ZOVIRAX ORAL RANGE
Approved Package Insert

SCHEDULING STATUS:

S4

PROPRIETARY NAMES AND DOSAGE FORMS:

ZOVIRAX 200 Dispersible Tablets

ZOVIRAX SUSPENSION

COMPOSITION:

Each ZOVIRAX 200 dispersible tablet contains: acyclovir 200 mg.

Excipients include microcrystalline cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone K30 and magnesium stearate. The film coat contains hypromellose, titanium dioxide and polyethylene glycol.

Each 5 ml of ZOVIRAX SUSPENSION contains: acyclovir 200 mg, methyl hydroxybenzoate 0,1 % *m/v* and propyl hydroxybenzoate 0,02 % *m/v*.

The excipients include sorbitol, glycerol, Avicel, vanillin, banana flavourant and purified water.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Acyclovir (ZOVIRAX) is active *in vitro* against *herpes simplex* virus (HSV) types I and II and *varicella-zoster* virus. Acyclovir is phosphorylated after entry into herpes-infected

cells to the active compound acyclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase. Acyclovir triphosphate acts as an inhibitor of and substrate for the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes.

INDICATIONS:

ZOVIRAX Oral formulations are indicated for the treatment of initial and recurrent *herpes simplex* infections of the skin and mucous membranes including initial and recurrent genital *herpes simplex* virus infections.

ZOVIRAX Oral formulations are indicated for the suppression of recurrent genital *herpes simplex* infections in immunocompetent patients.

ZOVIRAX Oral formulations are indicated for the prophylaxis of *herpes simplex* infections in immunocompromised patients.

ZOVIRAX Oral formulations are indicated for the treatment of *herpes zoster* (shingles) infections if the lesions are not older than 72 hours.

ZOVIRAX Oral formulations are indicated for the treatment of *varicella-zoster* (chickenpox) infection within 24 hours after appearance of the typical chickenpox rash.

ZOVIRAX Oral formulations are indicated for the 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 has been used in conjunction with oral zidovudine.

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

CONTRA-INDICATIONS:

ZOVIRAX 200 and ZOVIRAX SUSPENSION are contra-indicated in patients known to be hypersensitive to acyclovir or valaciclovir.

WARNINGS AND SPECIAL PRECAUTIONS:

There is limited data on the use of ZOVIRAX in pregnancy and lactation (see PREGNANCY AND LACTATION)**.**

Use in patients with renal impairment and in elderly patients:

Acyclovir as contained in ZOVIRAX, 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).

Hydration status:

Care should be taken to maintain adequate hydration in patients receiving high oral doses of acyclovir.

INTERACTIONS:

No clinically significant interactions have been identified.

Acyclovir as contained in ZOVIRAX, 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. Similarly, 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.

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

PREGNANCY AND LACTATION:

There is limited data on the use of ZOVIRAX in pregnancy and lactation. The data is insufficient to establish safety.

Pregnancy: A post-marketing acyclovir 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 ZOVIRAX-exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

Lactation: Following oral administration of 200 mg ZOVIRAX 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.

Fertility: There is no information on the effect of ZOVIRAX oral formulations 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:

ZOVIRAX 200 dispersible tablets may be dispersed in a minimum of 50 ml water or swallowed whole with a little water.

Dosage in adults:

For treatment of initial and recurrent *herpes simplex* infections of the skin and mucous membranes: 200 mg ZOVIRAX 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 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 acyclovir taken twice daily at approximately twelve-hourly intervals. Dosage titration down to 200 mg oral acyclovir 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 acyclovir. 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 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 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 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 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 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 per kilogram bodymass (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.

Dosage in the elderly:

In the elderly, total acyclovir body clearance declines in parallel with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of ZOVIRAX 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 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 acyclovir as contained in ZOVIRAX, 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

Further information:

ZOVIRAX Suspension may be diluted with an equal volume of either Syrup or Sorbitol 70 % Solution (Non-crystallising). The diluted product is stable for 4 weeks at 25 °C, but it is recommended that all dilutions are freshly prepared and discarded within 24 hours if unused.

SIDE 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.

Psychiatric and nervous system disorders

Frequent: Headache, dizziness.

Less frequent: 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

Less frequent: Dyspnoea.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pains.

Hepatobiliary disorders

Less frequent: Reversible rises in bilirubin and liver-related enzymes, hepatitis, jaundice.

Skin and subcutaneous tissue disorders

Frequent: Pruritus, rashes (including photosensitivity), urticaria, accelerated diffuse hair loss.

Less frequent: Angioedema.

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

Renal and urinary disorders

Less frequent: Increases in blood urea and creatinine, acute renal failure.

General disorders and administration site conditions

Frequent: Fatigue, fever.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See SIDE EFFECTS.

Symptoms and Signs: Patients have ingested overdoses of up to 20 g ZOVIRAX on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral acyclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion). Overdosage

of IV acyclovir 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 acyclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose. Treatment is symptomatic and supportive.

IDENTIFICATION:

ZOVIRAX 200 Dispersible Tablets:	White, round, biconvex, film-coated tablets, branded 'GXCF3' on one side and plain on the other side.
ZOVIRAX SUSPENSION:	An off-white, viscous suspension with a banana odour and taste.

PRESENTATION:

ZOVIRAX 200 Dispersible Tablets: Blister packs of 25 tablets.

ZOVIRAX SUSPENSION: Amber glass bottles closed with polypropylene child resistant (CR) caps fitted with a reseal line and Low Density Polyethylene (LDPE) tamper-evident ring. The reseal liner is an Expanded Polyethylene (EPE) core faced with Polyethylene-Polyvinylidene Chloride-Polyethylene (PE-PVDC-PE) cover film on both sides.

STORAGE INSTRUCTIONS:

Keep out of the reach of children.

Protect from light.

ZOVIRAX 200 Dispersible Tablets: Store below 30 °C and in dry place.

ZOVIRAX SUSPENSION: Store below 25 °C.

REGISTRATION NUMBERS:

ZOVIRAX 200 Dispersible Tablets: 29/20.2.8/0452

ZOVIRAX SUSPENSION: S/20.2.8/236

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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