

DATA SHEET

ZOVIRAX™ Oral Formulations

Aciclovir 200mg, 400mg or 800mg Dispersible Tablets.*

*Aciclovir Suspension 200mg/5mL**

Pharmaceutical form

Dispersible Tablets.

Oral suspension*.

Presentation

Dispersible Tablet 200mg: Blue, may be slightly mottled. Clear film-coated tablet. Biconvex and shield shaped. Branded Zovirax 200 on one side. Triangle impressed on other side.

Dispersible Tablet 400mg: Pale pink, maybe slightly mottled. Clear film-coated tablet. Biconvex and shield-shaped. Branded "Zovirax 400" on one side. Triangle impressed on other side.

***Dispersible Tablet 800mg:** white, biconvex, elongated, clear film-coated, impressed with ZOVIRAX 800 on one side and scored on the other.

***Suspension 200mg/5mL:** white, banana-flavoured, oral suspension containing 200mg Aciclovir in each 5mL.

Uses

Actions

Aciclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including Herpes simplex virus 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.

Indications

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

ZOVIRAX Oral Formulations are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immune-competent patients.

ZOVIRAX Oral Formulations are indicated for the prophylaxis of herpes simplex infections in immune-compromised patients.

ZOVIRAX Oral Formulations are indicated for the treatment of acute herpes zoster (shingles) infections; for the reduction of the duration and severity of acute symptoms and rash, for the reduction of all zoster-associated pain and for the reduction of the incidence and duration of post-herpetic neuralgia.

ZOVIRAX Oral Formulations are indicated for the management of patients with severe AIDS who have a CD4 count of less than 50/mcL. Studies have shown that oral ZOVIRAX given in conjunction with anti-retroviral therapy (mainly oral RETROVIR) reduced mortality in patients with advanced HIV disease.

ZOVIRAX Oral Formulations, preceded by one month's treatment with intravenous ZOVIRAX, are indicated for patients undergoing allogenic bone marrow transplantation who are at risk of developing CMV infection while immunosuppressed. Studies have shown that oral ZOVIRAX reduced mortality in allogenic bone marrow transplant recipients. In addition oral ZOVIRAX provided effective prophylaxis for herpes virus disease.

Dosage and administration

Dosage for treatment of herpes simplex in adults

For treatment of herpes simplex infections, 200mg ZOVIRAX should be taken five times daily at approximately four-hourly intervals, omitting the night-time dose. Treatment should continue for 5 days but in severe initial infections may have to be extended.

In severely immune-compromised patients (e.g. after marrow transplants) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg or alternatively intravenous dosing could be considered.

Dosing should begin as early as possible after the start of an infection. For recurrent episodes this should preferably be during the prodromal period or when lesions first appear.

Dosage for suppression of herpes simplex in adults

For suppression of herpes simplex infections in immune-competent patients, 200mg ZOVIRAX should be taken four times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regimen of 400mg ZOVIRAX taken twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200mg ZOVIRAX taken thrice daily 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 800mg ZOVIRAX.

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.

Dosage for prophylaxis of herpes simplex in adults

For prophylaxis of herpes simplex infections in immune-compromised patients, 200mg ZOVIRAX should be taken four times daily at approximately six-hourly intervals.

In severely immune-compromised patients (e.g. after marrow transplants) or in patients with impaired absorption from the gut the dose can be doubled to 400mg or alternatively intravenous dosing could be considered.

The duration of prophylactic administration is determined by the duration of the period at risk.

Dosage for treatment of herpes zoster in adults

For treatment of herpes zoster infections, 800mg 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 immune-compromised 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 onset of the rash, ideally within 48 hours, certainly within 72 hours.

Dosage in patients with severe aids with CD4 count <50/mcL

For management of patients with severe AIDS who have a CD4 count of less than 50/mcL, 800mg ZOVIRAX should be taken four times daily at approximately six-hourly intervals. In patients with advanced HIV disease,

study treatment was 12 months but it is likely that these patients would continue to benefit from a longer duration of treatment.

Dosage in allogenic bone marrow transplant patients

For management of allogenic bone marrow recipients, 800mg ZOVIRAX should be taken four times daily at approximately six-hourly intervals. This would normally be preceded by up to one month's therapy with intravenous ZOVIRAX (see ZOVIRAX IV for infusion prescribing information). The duration of treatment studied was 6 months (from 1 to 7 months post-transplant).

Dosage in children

For treatment of herpes simplex infections and for prophylaxis of herpes simplex infections in the immune-compromised, children aged two years and over should be given the adult dosages and children below the age of 2 years should be given half the adult dose.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immune-competent children.

Limited data suggest that for management of children, over two years of age, with severe AIDS who have a CD4 count of less than 50/mcL, the adult dose may be given.

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 should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

Dosage in renal impairment

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 above levels that have been established safe by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10mL/minute) an adjustment of dosage to 200mg twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of herpes zoster infections and in the management of severely immunocompromised patients it is recommended to adjust the dosage to:

800mg twice daily at approximately twelve-hourly intervals for patients with severe renal impairment (creatinine clearance less than 10mL/minute)

and

800mg three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10 to 25mL/minute).

Administration

ZOVIRAX Dispersible Tablets may be swallowed whole with a little water or dispersed in a minimum of 50mL of water.

ZOVIRAX Suspension 200mg/5mL may be diluted with an equal volume of either Syrup BP or Sorbitol Solution 70% (non-crystallising) BP. The diluted product is stable for 4 weeks at 25°C but it is recommended that all dilutions are freshly prepared.

Contraindications

ZOVIRAX Tablets and ZOVIRAX Suspensions are contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

Warnings and Precautions

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

Resistant strains have been isolated in vitro and in animals following treatment with aciclovir. HSV strains resistant in vitro to aciclovir have also been isolated from immunocompromised as well as immuno-competent patients receiving aciclovir for Herpes simplex infections. Therefore the potential for the development of resistant HSV strains in patients treated with aciclovir should be borne in mind. The relationship between the level of in vitro sensitivity of herpes viruses to aciclovir and clinical response to therapy has not been adequately established.

As aciclovir has been associated with reversible encephalopathic changes, it should be used with caution in patients with underlying neurological abnormalities, significant hypoxia or serious renal, hepatic or electrolyte abnormalities. It should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitantly interferon or intrathecal methotrexate.

Animal studies indicate that at high doses aciclovir is cytotoxic.

Use During Pregnancy and Lactation

Teratogenicity

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.

Fertility

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.

There is no experience of the effect of ZOVIRAX tablets on human female fertility. ZOVIRAX tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

Pregnancy

A post-marketing aciclovir 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.

Caution should however be exercised by balancing the potential benefits of treatment against any possible hazard.

Lactation

Following oral administration of 200mg 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 0.3mg/kg/day. Caution is therefore advised if ZOVIRAX is to be administered to a nursing woman.

Effects on Ability to Drive and Use Machines

The clinical status of the patient and the adverse event profile of Zovirax should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of Zovirax on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

Interactions

No clinically significant interactions have been identified.

Aciclovir 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 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 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 medicines are coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

In patients over 60 years of age concurrent use of diuretics increases plasma levels of aciclovir very significantly. It is not known whether a similar effect occurs in young adults. In patients receiving RETROVIR (zidovudine) no significant overall increase in toxicity was associated with the addition of Zovirax. No data are available on interactions between aciclovir and other antiretroviral therapies.

Adverse 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.

The following convention has been used for the classification of undesirable effects in terms of frequency:- Very common $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$.

Blood and lymphatic system disorders

Very rare: Anaemia, leukopenia, thrombocytopenia

Immune system disorders

Rare: Anaphylaxis

Psychiatric and nervous system disorders

Common: Headache, dizziness, confusion, hallucinations, somnolence, convulsions,

Very rare: Agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, coma

The above events are reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, or with other predisposing factors.

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, abdominal pains

Hepato-biliary disorders

Rare: Reversible rises in bilirubin and liver related enzymes

Very rare: Hepatitis, jaundice

Skin and subcutaneous tissue disorders

Common: Pruritus, rashes (including photosensitivity)

Uncommon: Urticaria. Accelerated diffuse hair loss.

Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Rare: Angioedema

Renal and urinary disorders

Rare: Increases in blood urea and creatinine

Very rare: Acute renal failure

General disorders and administration site conditions

Common: Fatigue, fever

Overdosage

Symptoms & signs

Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20g aciclovir on a single occasion, usually without

toxic effects. 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 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 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.

Pharmacological properties

Pharmacodynamic properties

Mode 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.

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

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C_{ssmax}) following doses of 200mg administered four-hourly were 3.1mcMol (0.7mcg/mL) and equivalent trough plasma levels (C_{ssmin}) were 1.8mcMol (0.4mcg/mL). Corresponding C_{ssmax} levels following doses of 400mg and 800mg administered four-hourly were 5.3mcMol (1.2mcg/mL) and 8mcMol (1.8mcg/mL) respectively, and equivalent C_{ssmin} levels were 2.7mcMol (0.6mcg/mL) and 4mcMol (0.9mcg/mL).

In adults the terminal plasma half life of aciclovir after administration of intravenous aciclovir is about 2.9 hours. Most of the medicine 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 10-15% of the administered dose recovered from 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 adults, mean C_{ssmax} levels following a one-hour infusion of 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7mcMol (5.1mcg/mL), 43.6mcMol (9.8mcg/mL) and 92mcMol (20.7mcg/mL), respectively. The corresponding C_{ssmin} levels 7 hours later were 2.2mcMol (0.5mcg/mL), 3.1mcMol (0.7mcg/mL) and 10.2mcMol (2.3mcg/mL), respectively. In children over 1 year of age similar mean C_{ssmax} and C_{ssmin} levels were observed when a dose of 250mg/m² was substituted for 5mg/kg and a dose of 500mg/m² was substituted for 10mg/kg. In neonates and young infants (0-3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours the C_{ssmax} was found to be 61.2mcMol (13.8mcg/mL) and the C_{ssmin} to be 10.1mcMol (2.3mcg/mL).

The terminal plasma half life in these patients was 3.8 hours. 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.

In patients with chronic renal failure the mean terminal half life was found to be 19.5 hours. The mean aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

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.

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

Preclinical Safety Data

Mutagenicity

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.

Carcinogenicity

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

Pharmaceutical precautions

Shelf life

36 months.

Special precautions for storage

ZOVIRAX Dispersible Tablets 200mg, 400mg, 800mg*

Store below 30°C, Keep dry. Protect from light.

ZOVIRAX Suspension 200mg/5mL*

Store below 25°C

Package quantities

Dispersible Tablet 200mg - 25 tablets*, 90 tablets

Dispersible Tablet 400mg - 56 tablets*, 100 tablets

*Dispersible Tablet 800mg - 35 tablets (Shingles Treatment pack)

*Suspension 200mg/5mL - 125mL

ZOVIRAX Dispersible Tablets may be swallowed whole with a little water, or dispersed in a minimum of 50mL of water.

Oral Suspensions:-

Dilution:-

ZOVIRAX Oral Suspension, 200mg/5mL, may be diluted with an equal volume of either Syrup or Sorbitol Solution 70 per cent (Non-crystallising).

The diluted product is stable for 4 weeks at 25 °C but it is recommended that all dilutions are freshly prepared

Medicine classification

Prescription Only Medicine.

Name and address

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* These presentations are not marketed in New Zealand.

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