



New Zealand Data Sheet

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

Presentation

APO-ACYCLOVIR 200mg tablets are blue, round, flat, bevelled-edged, compressed tablets imprinted with APO over 200 on one side. Each tablet contains 200mg acyclovir and typically weighs 280mg.

APO-ACYCLOVIR 400mg tablets are pink, round, flat, bevelled-edged, compressed tablets imprinted with APO 400 on one side. Each tablet contains 400mg acyclovir and typically weighs 500mg.

APO-ACYCLOVIR 800mg tablets are blue, biconvex elongated, scored, compressed tablets, imprinted with APO 800 on one side. Each tablet contains 800mg acyclovir and typically weighs 1000mg.

Uses

Actions

Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, varicella-zoster virus, Epstein-Barr virus and to a lesser extent cytomegalovirus

Acyclovir has an antiviral effect on herpes simplex viruses and varicella zoster virus resulting from its interference with DNA synthesis leading to inhibition of virus replication. The exact mechanism of acyclovir action in other susceptible viruses has not been fully elucidated.

Acyclovir triphosphate is the pharmacologically active metabolite of the drug. The initial phosphorylation of acyclovir to acyclovir monophosphate is catalyzed by virus-induced thymidine kinase. Thus selective activation of the drug is achieved principally in infected cells. Further phosphorylation to acyclovir diphosphate is catalyzed via cellular guanylate kinase and then phosphorylation to acyclovir triphosphate is catalysed via other intracellular enzymes (phosphoglycerate kinase, pyruvate kinase, phosphoenolpyruvate carboxykinase). The extent of formation of acyclovir monophosphate, diphosphate and triphosphate is directly related to the concentration of acyclovir in the cellular culture medium. In vitro studies indicate that acyclovir triphosphate is produced in low concentrations via unidentified cellular phosphorylating enzymes in cells infected with Epstein-Barr virus and cytomegalovirus.

Acyclovir triphosphate inhibits DNA synthesis by competing with deoxyguanosine triphosphate for viral DNA polymerase. Viral DNA polymerase exhibits a 10- to 30-fold greater affinity for acyclovir triphosphate than does cellular α -DNA polymerase. Following incorporation of acyclovir triphosphate into the growing viral DNA chain, DNA synthesis is terminated. Cytomegalovirus does not produce thymidine kinase and so the antiviral activity of acyclovir in cytomegalovirus-induced infections is poor. The selective action of acyclovir on the infected cells is due to poor uptake of acyclovir into uninfected cells, minimal phosphorylation of acyclovir to acyclovir monophosphate in uninfected cells and low cellular DNA polymerase affinity for acyclovir triphosphate.

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

Pharmacokinetics

Following oral administration absorption of acyclovir is slow, variable and incomplete. The bioavailability of oral acyclovir is low (15% to 30% of an oral dose is absorbed) and decreases with increasing dosage. Peak plasma concentrations occur within 1.5 and 2.5 hours after oral administration.

In an uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200mg to 1000mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200mg dose were 0.49µg/mL (0.47 - 0.54µg/mL) and 0.31µg/mL (0.18 - 0.41µg/mL) respectively, and following the final 800mg dose were 2.8µg/mL (2.3 - 3.1µg/mL) and 1.8µg/mL (1.3 - 2.5µg/mL) respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4µg/mL (0.66 - 1.8µg/mL) and 0.55µg/mL (0.14 - 1.1µg/mL) respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300mg/m² and 600mg/m² in children aged 7 months to 7 years was 2.6 hours (range 1.59 - 3.74 hours).

Some data suggest that the absorption of acyclovir is a saturable process. In a multiple-dose cross-over study where 23 volunteers received acyclovir as one 200mg capsule, one 400mg tablet and one 800mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15% and 10% respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200mg to 800mg. In this study steady state peak and trough concentrations of aciclovir were 0.83 and 0.46µg/mL, 1.21 and 0.63µg/mL, and 1.61 and 0.83µg/mL for the 200mg, 400mg and 800mg dosage regimens respectively.

Absorption is not markedly affected by food.

Acyclovir is widely distributed into body tissues and fluids, including principally the kidney, brain, liver, muscle, spleen, uterus, saliva, vaginal mucosa and secretions, cerebrospinal fluid and hepatic vesicular fluid. The apparent volume of distribution of acyclovir is 32.4L to 61.8L per 1.73m² in adults.

Acyclovir is approximately 9% to 33% bound to plasma proteins at plasma concentrations of 0.41 to 4.2µg/mL.

The plasma concentrations of acyclovir appear to decline in a biphasic manner. In adult patients with normal renal function, the elimination half-life of acyclovir in the initial phase is 0.34 hours and in the terminal phase 2.1 to 3.5 hours. In neonates up to 3 months of age the elimination half-life appears to be slightly prolonged (1.5 to 4.0 hours) with the total body clearance being much less.

Acyclovir is excreted mainly through the kidneys by glomerular filtration and tubular secretion with 8.5 – 14% of the dose being oxidised to 9-carboxymethoxymethylguanine. Less than 2% of an administered dose is excreted in the faeces.

Up to 80% of a dose may be excreted unchanged in the urine. In anuric patients the elimination half-life may be extended to 19.5 hours.

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

The clearance of acyclovir depends on renal function. Total body clearance of acyclovir is reported as 327, 248, 190 or 29mL/min per 1.73m² in patients with creatine clearance greater than 80, 50-80, 15-50 or 0 mL/min per 1.73m² respectively.

Acyclovir is removed by haemodialysis and peritoneal dialysis. A single 6-hour course of haemodialysis reduced acyclovir concentrations by 50% - 60%.

Indications

Apo-Acyclovir tablets are indicated for the treatment of herpes simplex infections including initial episodes and the management of recurrent episodes of genital herpes, suppression of herpes simplex infection in immune-compromised patients and for the acute treatment of herpes zoster (shingles).

Genital Herpes Infections

Initial Episodes –

The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe disease.

Recurrent Episodes –

In patients with frequent recurrences (6 or more episodes per year) chronic suppressive therapy may be appropriate, if in the judgement of the physician the benefits of such a regimen outweigh known or potential adverse effects. After 1 year of therapy the need for acyclovir should be reassessed. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy.

Limited studies have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Herpes Zoster Infections

Acyclovir is indicated for acute treatment, for reduction of the duration and severity of acute symptoms and rash, for reduction of zoster-associated pain and for reduction of the incidence and duration of post-herpetic neuralgia.

Immunosuppressed Patients

Acyclovir is indicated for the management of patients with severe AIDS who have a CD4 count of less than 50/μL. Studies have shown that oral acyclovir given in conjunction with anti-retroviral therapy reduced mortality in patients with advanced HIV disease.

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

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

Dosage and Administration

Herpes Simplex:

Treatment of Herpes Simplex-

For adults and children over 2 years, 200mg 5 times daily (approximately every 4 hours) for 5 days although this may need to be extended in severe initial infections. For children under 2 years, half the adult dose. In severely immune-compromised patients or in patients with impaired absorption from the gut, the dose can be doubled to 400mg or intravenous dosing can be considered. Dosage should be as soon as possible after the start of the infection. For recurrent episodes this should preferably be in the prodromal period or when lesions first appear.

Suppression of Herpes Simplex-

In immune-competent patients 200mg 4 times daily (approximately every 6 hours). Many patients may be managed on 400mg doses taken twice daily at approximately 12 hourly intervals. Dosage titration down to either 200mg 3 times daily or twice daily may be effective. The patients condition should be reassessed every 6 - 12 months.

Prophylaxis of Herpes Simplex-

In immune-compromised patients 200mg every 4 times daily (approximately every 6 hours) although in severely immune-compromised patients or in patients with impaired absorption from the gut the dose may be increased to 400mg or intravenous dosing could be considered. The duration of prophylactic administration is determined by the duration of the period at risk.

Herpes Zoster

800mg 5 times daily (approximately every 4 hours) for 7 days. Dosing should begin as soon as possible after the onset of infection. Best results are obtained if treatment begins within 48 hours of the onset of the rash.

Patients with severe AIDS with CD4 count < 50/ μ L

For adults and children over 2 years of age, 800mg every 6 hours 4 times daily. In patients with advanced HIV disease, 12 months treatment has been studied but it is likely that these patients would continue to benefit from a longer duration of treatment.

Allogenic Bone Marrow Transplant Patients

800mg every 6 hours 4 times daily. This would normally be preceded by up to one month's therapy with intravenous acyclovir. The duration of treatment studied was 6 months (from 1 to 7 months post-transplant).

Elderly Patients

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.

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

Patients with Acute or Chronic Renal Impairment

The following dosage adjustments are recommended for genital herpes and herpes zoster indications: -

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m ²)	Adjusted Dosage Regimen
200mg every 4 hours	>10 0 – 10	200mg every 4 hours, 5x daily 200mg every 12 hours
400mg every 12 hours	>10 0 – 10	400mg every 12 hours 200mg every 12 hours
800mg every 4 hours	>25 10 – 25 0 – 10	800mg every 4 hours, 5x daily 800mg every 8 hours 800mg every 12 hours

Haemodialysis

The mean plasma half-life of acyclovir during haemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentration following a 6 hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.

Contraindications

Apo-Acyclovir tablets are contraindicated in patients with a hypersensitivity to acyclovir

Warnings and Precautions

Apo-Acyclovir tablets should be used with caution in patients with impaired renal function to prevent accumulation of the drug and to decrease the risk of nephrotoxicity and neurotoxicity.

Both the dose and the dosing interval should be carefully adjusted in patients undergoing haemodialysis to maintain adequate plasma concentrations of acyclovir.

Apo-Acyclovir tablets should be used with caution in patients with underlying neurologic abnormalities, in patients with nutritional and metabolic disorders (dehydration, electrolyte abnormalities) and in patients with impaired kidney and liver function.

The recommended dosage should not be exceeded.

The possibility of the appearance of less sensitive viruses in humans must be considered when treating patients. Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy.

Use in Pregnancy and Lactation

Category B3.

There are no adequate and well-controlled studies in pregnant women. Apo-Acyclovir tablets should not be used during pregnancy unless the potential benefit justifies the potential risk to the

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

foetus. Although acyclovir is not teratogenic in standard animal studies, the drug's potential for causing chromosomal breaks at high concentrations should be taken into consideration in making this determination

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3mg/kg/day. Caution should be exercised when Apo-Acyclovir tablets are administered to a nursing woman.

Adverse Effects

Acyclovir is generally well-tolerated and adverse events are uncommon. Reported adverse events are:-

General - fever, headache, pain, peripheral oedema, and rarely anaphylaxis

Neurological - confusion, dizziness, hallucinations, paraesthesia, somnolence

Digestive - diarrhoea, elevated liver function tests, gastrointestinal distress, nausea and vomiting

Haemic and Lymphatic - leukopenia, lymphadenopathy

Musculoskeletal – myalgia

Skin - alopecia, pruritis, rash, urticaria

Special Senses - visual abnormalities

Urogenital - elevated creatinine

Interactions

Probenicid - co-administration of probenecid with intravenous acyclovir increases the terminal half-life of acyclovir by 18% and the area under the concentration-time curve by 40% as a result of decreased tubular secretion of acyclovir. Urinary excretion and renal clearance are correspondingly reduced.

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

Overdosage

Patients have ingested intentional overdoses of up to 20g of acyclovir with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5mg/mL) in the intratubular fluid is exceeded. Ingestion of doses of acyclovir in excess of 5g warrants close observation of the patient.

A 6-hour haemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from haemodialysis until renal function is restored.

APO-ACYCLOVIR

Acyclovir 200mg, 400mg and 800mg tablets USP

Pharmaceutical Precautions

Store below 25°C.
Protect from heat, light and moisture.

Medicine Classification

Prescription Only Medicine

Package Quantities

Apo-Acyclovir 200mg: Bottle packs of 25, 50, 100, 250 and 500 tablets.
Blister packs of 25 tablets.

Apo-Acyclovir 400mg: Bottle packs of 50, 56, 100, 250 and 500 tablets.
Blister packs of 56 tablets.

Apo-Acyclovir 800mg: Bottle packs of 35, 50, 100, 250 and 500 tablets.
Blister packs of 35 tablets.

Further Information

Apo-Acyclovir 200mg tablets contain lactose. Colouring agents used are Indigotine Lake (200mg tablets), red ferric oxide (400mg tablets) and Brilliant Blue Lake (800mg tablets).

Name and Address

Apotex NZ Ltd
32 Hillside Road
Glenfield
Private Bag 102-995
North Shore Mail Centre
Auckland
Tel: (09) 444-2073
Fax: (09) 444-2951

Date of Preparation

24 January 2000