SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

ZOVIRAX SUSPENSION

(aciclovir 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5 mL of ZOVIRAX SUSPENSION contains: aciclovir 200 mg, methyl hydroxy benzoate 0,1 % *m/v* and propyl hydroxybenzoate 0,02 % *m/v*.

Contains sugar (sorbitol 2 250 mg/5mL).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

ZOVIRAX SUSPENSION:

Suspension.

An off-white, viscous suspension with a banana odour and taste.

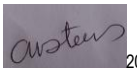
4. CLINICAL PARTICULARS:

4.1 Indications:

Treatment of initial and recurrent herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes simplex virus infections.

Suppression of recurrent genital herpes simplex infections in immunocompetent patients.

Prophylaxis of herpes simplex infections in immunocompromised patients.



Treatment of herpes zoster (shingles) infections if the lesions are not older than 72 hours.

Treatment of varicella-zoster (chickenpox) infection within 24 hours after appearance of the typical chickenpox rash.

Reduction of mortality and risk of developing herpes virus infections in certain severely immunocompromised patients, namely those with advanced HIV disease (CD4+ counts < 200/mm^3 including patients with AIDS or ARC) or following bone marrow transplantation.

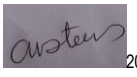
In patients with advanced HIV disease, oral ZOVIRAX SUSPENSION has been used in conjunction with oral zidovudine.

In patients following bone-marrow transplantation oral ZOVIRAX SUSPENSION must be preceded by one month's intravenous treatment with acyclovir.

4.2 Posology and method of administration:

Dosage in adults:

For treatment of initial and recurrent herpes simplex infections of the skin and mucous membranes: 200 mg ZOVIRAX SUSPENSION should be taken five times per day at approximately four-hourly intervals, omitting the night-time dose. Treatment should continue for 5 days, but in a case of severe initial infection, may have to be extended. In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg or, alternatively, intravenous dosing could be considered. The first dose should be administered as early as possible after the start of an infection, and for recurrent episodes this should preferably be during the prodromal period or when the lesions first appear.



For suppression of recurrent genital herpes simplex infections in immunocompetent adults:

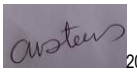
A dose of 200 mg of ZOVIRAX SUSPENSION should be taken four times daily at approximately six-hourly intervals. Many patients may be conveniently managed on a regimen of 400 mg of oral aciclovir taken twice daily at approximately twelve-hourly intervals. Dosage titration down to 200 mg oral aciclovir taken at approximately eight-hourly intervals, or even twice daily at approximately twelve-hourly intervals, may prove effective. Some patients may experience breakthrough infections on total daily doses of 800 mg aciclovir. Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.

For prophylaxis of herpes simplex infections in immunocompromised adults:

200 mg ZOVIRAX SUSPENSION should be taken four times daily at approximately six-hourly intervals. In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg, or alternatively intravenous dosing could be considered. The duration of prophylactic administration is determined by the duration of the period at risk.

For treatment of varicella-zoster infections in adolescents (12 to 18 years):

A dose of 800 mg oral ZOVIRAX SUSPENSION should be taken four times daily for five days.



For treatment of varicella-zoster and herpes zoster infections in adults:

A dose of 800 mg oral ZOVIRAX SUSPENSION should be taken five times daily at approximately four-hourly intervals, omitting the night-time dose. Treatment should continue for seven days. In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing. Dosing should begin as early as possible after the start of an infection: treatment yields better results if initiated as soon as possible after rash onset.

Dosage for management of severely immunocompromised patients:

For the management of severely immunocompromised patients, 800 mg ZOVIRAX SUSPENSION should be taken four times daily at approximately six-hourly intervals. In the management of bone marrow recipients this would be preceded by up to one month's therapy with intravenous ZOVIRAX 500 mg/m^2 three times daily. The duration of treatment studied in bone marrow transplant patients was 6 months (from 1 to 7 months post-transplant). In patients with advanced HIV disease, study treatment was 12 months.

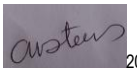
Dosage in children:

For the treatment of herpes simplex infections and prophylaxis of herpes simplex infections in immunocompromised children:

Two years and older: Adult dosage

Below two years: Half the adult dosage

Orally administered ZOVIRAX SUSPENSION in children less than 2 years of age has not been fully studied. Dosing for varicella (chickenpox) may be more accurately calculated as 20 mg ZOVIRAX SUSPENSION per kilogram body mass (not to exceed 800 mg) four times daily. Treatment should continue for five days and should start within



24 hours after appearance of typical chickenpox rash. Limited data suggest that for management of severely immunocompromised children, over two years of age, the adult dose may be given.

Do not dilute the oral suspension.

Dosage in the elderly:

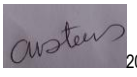
In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of ZOVIRAX SUSPENSION should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

Dosage in renal impairment:

Caution is advised when administering ZOVIRAX SUSPENSION to patients with impaired renal function. Adequate hydration should be maintained.

In the treatment and prophylaxis of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir, as contained in ZOVIRAX SUSPENSION, above levels that have been established safe by intravenous infusion. For patients with severe renal impairment (creatinine clearance less than 10 mL/minute) a dose of 200 mg every 12 hours is recommended.

In the treatment of varicella and herpes zoster infections, and in the management of severely immunocompromised patients, it is recommended to adjust the dosage to 800 mg twice daily at approximately twelve-hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 mL/minute), and to 800 mg three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25 mL/minute).



			Adjusted Dosage
Normal Dosage (5 times daily)	**Creatinine Clearance (mL/min/1,73 m^2)**	**Dose (mg)**	**Dosing Interval (hours)**
200 mg every 4 hours	>10	200	every 4 hours 5 times daily
	0-10	200	every 12 hours
800 mg every 4 hours	10-25	800	every 8 hours
	0-10	800	every 12 hours

4.3 Contraindications:

ZOVIRAX SUSPENSION is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir or any of the ingredients of ZOVIRAX SUSPENSION (see section 2 and section 6.1).

4.4 Special warnings and precautions for use:

There is limited data on the use of ZOVIRAX SUSPENSION in pregnancy and lactation (see section 4.6)**.**

Use in patients with renal impairment and in elderly patients:

Aciclovir, as contained in ZOVIRAX SUSPENSION, 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).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

Excipient warning: ZOVIRAX SUSPENSION contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol/maltitol/lactitol intolerance should not take ZOVIRAX SUSPENSION.

Drug reaction with eosinophilia and systemic symptoms (DRESS):

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, ZOVIRAX SUSPENSION should be withdrawn immediately, and an alternative treatment should be considered (as appropriate). If the patient has developed DRESS with the use of ZOVIRAX SUSPENSION, which can be life-threatening or fatal, treatment with ZOVIRAX SUSPENSION must not be restarted in this patient at any time.

4.5 Interaction with other medicines and other forms of interaction:

Aciclovir as contained in ZOVIRAX SUSPENSION, 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. Similarly, 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.

In patients receiving antiretroviral therapy (oral zidovudine), no significant increase in toxicity was associated with the addition of ZOVIRAX SUSPENSION.

There has been a study that indicates that concomitant therapy with aciclovir increases AUC of totally administered theophylline with approximately 50 %. It is recommended to measure plasma concentrations during concomitant therapy with acyclovir.

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

There is limited data on the use of ZOVIRAX SUSPENSION in pregnancy and lactation.

Lactation: Following oral administration of 200 mg ZOVIRAX SUSPENSION 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.

4.7 Effects on ability to drive and use machines:

ZOVIRAX SUSPENSION can cause dizziness. Therefore, patients should see how ZOVIRAX SUSPENSION affects them before driving or operating machinery.

4.8 Undesirable 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.

Blood and lymphatic system disorders

Less frequent: anaemia, leucopenia and thrombocytopenia

Immune system disorders

Less frequent: anaphylaxis, angioedema

Psychiatric and nervous system disorders

Frequent: headache, dizziness

Less frequent: 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

Less frequent: dyspnoea

Gastrointestinal disorders

Frequent: nausea, vomiting, diarrhoea, abdominal pains

Hepatobiliary disorders

Less frequent: reversible rises in bilirubin and liver-related enzymes

Less frequent: hepatitis, jaundice

Skin and subcutaneous tissue disorders

Frequent: pruritus, rashes, photosensitivity urticaria, accelerated diffuse hair loss

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

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Renal and urinary disorders

Less frequent: increases in blood urea and creatinine, acute renal failure, renal pain

Renal pain may be associated with renal failure and crystalluria.

General disorders and administration site conditions

Frequent: fatigue, fever.

Reporting of suspected 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 (HCPs) are requested to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
HCPs can also report adverts events to GlaxoSmithKline's adverse event reporting line at aereporting.za@gsk.com, or phone at +27 (0) 10 300 1000.

4.9 Overdose:

See section 4.8.

Symptoms and Signs: Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion). Overdosage of IV 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 intravenous overdosage.

Management: 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. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 20.2.8 Antiviral agents

Aciclovir (ZOVIRAX SUSPENSION) is active *in vitro* against herpes simplex virus (HSV) types I and II and varicella-zoster virus. Aciclovir is phosphorylated after entry into herpes- infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of and substrate for the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes.

5.2 Pharmacokinetic properties:

Absorption:

Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20 %. Under fasting conditions, mean peak concentrations (C_{max}) of 0,4 microgram/mL are achieved at approximately 1,6 hours after a 200 mg dose administered as oral suspension or capsule. Mean peak plasma concentrations (C_{ssmax}) increase to 0,7 microgram/mL (3,1 micromoles) at steady state following doses of 200 mg administered every four

hours. A less than proportional increase is observed for C_{ssmax} levels following doses 400 mg and 800 mg administered four-hourly, with values reaching 1,2 and 1,8 microgram/mL (5,3 and 8 micromoles), respectively.

Distribution:

The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2,3 to 17,8 L/kg.

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.

Metabolism:

Aciclovir is predominantly excreted unchanged by the kidney. The only known urinary metabolite is 9-[(carboxymethoxy) methylguanine, and accounts for 10-15 % of the dose excreted in the urine.

Elimination:

Mean systemic exposure ($AUC_{0-\infty}$) to aciclovir ranges between 1,9 and 2,2 microgram*h/mL after a 200 mg dose. In adults the terminal plasma half-life after oral administration has been shown to vary between 2,8 and 4,1 hours. Renal clearance of aciclovir (CLr = 14,3 L/h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

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.

Studies have shown no apparent changes in the pharmacokinetic behaviour of aciclovir or zidovudine when both are administered simultaneously to HIV infected patients.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

ZOVIRAX SUSPENSION:

Excipients include Avicel, banana flavourant, glycerol, purified water and vanillin.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

ZOVIRAX SUSPENSION: 24 months

6.4 Special precautions for storage:

Protect from light.

ZOVIRAX SUSPENSION: Store at or below 25 °C.

6.5 Nature and contents of container:

ZOVIRAX SUSPENSION: Glass bottles of 125 mL

6.6 Special precautions for disposal (and other handling):

For administration of the 100 mg dose, the measuring device provided may be used or alternatively a graduated syringe.

7. HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

+27 (0) 10 300 1000

8. REGISTRATION NUMBERS:

ZOVIRAX SUSPENSION: S/20.2.8/236

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION:

ZOVIRAX SUSPENSION: 10 December 1991

10. DATE OF REVISION OF TEXT:

31 October 2025

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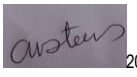

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