APO-ACYCLOVIR 400MG TABLETS
Acyclovir Tablets

Antiviral Agent

Pharmacology : Acyclovir, a synthetic acyclic purine nucleoside analog, is a substrate with a high degree of specificity for herpes simplex and varicella-zoster specified thymidine kinase. Acyclovir is a poor substrate for host cell-specified thymidine kinase. Herpes simplex and varicella-zoster specified thymidine kinase transform acyclovir to its monophosphate which is then transformed by a number of cellular enzymes to acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate is both an inhibitor of, and a substrate for, herpesvirus-specified DNA polymerase. Although the cellular α-DNA polymerase in infected cells may also be inhibited by acyclovir triphosphate, this occurs only at concentrations of acyclovir triphosphate which are higher than those which inhibit the herpesvirus-specified DNA polymerase. Acyclovir is selectively converted to its active form in herpesvirus-infected cells and is thus preferentially taken up by these cells. Acyclovir has demonstrated a very much lower toxic potential in *vitro* for normal uninfected cells because : 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase has a lower sensitivity to the action of the active form of the drug. A combination of the thymidine kinase specificity, inhibition of DNA polymerase and premature termination of DNA synthesis results in inhibition of herpesvirus replication. No effect on latent non-replicating virus has been demonstrated. Inhibition of the virus reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing. During suppression there is no evidence that acyclovir prevents neural migration of the virus. It aborts episodes of recurrent herpes due to inhibition of viral replication following reactivation.
The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection given acyclovir capsules in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, the bioavailability was estimated to be 15 to 20%. In this study, steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the last 200 mg dose were 0.49 μg/mL (0.47 to 0.54 μg/mL) and 0.31 μg/mL (0.18 to 0.41 μg/mL), respectively and following the last 800 mg dose were 2.8 μg/mL (2.3 to 3.1 μg/mL) and 1.8 μg/mL (1.3 to 2.5 μg/mL). In another study, 20 immunocompetent patients with recurrent genital herpes simplex infections given acyclovir capsules in doses of 800 mg every 6 hours, 4 times daily for 5 days, the mean steady-state peak and trough concentrations were 1.4 μg/mL (0.66 to 1.8 μg/mL) and 0.55 μg/mL (0.14 to 1.1 μg/mL).

Indications : **APO-ACYCLOVIR** (acyclovir) is indicated for the following conditions :
The treatment of initial episodes of herpes genitalis.
The suppression of unusually frequent recurrences of herpes genitalis (6 or more episodes per year).
The acute treatment of herpes zoster (shingles).
The results of clinical studies suggest that some patients with recurrent genital herpes may derive clinical benefit from the administration of oral acyclovir if taken at the first sign of an impending episode. Those most likely to benefit are patients who experience severe, prolonged recurrences; such intermittent therapy may be more appropriate than suppressive therapy when these recurrences are infrequent.
Early treatment of acute herpes zoster (shingles) in immune competent individuals with oral acyclovir resulted in decreased viral shedding; decreased time to healing; less dissemination; and alleviation of acute pain.

Adverse Effects :
Treatment of Herpes Simplex :
Short-Term Administration (5-10 days) :
The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with oral acyclovir in 298 patients are listed below : -

Adverse Reactions	Total	Percent (%)
Nausea and/or vomiting	8	2.7
Headache	2	0.6

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments (0.3%), included : diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.
Suppression : Long-Term Administration :
The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily are nausea, diarrhea, headache, rash, paresthesia and asthenia.
Evidence so far from clinical trials suggests that the severity and frequency of adverse events is unlikely to necessitate discontinuation of therapy.
Herpes Zoster :

The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 or 10 days or placebo are malaise, nausea, headache, vomiting, diarrhea and constipation.

Precautions : General : The recommended dosage and length of treatment should not be exceeded (see DOSAGE). Acyclovir has caused mutagenesis in some acute studies at high concentrations of drug. Also, decreased spermatogenesis was observed in some animals at high parenteral doses. However, no adverse effects on sperm counts were reported in humans given recommended oral doses of acyclovir.
The decision to prescribe a course of suppressive therapy should be weighed in the light of present knowledge about the long-term effects of acyclovir and must clearly relate to the condition of the patient.
It is suggested that periodic discontinuation of the suppressive regimen occur so that the patient's status and need for continued suppressive therapy can be monitored.
Whereas cutaneous lesions associated with herpes simplex infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in the diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis. Appropriate examinations should be performed to rule out other sexually transmitted diseases. 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.
Caution should be exercised when administering to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.
Use in Pregnancy : Teratology studies carried out to date in animals have been negative in general. However, in a non-standard test in rats, there were fetal abnormalities such as head and tail anomalies, and maternal toxicity; since such studies are not always predictive of human response.
APO-ACYCLOVIR (acyclovir) should not be used during pregnancy unless the physician feels the potential benefit justifies the risk of possible harm to the fetus. The potential for high concentrations of acyclovir to cause chromosome breaks in *vitro* should be taken into consideration in making this decision.
Nursing Mothers : Acyclovir is excreted in human milk. Caution should therefore be exercised when APO-ACYCLOVIR is administered to a nursing mother.
Use in Children : Safety and effectiveness in children less than 2 years of age have not been adequately studied.

Warnings : Suppressive therapy of herpes genitalis with **APO-ACYCLOVIR** (acyclovir) should be considered only for severely affected patients. Periodic evaluation of the need for continued suppressive therapy is recommended. In some patients, there is a tendency for the first recurrent episode to be more severe following cessation of suppressive therapy.
In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses associated with infections which may not respond.

Contraindications : **APO-ACYCLOVIR** (acyclovir) is contraindicated for patients who develop hypersensitivity or who are hypersensitive to the components of the formulation.

Drug Interactions : Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

Dosage : Herpes Genitalis :
Treatment of Initial Infection : 200 mg every 4 hours, 5 times daily, for a total of 1 gram daily for 10 days. Therapy should be initiated as early as possible following onset of signs and symptoms.
Suppressive Therapy for Recurrent Disease : The initial dose recommended is 200 mg three times daily. This can be increased if breakthrough occurs up to a dosage of 200 mg 5 times daily. If necessary, a dose of one 400 mg tablet (two 200 mg tablets) given twice daily may be considered. Periodic re-evaluation of the need for therapy is recommended.
Administration of **APO-ACYCLOVIR** (acyclovir) for intermittent therapy is one 200 mg tablet every 4 hours 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.
Herpes Zoster : 800 mg every 4 hours, 5 times daily for 7 to 10 days. Treatment should be initiated within 72 hours of the onset of lesions. In clinical trials, the greatest benefit occurred when treatment was begun within 48 hours of the onset of lesions.
Patients with acute or chronic renal impairment : Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment.
Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications :

Normal Dosage Regimen (5 x daily)	Creatinine Clearance (mL/min/1.73m^2)	Adjust Dosage Regimen	
		Dose(mg)	Dosing Interval(hours)

200 mg every 4 hours	> 10 0-10	200 200	every 4 hours,5 x daily every 12 hours
400 mg every 12 hours	> 10 0-10	400 200	every 12 hours every 12 hours
800 mg every 4 hours	> 25 10-25 0-10	800 800 800	every 4 hours,5 x daily every 8 hours every 12 hours

Hemodialysis : For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-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 supplement dose appears to be necessary after adjustment of the dosing interval.

Children : For treatment of herpes simplex infections, and for prophylaxis of herpes simplex infections in the immune-compromised, children 2 years and over should be given adult dosages and children <2 years should be given ½ the adult dose.

For treatment of varicella infections, children >6 years : 800 mg 4 times daily ; 2-6 years : 400 mg 4 times daily; below 2 years : 200 mg 4 times daily. Dosing may be more accurately calculated as 20 mg **APO-ACYCLOVIR**/kg body weight (not to exceed 800 mg) 4 times daily. Treatment should continue for 5 days.

Symptoms And Treatment Of Overdosage : Overdosage of **APO-ACYCLOVIR** (acyclovir) during oral use is unlikely because of incomplete bioavailability from the gastrointestinal tract. Doses as high as 800 mg 6 times daily for 5 days have been administered to humans without untoward effects. In clinical studies, the highest plasma concentration observed in a single patient at these doses was 10.0 μg/mL.
Intravenous doses administered to humans have been as high as 1200 mg/m^2 (28 mg/kg) 3 times daily for up to 2 weeks. Peak plasma concentrations have reached 80 μg/mL. No acute massive overdosage of acyclovir has been reported; however, in the case of an excessively high ingestion of acyclovir, precipitation of acyclovir in renal tubules may occur if the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. In the event of renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored.

Availability Of Dosage Forms :
APO-ACYCLOVIR (acyclovir) 400 mg :
Pink, round, flat-faced, bevelled-edge tablet, engraved APO over 400 on one side, other side plain.
Available in HDPE bottles of 25 tablets and 100 tablets.

Storage : Store below 30°C.

Manufacturer: Apotex Inc, 150 Signet Drive, Weston (Toronto), Ontario, Canada, M9L 1T9.

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