis of CMV infection in children, over 2 years of age, who have undergone bone marrow transplantation, the adult dose may be given.

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:-

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

Adequate hydration should be maintained.

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. Adequate hydration should be maintained.

Creatinine Clearance	Dosage
25-50mL/min	The dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be given every 12 hours.
10-25mL/min	The dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be given every 24 hours.
0 (anuric)-10mL/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) 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.

Administration

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

ZOVIRAX I.V. for Infusion should be reconstituted in 10mL of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing 25mg aciclovir per mL. From the calculated dose, determine the appropriate number 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.

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 aciclovir 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 on the basis of 4mL reconstituted solution (100mg aciclovir) 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 aciclovir concentration substantially below 0.5%w/v. Thus one 100mL infusion bag may be used for any dose between 250mg and 500mg aciclovir (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°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).

ZOVIRAX I.V. 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.

Contraindications

ZOVIRAX I.V. for Infusion is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

Warnings and Precautions

Use in patients with renal impairment and in elderly patients

ZOVIRAX I.V. is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see Dosage and Administration). 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 Adverse Reactions).

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.

Pregnancy and Lactation

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of ZOVIRAX. The registry findings have not shown any increase in the number of birth defects amongst ZOVIRAX exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

The use of ZOVIRAX Powder for I.V. Infusion should be considered only when the potential benefits outweigh the possibility of unknown risks.

Teratogenicity:-

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.

Lactation

Following oral administration of 200mg aciclovir 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 0.3mg/kg bodyweight/day. Caution is therefore advised if ZOVIRAX is to be administered to a nursing woman.

Effects on ability to drive and use machines

ZOVIRAX I.V. 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 ZOVIRAX on driving performance or the ability to operate machinery.

Adverse 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 $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ 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, 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 (see Warnings and Precautions).

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, renal pain

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. Renal pain may be associated with renal failure

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 ZOVIRAX I.V. for Infusion has been inadvertently infused into extracellular tissues.

Interactions

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 ZOVIRAX, 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 coadministered.

Care is also required (with monitoring for changes in renal function) if administering intravenous ZOVIRAX with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

Overdosage

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. Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose of this drug.

Pharmaceutical Precautions

Shelf Life

60 months. Store below 25°C.

Special precautions for storage

Reconstituted or diluted solutions should not be refrigerated.

Nature and contents of container

Pack of 5 vials.

Instructions for use/handling

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.

When reconstituted as directed, ZOVIRAX I.V. for Infusion has a pH of approximately 11.

Reconstituted or diluted solutions should not be refrigerated.

Reconstitution

ZOVIRAX I.V. for Infusion should be reconstituted using 10mL of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing 25mg aciclovir per mL (see Dosage and Administration).

Medicines Classification

Prescription Only Medicine

Further Information

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.

Carcinogenicity:-

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 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 information on the effect of ZOVIRAX I.V. for Infusion 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.

Name and Address

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown Auckland
NEW ZEALAND

Phone: (09) 367 2900
Fax: (09) 367 2506

Date of Preparation

Issue Date: 21 February 2012

Version: 2.0

ZOVIRAX[®] is a registered trade mark of the GlaxoSmithKline group of companies

© This data sheet is copyrighted to GlaxoSmithKline and may be reproduced but not altered in any way.