10000000143917

Zovirax

Powder for I.V. Infusion

Aciclovir

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOVIRAX 125 mg: The sodium ion content is approximately 13 mg per vial.
ZOVIRAX 250 mg: The sodium ion content is approximately 26 mg per vial.
ZOVIRAX 500 mg: The sodium ion content is approximately 52 mg per vial.

PHARMACEUTICAL FORM

Freeze dried powder for Injection.

CLINICAL PARTICULARS

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 is 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

To be given as intravenous infusion over 1 hour.

A course of treatment with *ZOVIRAX 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 usually lasts 10 days. Treatment for neonatal herpes usually lasts 14 – 21 days.

The duration of prophylactic administration of *ZOVIRAX IV* for infusion is determined by the duration of the period at risk.

Adults

Treatment and of herpes simplex

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) should be given aciclovir IV for infusion in doses of 5 mg/kg bodyweight every eight hours if renal function is not impaired.

Patients with herpes encephalitis should be given aciclovir IV for infusion in doses of 10 mg/kg bodyweight every eight hours provided renal function is not impaired.

Prophylaxis of herpes simplex in immune-compromised patients

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

Refer to adult dosing recommendations for the treatment of herpes simplex with *ZOVIRAX IV* for infusion.

Treatment of varicella and herpes zoster

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

Patients with varicella zoster infections should be given aciclovir IV for infusion in doses of 5 mg/kg bodyweight every eight hours if renal function is not impaired.

Immune-compromised patients with varicella zoster infections should be given aciclovir IV for infusion in doses of 10 mg/kg bodyweight every eight hours provided renal function is not impaired.

Prophylaxis of CMV infection

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

For prophylaxis of CMV infection in bone marrow transplant recipients 500 mg/m^2 aciclovir should be given intravenously three times daily at approximately eight hourly intervals if renal function is not impaired. The duration of treatment recommended in bone marrow transplant recipients is from five days before to up to 30 days after transplant.

Infants and children

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

Infants and children 3 months of age or older with herpes simplex (except herpes encephalitis) or varicella zoster infections should be given *ZOVIRAX IV* for infusion in doses of 250 mg per square metre body surface area every 8 hours if renal function is not impaired.

In immune-compromised infants and children with varicella zoster infections or herpes encephalitis, *ZOVIRAX 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.

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.

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

Neonates

The dosage of *ZOVIRAX IV* for infusion in neonates is calculated on the basis of bodyweight.

The recommended regimen for treatment for known or suspected neonatal herpes is aciclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes. Patients with impaired renal function require an appropriately modified dose, according to the degree of impairment (*see Renal impairment*).

Elderly

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

Adequate hydration should be maintained.

Renal Impairment

Caution is advised when administering *ZOVIRAX IV* 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:

Table 1: Dosage adjustments for IV aciclovir in adults and adolescents with renal impairment for treatment of Herpes Simplex virus infections.

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

Table 2: Dosage adjustments for IV aciclovir in neonates, infants and children with renal impairment for treatment of Herpes Simplex virus infections

Creatinine Clearance	Dosage
25 to 50 mL/min/1.73 m^2	The recommended dose (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/1.73 m^2	The recommended dose (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/1.73 m^2	The recommended dose (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours.
Patients on haemodialysis	In patients receiving haemodialysis, the recommended dose (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.

Contraindications

ZOVIRAX IV for infusion is contra-indicated in patients known to be hypersensitive to aciclovir or valaciclovir.

Warnings and Precautions

In patients receiving *ZOVIRAX 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 *ZOVIRAX 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:

Aciclovir 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*).

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).

Pregnancy and Lactation

Pregnancy

A post-marketing *ZOVIRAX* pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of *ZOVIRAX*. 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.

The use of *ZOVIRAX* should be considered only when the potential benefits outweigh the possibility of unknown risks.

Lactation

Following oral administration of 200 mg *ZOVIRAX* five times a day, aciclovir has been detected in 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/day. Caution is therefore advised if *ZOVIRAX* is to be administered to a nursing woman.

Effects on Ability to Drive and Use Machines

ZOVIRAX IV 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.

Adverse Reactions

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 ≥1/1000 and <1/100, rare ≥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, when administered intravenously the drug should not be given as an intravenous bolus injection but by 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 IV* for infusion has been inadvertantly infused into extracellular tissues.

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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 aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of Action

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, 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, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non- infected 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.

Pharmacodynamic Effects

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 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.

Pharmacokinetic Properties

Absorption

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 22.7 micromolar (5.1 micrograms/mL), 43.6 micromolar (9.8 micrograms/mL), 92 micromolar (20.7 micrograms/mL) and 105 micromolar (23.6 micrograms/mL), respectively. The corresponding trough levels (C_{ssmin}) 7 h later were 2.2 micromolar (0.5 micrograms/mL), 3.1 micromolar (0.7 micrograms/mL), 10.2 micromolar (2.3 micrograms/mL) and 8.8 micromolar (2.0 micrograms/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 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 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C_{ssmax} was found to be 61.2 micromolar (13.8 micrograms/mL) and the C_{ssmin} to be 10.1 micromolar (2.3 micrograms/mL). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a C_{max} of 83.5 micromolar (18.8 micrograms/mL) and C_{min} of 14.1 micromolar (3.2 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 are not anticipated.

Elimination

In adults the terminal plasma half life of aciclovir after administration of aciclovir IV 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 to 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 neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the terminal plasma half life was 3.8 hours.

Special Patient Populations

In patients with chronic renal failure the mean terminal half life was found to be 19.5 h. The mean aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir 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.

Clinical Studies

There is no information on the effect of *ZOVIRAX IV* 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.

Preclinical Safety Data

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.

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

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.

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.

PHARMACEUTICAL PARTICULARS

List of Excipients

As registered locally.

Incompatibilities

No data.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

As registered locally.

NOTE: The storage precautions may vary according to pharmaceutical formulation or the marketing outlet.

Nature and Contents of Container

As registered locally.

Instructions for Use/Handling

Reconstitution

The required dose of *ZOVIRAX IV* for infusion should be administered by slow IV infusion over a one-hour period.

ZOVIRAX IV for infusion should be reconstituted using the following volumes of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing 25 mg *ZOVIRAX* per mL:-

Formulation	Volume of fluid for reconstitution
125 mg vial	5 mL
250 mg vial	10 mL
500 mg vial	20 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.

After reconstitution *ZOVIRAX IV* for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give a *ZOVIRAX* 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 *ZOVIRAX*) 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 *ZOVIRAX* 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 *ZOVIRAX* (10 and 20 mL of reconstituted solution) but a second bag must be used for doses between 500 and 1000 mg.

When diluted in accordance with the recommended schedules, *ZOVIRAX IV* 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 IV for infusion when diluted in accordance with the above schedule will give a *ZOVIRAX* concentration not greater than 0.5% w/v.

When reconstituted as directed, *ZOVIRAX IV* for infusion has a pH of approximately 11.

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.

Reconstituted or diluted solutions should not be refrigerated.

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

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Manufactured by: GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana, 90, 43056 San Polo di Torrile, Parma, Italy

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