ZOVIRAX IV

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

ZOVIRAX IV Injection

Powder for Injection

Aciclovir 250 mg per vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

The sodium ion content is approximately 26 mg per vial.

Sugar-free.

3. PHARMACEUTICAL FORM:

Powder for Injection

Vial containing a white to off-white powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic 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 pneumonial 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.

4.2 Posology and method of administration:

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 usually lasts 10 days. Treatment for neonatal herpes usually lasts 14-21 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 body weight every 8 hours
Varicella zoster infection	Immunocompromised (normal renal function)	10 mg/kg body weight every 8 hours
Herpes simplex encephalitis	Normal or immuno-compromised (normal renal function)	10 mg/kg body weight 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 weight.

INDICATION	IMMUNE STATUS	DOSAGE
Herpes simplex (except herpes encephalitis)	Immunocompromised	20 mg/kg body weight every 8 hours for 14 days
Varicella zoster infection	Immunocompromised (normal renal function)	20 mg/kg body weight four time per day for 5 days
Herpes simplex encephalitis	Normal (normal renal function)	20 mg/kg body weight every 8 hours for 21 days

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 and infants up to 3 months of age is calculated on the basis of bodyweight. Neonates with herpes simplex infections should be given ZOVIRAX IV in doses of 20 mg/kg every 8 hours for 21 days.

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Dosage in 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:

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

Dosage adjustments in Adults and adolescents:

Creatinine Clearance (mL/min/1,73m^2)	***Percentage of recommended dose or 10 mg/kg body weight) (%)***	**Dosing interval (hours)**
> 50	100 %	8
25 – 50	100 %	12
10 – 25	100 %	24
0 – 10	50 %	24
	Haemodialysis: 50 %	24 and after dialysis

Dosage adjustments in neonates, infants and children:

Creatinine Clearance (mL/min/1,73m^2)	***Dosage recommendation***	**Dosing interval**
Normal renal function	20 mg/kg body weight	Three times per day

Creatinine Clearance (mL/min/1,73m^2)	***Dosage recommendation***	**Dosing interval**
25 – 50	20 mg/kg body weight	Twice a day
10 – 25	10 mg/kg body weight	Twice a day
0 to 10	5 mg/kg body weight *Haemodialysis:* 5 mg/kg body weight	Twice a day Twice daily after dialysis

Dosage recommendation in adults and adolescents with impaired renal function for prophylaxis of CMV infection:

Creatinine Clearance	**Dosage**
25 to 50 mL/min	500 mg/m^2 given every 12 hours
10 to 25 mL/min	500 mg/m^2 given every 24 hours
0 (anuric) to 10 mL/min	500 mg/m^2 halved and administered every 24 hours.
Patients on haemodialysis	500 mg/m^2 halved and administered every 24 hours and after dialysis

Dosage recommendations in infants and children with renal impairment for prophylaxis of CMV infection:

Creatinine Clearance (mL/min/1.73m^2)	Dosage
25 to 50 mL/min	20 mg/kg body weight given every 12 hours
10 to 25 mL/min	20 mg/kg body weight given every 24 hours
0 (anuric) to 10 mL	20 mg/kg body weight halved and administered every 24 hours
Patients on haemodialysis	20 mg/kg body weight halved and administered every 24 hours after dialysis

4.3 Contraindications:

ZOVIRAX IV is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

4.4 Special warnings and precautions for use:

Safety of ZOVIRAX IV treatment in pregnancy and lactation has not been established (see section 4.6).

Use in patients with renal impairment and in elderly patients:

Aciclovir as contained in ZOVIRAX IV is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2).

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 may be reversible on discontinuation of treatment (see section 4.8).

The dose of ZOVIRAX IV must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body (see section 4.2 – 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.
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 IV 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 usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of ZOVIRAX IV. Progression to acute renal failure, may occur.

4.5 Interactions with other medicines and other forms of interaction:

No clinically significant interactions have been identified.
Aciclovir 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 aciclovir plasma concentrations. Probenecid and cimetidine increases the AUC of aciclovir by this mechanism and reduces aciclovir renal clearance.
In patients receiving intravenous ZOVIRAX, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant medicine 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. ciclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established (see section 4.4).

Lactation:

Following oral administration of 200 mg 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.

Lactating women on ZOVIRAX IV treatment should not breastfeed.

4.7 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.

4.8 Undesirable 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 IV 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 < 1/1000, 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.

Adverse Effects Derived from Post-Marketing Data:

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

Immune system disorders: anaphylaxis, angioedema.

Psychiatric and nervous system disorders: headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.

The above effects may be reversible and usually reported in patients with renal impairment, or with other predisposing factors (see section 4.4).

Respiratory, thoracic and mediastinal disorders: dyspnoea

Gastrointestinal disorders: diarrhoea, abdominal pain

Hepatobiliary disorders: reversible increases in bilirubin, hepatitis jaundice

Skin and subcutaneous tissue disorders: accelerated diffuse hair loss. The relationship of accelerated diffuse hair loss to ZOVIRAX IV therapy is uncertain.

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

Renal pain may be associated with renal failure and crystalluria.

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.

Reporting of adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **'6.04 Adverse Drug Reactions Reporting Form'**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

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 aciclovir from the blood and may, therefore, be considered an option in the management of overdose of ZOVIRAX IV. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

A 20.2.8 Antiviral Agents

5.1 Pharmacodynamic properties:

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

5.2 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 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_{ssmin}) 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_{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 h the C_{ssmax} was found to be 61,2 micromoles (13,8 micrograms/mL) and the C_{ssmin} 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 are not anticipated.

Elimination:

In adults the terminal plasma half life of aciclovir after administration of aciclovir IV for infusion is about 2,9 h. 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 h the terminal plasma half life was 3,8 h.

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 h. 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Sodium hydroxide.

6.2 Incompatibilities:

None known

6.3 Shelf-life:

60 months

6.4 Special precautions for storage:

Store at or below 25 °C.

Use immediately after reconstitution and discard any excess.

Reconstituted or diluted solution should not be refrigerated.

6.5 Nature and contents of container:

Carton containing 5 clear, colourless Type I glass vials, with a bromobutyl rubber stopper, sealed with an aluminium collar and fitted with a plastic flip-top cover.

6.6 Special precautions for disposal and other handling:

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 aciclovir 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 aciclovir 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 aciclovir) 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 aciclovir 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 aciclovir (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 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 aciclovir 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

Q/20.2.8/164

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