Zovirax™

Oral Formulations

To the Medical and Pharmaceutical Professions

Presentations

Not all presentations are registered in every country.

Tablets 200 mg: Each white, round tablet, engraved GXCL3 on one face, contains 200 mg aciclovir.

Tablets 400 mg: Each white, concave, shield shaped tablet, engraved GXCM1 on one face, contains 400 mg aciclovir.

Tablets 800 mg: Each white, oval tablet, engraved GXCX5 on one face, contains 800 mg aciclovir.

Dispersible tablets 200 mg: Each white, round tablet, branded GXCF3 on one face, contains 200 mg aciclovir.

Dispersible tablets 400 mg: Each white, concave, shield shaped tablet, branded GXCF5 on one face, contains 400 mg aciclovir.

Dispersible tablets 800 mg: Each white, oval tablet, branded GXCG1 on one face, contains 800 mg aciclovir.

Suspension 200 mg/5 ml: It is a white, banana-flavoured, oral suspension containing 200 mg aciclovir in each 5 ml.

Suspension 400 mg/5 ml: It is a white, orange-flavoured, oral suspension containing 400 mg aciclovir in each 5 ml.

Indications

Not all indications are registered in every country.

Zovirax Tablets and Suspension are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.

Zovirax Tablets and Suspension are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immune-competent patients.

Zovirax Tablets and Suspension are indicated for the treatment of herpes zoster (shingles) infections. Studies have shown that early treatment of shingles with Zovirax has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zoster-associated pain).

Dosage and Administration

Dosage in adults:

Treatment of Herpes simplex:

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

In severely immune-compromised 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.

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.

Suppression of Herpes simplex:

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

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

Dosage titration down to 200 mg 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 break-through infections on total daily doses of 800 mg 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.

Treatment of Herpes zoster:

For treatment of Herpes zoster infections, 800 mg 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.

Dosage in children:

For treatment of Herpes simplex infections, children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.

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 suppression 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 10 ml/minute) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of Herpes zoster infection 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 to 25 ml/minute).

Contra-indications

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

Precautions and Warnings

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

Drug Interactions

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs 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. Similarly 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 drugs are coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Pregnancy and Lactation

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.

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.

Lactation: Following oral administration of 200 mg aciclovir 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. Caution is therefore advised if Zovirax is to be administered to a nursing woman.

Adverse Reactions

Gastrointestinal: Nausea, vomiting, diarrhoea and abdominal pains have been reported.

Haematological: Very rarely, anaemia, leukopenia and thrombocytopenia.

Hypersensitivity and skin: Rashes including photosensitivity, urticaria, pruritus and rarely dyspnoea, angioedema and anaphylaxis.

Kidney: Rare reports of increases in blood urea and creatinine. Acute renal failure has been reported on very rare occasions.

Liver: Rare reports of reversible rises in bilirubin and liver-related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Neurological: Headaches. Occasionally reversible neurological reactions, notably dizziness, confusional states, hallucinations, convulsions, somnolence and coma have been reported, usually in patients with renal impairment in whom the dosage was in excess of that recommended or with other predisposing factors.

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Other: Fatigue. Occasional reports of accelerated diffuse hair loss. As this type of hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Overdosage

Symptoms & signs: Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g 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.

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 (Css max) following doses of 200 mg administered four-hourly were 3.1 μMol (0.7 μg/ml) and equivalent trough plasma levels (Css min) were 1.8 μMol (0.4 μg/ml). Corresponding Css max levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 μMol (1.2 μg/ml) and 8 μMol (1.8 μg/ml) respectively, and equivalent Css min levels were 2.7 μMol (0.6 μg/ml) and 4 μMol (0.9 μg/ml).
In adults the terminal plasma half life of aciclovir after administration of intravenous aciclovir is about 2.9 hours. 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 10-15% 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 Css max levels following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 μMol (5.1 μg/ml), 43.6 μMol (9.8 μg/ml) and 92 μMol (20.7 μg/ml), respectively. The corresponding Css min levels 7 hours later were 2.2 μMol (0.5 μg/ml), 3.1 μMol (0.7 μg/ml) and 10.2 μMol (2.3 μg/ml), respectively. In children over 1 year of age similar mean Css max and Css min 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 and young infants (0-3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the Css max was found to be 61.2 μMol (13.8 μg/ml) and the Css min to be 10.1 μMol (2.3 μg/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.

Pharmaceutical Precautions and Recommendations

Tablets 200 mg, 400 mg and 800 mg: Store below 25°C, protect from light, keep dry.

Dispersible tablets 200 mg, 400 mg and 800 mg: Store below 30°C, keep dry and protected from light.

Suspension 200 mg/5 ml: Store below 25°C.

Suspension 400 mg/5 ml: Store below 30°C.
Zovirax suspension 200 mg/5 ml may be diluted with an equal volume of either Syrup B.P. or Sorbitol Solution 70 per cent (non-crystallising) B.P. The diluted product is stable for 4 weeks at 25°C, but it is recommended that all dilutions are freshly prepared.
When a dilution of Zovirax Oral Suspension 400 mg/5 ml is prescribed, it is recommended that the 200 mg/5 ml suspension is dispensed.
Keep dry.

List of Excipients

200 mg tablets: Lactose monohydrate, Microcrystalline Cellulose, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate.

400 mg tablets: Microcrystalline Cellulose, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate.

800 mg tablets: Microcrystalline Cellulose, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate.

200 mg Dispersible tablets: Microcrystalline Cellulose, Aluminium Magnesium Silicate, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate, white pigment 7000, Polyethylene Glycol 8000.

400 mg Dispersible tablets: Microcrystalline Cellulose, Aluminium Magnesium Silicate, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate, white pigment 7000, Polyethylene Glycol 8000.

800 mg Dispersible tablets: Microcrystalline Cellulose, Aluminium Magnesium Silicate, Sodium Starch Glycollate, Povidone K30, Magnesium Stearate, white pigment 7000, Polyethylene Glycol 8000.

Further Information

Instructions for Use/Handling

Dispersible Tablets: Zovirax Dispersible Tablets may be swallowed whole with a little water, or dispersed in a minimum of 50 ml of water.

Oral Suspensions:
Dilution:
Zovirax Oral Suspension, 200 mg/5 ml, 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.
When a dilution of Zovirax Oral Suspension, 400 mg/5 ml is prescribed, it is recommended that the 200 mg/5 ml suspension is dispensed.

Pre-clinical Safety

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.

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 information on the effect of Zovirax Oral Formulations on human female fertility. In patients with normal sperm count, chronically administered oral aciclovir has been shown to have no clinically significant effect on sperm count, motility or morphology.

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