

PACKAGE INSERT TEMPLATE FOR ACYCLOVIR DISPERSIBLE TABLET & ACYCLOVIR ORAL SUSPENSION

Brand or Product Name

[Product name] Dispersible Tablet 200mg

[Product name] Dispersible Tablet 800mg

[Product name] Oral Suspension 200mg/5ml

Name and Strength of Active Substance(s)

[Dispersible Tablet]

Acyclovir 200mg

Acyclovir 800mg

[Oral suspension]

Acyclovir 200mg/5ml

Product Description

[Visual description of the appearance of the product (eg colour, markings etc) eg :

Tablet - White, circular flat beveled edge film-coated dispersible tablets marked '100' on one side

Oral suspension - Clear, orange-colored viscous syrup with the odour and flavor of oranges and sweet taste]

Pharmacodynamics

Acyclovir 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, acyclovir 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 Acyclovir 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 Acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

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Prolonged or repeated courses of Acyclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued acyclovir 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 acyclovir 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 acyclovir therapy is not clear.

Pharmacokinetics

Acyclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations ($C^{ss}max$) following doses of 200mg administered four-hourly were 3.1 μ Mol (0.7 μ g/ml) and equivalent trough plasma levels ($C^{ss}min$) were 1.8 μ Mol (0.4 μ g/ml). Corresponding $C^{ss}max$ levels following doses of 400mg and 800mg administered four-hourly were 5.3 μ Mol (1.2 μ g/ml) and 8 μ Mol (1.8 μ g/ml) respectively, and equivalent $C^{ss}min$ levels were 2.7 μ Mol (0.6 μ g/ml) and 4 μ Mol (0.9 μ g/ml).

In adults the terminal plasma half life of acyclovir after administration of intravenous acyclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of acyclovir 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 acyclovir and accounts for approximately 10-15% of the administered dose recovered from the urine.

When acyclovir 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 $C^{ss}max$ levels following a one-hour infusion of 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7 μ Mol (5.1 μ g/ml), 43.6 μ Mol (9.8 μ g/ml) and 92 μ Mol (20.7 μ g/ml), respectively. The corresponding $C^{ss}min$ levels 7 hours later were 2.2 μ Mol (0.5 μ g/ml), 3.1 μ Mol (0.7 μ g/ml) and 10.2 μ Mol (2.3 μ g/ml), respectively. In children over 1 year of age similar mean $C^{ss}max$ and $C^{ss}min$ 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 $C^{ss}max$ was found to be 61.2 μ Mol (13.8 μ g/ml) and the $C^{ss}min$ to be 10.1 μ Mol (2.3 μ g/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

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mean acyclovir half life during haemodialysis was 5.7 hours. Plasma acyclovir 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.

Indication

Acyclovir Dispersible Tablets and Acyclovir Oral Suspension are indicated for

- the treatment of Herpes simplex virus infections of the skin and mucous membranes, including initial and recurrent genital herpes.
- the suppression (prevention of recurrence) of recurrent Herpes simplex infections in immune-competent patients.
- the prophylaxis of Herpes simplex infections in immune-compromised patients.
- the treatment of Varicella (Chickenpox) and Herpes zoster (Shingles) infections.

Studies have shown that early treatment of shingles with acyclovir has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zoster-associated pain).

Recommended Dosage

Dosage for treatment of Herpes simplex in adults

For treatment of Herpes simplex infections, 200mg acyclovir 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 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 acyclovir should be taken four times daily at approximately six-hourly intervals. Many patients may be conveniently managed on a regimen of 400mg acyclovir taken twice daily at approximately twelve-hourly intervals. Dosage titration down to 200mg acyclovir taken three times daily at

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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 800mg 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.

Dosage for prophylaxis of Herpes simplex in adults

For prophylaxis of Herpes simplex infections in immune-compromised patients, 200mg acyclovir should be taken four times daily at approximately six-hourly intervals. 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 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 Varicella and Herpes zoster in adults

For treatment of Varicella and Herpes zoster infections, 800mg acyclovir 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, and for prophylaxis of Herpes simplex infections in the immune-compromised, 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.

For treatment of Varicella infections, children over the age of six years can be given 800mg Acyclovir four times daily and children between the ages of two and six years can be given 400mg acyclovir four times daily.

Children below the age of two years can be given 200mg acyclovir four times daily. Dosing may be more accurately calculated as 20mg acyclovir/kg bodyweight (not to exceed 800mg) four times daily.

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Treatment should continue for five days. No specific data are available on the suppression of Herpes simplex infections or the treatment of Herpes zoster infections in immunocompetent children.

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

Dosage in renal impairment

In the management of Herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of Acyclovir 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 Varicella and Herpes zoster infections 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 10 ml/minute) and to 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).

Mode of Administration

Oral

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

Contraindications

Acyclovir Dispersible Tablets and Acyclovir Oral Suspensions are contraindicated in patients known to be hypersensitive to acyclovir.

Warnings and Precautions

Mutagenicity

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that acyclovir is unlikely to pose a genetic risk to man.

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Carcinogenicity

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

Teratogenicity

Systemic administration of acyclovir 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 acyclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of orally administered acyclovir on fertility.

There is no experience of the effect of acyclovir tablets on human female fertility. Acyclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man. All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Interactions with Other Medicaments

Probenecid increases the acyclovir mean half life and area under the plasma concentration-time curve. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of acyclovir. However, clinical experience has not identified other drug interactions with acyclovir.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Limited data are available on the use of acyclovir in pregnancy. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

Lactation

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

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Adverse Effects / Undesirable Effects

Skin rashes have been reported in a few patients receiving acyclovir oral formulations; the rashes have resolved on withdrawal of the drug.

Gastrointestinal effects, including nausea, vomiting, diarrhoea and abdominal pains have been reported in some patients receiving acyclovir oral formulations.

The incidence of gastrointestinal events has not been found to differ between placebo and acyclovir recipients.

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

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

Other events reported rarely in patients receiving oral formulations of acyclovir include mild, transient rises in bilirubin and liver-related enzymes, small increases in blood urea and creatinine, small decreases in haematological indices, headaches and fatigue.

In patients receiving anti-retroviral therapy (mainly oral zidovudine), no significant increase in toxicity was associated with the addition of acyclovir.

Overdose and Treatment

Acyclovir is only partly absorbed in the gastrointestinal tract. It is unlikely that serious toxic effects would occur if a dose of up to 5g were taken on a single occasion. No data are available on the consequences of the ingestion of higher doses. Single intravenous doses of up to 80mg/kg have been inadvertently administered without adverse effects.

Treatment

Ingestion of doses of acyclovir in excess of 5g warrants close observation of the patient. Acyclovir is dialysable by haemodialysis.

Instruction for Use

Acyclovir Oral Suspension 200mg/5ml may be diluted with an equal volume of either Syrup BP or Sorbitol Solution 70 per cent (Non-crystallising), BP. It is recommended that all dilutions are

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freshly prepared. Where a dilution of Acyclovir Oral Suspension, 400mg/5ml is prescribed, it is recommended that the 200mg/5ml suspension is dispensed.

Storage Conditions

Finished product - Store below°C

Diluted product of oral suspension – Store below°C for weeks]

Dosage Forms and Packaging Available

[Packaging type & pack size eg

Tablet - Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box

Oral suspension – amber glass bottle of 60ml/box]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]