ZOVIRAX® IV INJECTION
PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ZOVIRAX® IV Injection

COMPOSITION:

Each vial supplies acyclovir 250 mg as the freeze-dried sodium salt.

The sodium ion content is approximately 26 mg per vial.

PHARMACOLOGICAL CLASSIFICATION: A 20.2.8 Antiviral Agents

PHARMACOLOGICAL ACTION:

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 and *varicella zoster* virus (VZV). In cell culture, acyclovir has the greatest anti-viral activity against HSV-1, followed (in decreasing order of potency) by HSV-2 and VZV. The inhibitory activity of acyclovir for HSV-1, HSV-2 and VZV 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 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.

INDICATIONS:

I *Herpes simplex* infections in immunocompromised patients:

ZOVIRAX IV is indicated for the treatment of *herpes simplex* infections.

ZOVIRAX IV is indicated for the prophylaxis of *herpes simplex* infections in patients.

II ZOVIRAX IV is indicated in the treatment of *varicella zoster* infections in immuno-compromised patients:

Chickenpox - prophylaxis and therapy of pneumonia complications.

Shingles - only if the lesions are not older than 72 hours.

III ZOVIRAX IV is indicated for treatment of *herpes simplex* infections in the neonate.

IV ZOVIRAX IV is indicated for the treatment of *herpes simplex* encephalitis.

V ZOVIRAX IV is indicated for the prevention of reactivation of cytomegalovirus infection in seropositive patients following bone marrow transplantation.

CONTRA-INDICATIONS:

ZOVIRAX IV is contra-indicated in patients known to be previously hypersensitive to acyclovir or valaciclovir.

WARNINGS AND SPECIAL PRECAUTIONS:

Safety of ZOVIRAX treatment in pregnancy and lactation has not been established (see PREGNANCY AND LACTATION).

Use in patients with renal impairment and in elderly patients:

Acyclovir, as contained in ZOVIRAX IV, is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see DOSAGE AND DIRECTIONS FOR USE).

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 SIDE EFFECTS).

The dose of ZOVIRAX IV 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 IV 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 has a pH of approximately 11,0 and should not be administered by mouth.

INTERACTIONS:

No clinically significant interactions have been identified.

Acyclovir as contained in ZOVIRAX IV is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increases the AUC of acyclovir by this mechanism, and reduces acyclovir renal clearance.

In patients receiving intravenous ZOVIRAX, caution is required during concurrent administration with medicines which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites.

Increases in plasma AUCs of acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the medicines are co-administered.

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

PREGNANCY AND LACTATION:

Safety in pregnancy has not been established (see WARNINGS AND SPECIAL PRECAUTIONS).

Lactation:

Following oral administration of 200 mg five times a day, acyclovir 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 acyclovir dosages of up to 0,3 mg/kg/day.

Lactating women on ZOVIRAX treatment should not breastfeed.

Fertility:

There is no information on the effect of ZOVIRAX IV on human female fertility. In a study of 20 male patients with normal sperm count, oral acyclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

DOSAGE AND DIRECTIONS FOR USE:

The required dose of ZOVIRAX IV should be administered by slow intravenous infusion over a one hour period. A course of treatment with ZOVIRAX IV 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 IV is determined by the duration of the period at risk.

Dosage in adults:

INDICATION	IMMUNE STATUS	DOSAGE
Herpes simplex infection (except herpes encephalitis)	Immunocompromised	5 mg/kg every 8 hours
Varicella zoster infection	Immunocompromised (normal renal function)	10 mg/kg every 8 hours
Herpes simplex encephalitis	Normal or immuno-compromised (normal renal function)	10 mg/kg every 8 hours

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

Dosage in children:

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

INDICATION	IMMUNE STATUS	DOSAGE
Herpes simplex (except herpes encephalitis)	Immunocompromised	250 mg/m^2 every 8 hours
Varicella zoster infection	Immunocompromised (normal renal function)	500 mg/m^2 every 8 hours
Herpes simplex encephalitis	Normal (normal renal function)	500 mg/m^2 every 8 hours

Children with impaired renal function require an appropriately modified dose and/or dose interval, according to the degree of impairment as indicated under 'Dosage in renal impairment'.

Dosage in neonates:

The dosage of ZOVIRAX IV in neonates is calculated on the basis of bodymass. Neonates with *herpes simplex* infections should be given ZOVIRAX IV in doses of 10 mg/kg 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 for the prevention of cytomegalovirus reactivation following bone marrow transplantation:

Adults: 500 mg/m^2 ZOVIRAX IV should be given intravenously 3 times daily at approximately 8 hour intervals. The duration of treatment recommended in bone marrow transplant recipients is from 5 days before, up to 30 days after transplant.

Children: Limited data suggest that for the prevention of cytomegalovirus reactivation in children over 2 years of age, who have undergone bone marrow transplantation, the adult dose may be given.

Dosage in renal impairment for adult and paediatric patients:

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

Adults:

Creatinine Clearance (ml/min/1,73m^2)	**Percentage of recommended dose (%)**	**Dosing interval (hours)**
> 50	100 %	8
25-50	100 %	12
10-25	100 %	24

0-10	50 %	24

Guidelines for acyclovir administration in neonates with renal impairment:

Creatinine clearance of 20-50 ml/min/1,73 m^2 or serum creatinine 70-100 µmol/l: a dose of 10 mg/kg/12 hours. Creatinine clearance of 10-25 ml/min/1,73 m^2 or serum creatinine 110-130 µmol/l with decreasing urine output: a dose of 10 mg/kg/24 hours. Renal failure with creatinine clearance of < 10 ml/min/1,73 m^2 or serum creatinine > 130 µmol/l or urine output < 1 ml/kg/hour and peritoneal dialysis: a dose of 5 mg/kg/24 hours.

Reconstitution:

ZOVIRAX IV should be reconstituted using the following volumes of either Water for Injections BP or Sodium Chloride Intravenous Infusion BP (0,9 % *m/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. Reconstitute each vial by adding the recommended volume of infusion fluid and shaking gently until contents of the vial have dissolved completely.

Administration:

After reconstitution, ZOVIRAX IV may be administered intravenously over a one hour period 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 % *m/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 % m/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 and 1 000 mg. When diluted in accordance with the recommended schedules, ZOVIRAX 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 % *m/v*)
- Sodium Chloride (0,18 % *m/v*) and Glucose (4 % *m/v*) Intravenous Infusion BP
- Sodium Chloride (0,45 % *m/v*) and Glucose (2,5 % *m/v*) Intravenous Infusion BP
- Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution).

ZOVIRAX IV when diluted in accordance with the above schedule, will give an acyclovir concentration not greater than 0,5 % *m/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. 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.

SIDE EFFECTS:

Adverse Effects Derived from Clinical Trials:

The adverse reactions listed have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received ZOVIRAX at ~5 mg/kg (250 mg/m^2) 3

times daily and approximately 300 patients who received 10 mg/kg (500 mg/m^2) 3 times daily.

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 ≥ 1/1 000 and < 1/100, rare ≥ 1/10 000 and < 1/1 000, very rare < 1/10 000.

Blood and lymphatic system disorders

Uncommon: decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Vascular disorders

Common: phlebitis.

Gastrointestinal disorders

Common: nausea, vomiting.

Hepatobiliary disorders

Common: reversible increases in liver-related enzymes.

Skin and subcutaneous tissue disorders

Common: rashes (including photosensitivity), urticaria, pruritus, fevers.

Renal and urinary disorders

Common: increases in blood urea and creatinine levels.

Rapid increases in blood urea and creatinine levels are believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect, ZOVIRAX should not be given as an intravenous bolus injection, but by slow infusion over a one hour period.

Adverse Effects Derived from Post-Marketing Data:

The following events have been identified during post-approval use of ZOVIRAX from spontaneous reports. As these are reported from a population of unknown size, precise estimates of frequency cannot be made.

Immune system disorders: Anaphylaxis.

Psychiatric and nervous system disorders: 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 SPECIAL PRECAUTIONS).

Respiratory, thoracic and mediastinal disorders: Dyspnoea.

Gastrointestinal disorders: Diarrhoea, abdominal pain.

Hepatobiliary disorders: Reversible increases in bilirubin, hepatitis, jaundice.

Skin and subcutaneous tissue disorders: Angioedema, accelerated diffuse hair loss.

The relationship of accelerated diffuse hair loss to ZOVIRAX therapy is uncertain.

Renal and urinary disorders: Renal impairment, acute renal failure.

Adequate hydration of the patient should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of ZOVIRAX. Progression to acute renal failure, may occur.

General disorders and administration site conditions: Fatigue, fever, local inflammatory reactions.

Severe local inflammatory reactions sometimes leading to ulceration have occurred when ZOVIRAX IV has been inadvertently infused into extravascular tissues.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage of intravenous ZOVIRAX has resulted in elevations in 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. Haemodialysis significantly enhances the removal of acyclovir from the blood and may, therefore, be considered an option in the management of overdose of ZOVIRAX. Treatment is symptomatic and supportive.

IDENTIFICATION:

Vial containing a white to off-white powder.

PRESENTATION:

Carton containing 5 clear, colourless glass vials.

STORAGE INSTRUCTIONS:

Store below 25 °C.

Keep out of reach of children.

Use immediately after reconstitution and discard any excess.

Reconstituted or diluted solution should not be refrigerated.

REGISTRATION NUMBER: Q/20.2.8/164

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

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