Xovir
Acyclovir

COMPOSITION
Xovir 200 Tablet: Each tablet contains Acyclovir USP 200 mg.
Xovir 400 Tablet: Each tablet contains Acyclovir USP 400 mg.
Xovir Suspension: Each 5 mL suspension contains Acyclovir USP 200 mg.
Xovir Injection : Each vial contains Acyclovir Sodium equivalent to Acyclovir USP 250 mg.
Xovir 500 Injection: Each vial contains Acyclovir Sodium equivalent to Acyclovir USP 500 mg.
Xovir 1g Injection: Each vial contains Acyclovir Sodium equivalent to Acyclovir USP 1 g.

PHARMACOLOGICAL INFORMATION
Therapeutic class: Antiviral agent

PHARMACOLOGICAL ACTION
Mechanism of action
Acyclovir 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, 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 and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected 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.

CLINICAL PHARMACOLOGY
Pharmacokinetic Properties
Acyclovir exerts its antiviral effect on herpes simplex viruses (HSV) and varicella-zoster virus by interfering with DNA synthesis and inhibiting viral replication. The exact mechanisms of action against other susceptible viruses have not fully elucidated. In vitro studies with herpes simplex viruses indicate that Acyclovir triphosphate is the pharmacologically active form of the drug; the triphosphate functions as both a substrate for and preferential inhibitor of viral DNA polymerase. Absorption of Acyclovir from the GI tract is variable and incomplete. It is estimated that 15-30% of an oral dose of the drug is absorbed . Acyclovir is widely distributed into body tissues and fluids including the brain, kidney,saliva, lung, liver, muscle, spleen, uterus, vaginal mucosa and secretions, CSF, and herpetic vesicular fluid. The drug is also distributed into semen,achieving concentrations about 1.4 and 4 times those in plasma during chronic oral therapy at dosages of 400 mg and 1 g daily, respectively. Plasma concentrations of Acyclovir appear to decline in a biphasic manner. In adults with normal renal function, the half-life of Acyclovir in the initial phase averages 0.34 hours and the half-life in the terminal phase averages 2.1-3.5 hours. The pharmacokinetics of Acyclovir after intravenous administration have been evaluated in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing. Average steady state peak and trough concentrations from 1 hour infusions administered every 8 hours are given in Table:

Dosage Regimen	C^{SS} max	C^{SS} trough
5 mg/kg q 8 hr (n=8)	9.8 mcg/mL range: 5.5 to 13.8	0.7 mcg/mL range: 0.2 to 1.0
10 mg/kg q 8 hr (n=7)	22.9 mcg/mL range: 14.1 to 44.1	1.9 mcg/mL range: 0.5 to 2.9

C^{SS} max = Maximum concentration after infusion C^{SS} trough = Normal concentration after infusion

Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.

Renal excretion of unchanged drug is the major route of Acyclovir elimination accounting for 62% to 91% of the dose. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine accounting for up to 14.1% of the dose in patients with normal renal function.

CLINICAL INFORMATION
Therapeutic Indications
Xovir is indicated for the treatment of

- Herpes Simplex Infections in Immunocompromised Patients
- Initial and recurrent mucosal and cutaneous Herpes Simplex (HSV-1 and

HSV-2) in immunocompromised patients.

- Initial Episodes of Herpes Genitalis
- Severe initial clinical episodes of Herpes Genitalis in immunocompetent patients.
- Herpes Simplex Encephalitis
- Neonatal Herpes Simplex Virus Infection
- Varicella-Zoster Infections in Immunocompromised Patients

Dosage and Administration

Xovir Tablet:

Acute Treatment of Herpes Zoster: 800 mg every 4 hours orally, 5 times daily for 7 to 10 days.

Genital Herpes: Treatment of Initial Genital Herpes:200 mg every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg 2 times daily for up to 12 months, followed by re-evaluation.Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily. The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with XOVIR.

Intermittent Therapy: 200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of Chickenpox: Children (2 years of age and older): 20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and Children over 40 kg: 800 mg 4 times daily for 5 days.Intravenous XOVIR is indicated for the treatment of varicella-zoster infections in immunocompromised patients. When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

Xovir Suspension:

Children (Two Years of Age and Older): 20 mg/kg per dose orally four times daily (80 mg/kg/day) for five days. Children over 40 kg should receive the adult dose.

Xovir Injection:

Indication	Immune status	Dosage
Herpes simplex infection	Normal or immunocompromised	5 mg/kg every 8 hours
Herpes simplex encephalitis	Normal or immunocompromised	10 mg/kg every 8 hours
Very severe Herpes ***zoster*** infection (shingles)	Normal	5 mg/kg every 8 hours
Varicella zoster infection	Immunocompromised	10 mg/kg every 8 hours

Each dose should be administered by slow intravenous infusion over a one-hour period.

Dosage in children: The dose of Xovir Injection in children aged 1-12 years should be calculated on the basis of body surface area.

Children in this age group with Herpes simplex infections (except Herpes simplex encephalitis) or Varicella zoster infections should be given Xovir Injection in doses of 250 mg per square metre of body surface area (equivalent to 5 mg/kg in adults).

Immunocompromised children in this age group with Varicella zoster virus infection or with Herpes simplex encephalitis should be given Xovir Injection in doses of 500 mg per square metre of body surface area (equivalent to 10 mg/kg in adults).

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Dosage in Neonates and infant up to 3 months: The dosage of Xovir Injection in neonates and infant up to 3 months of age is calculated on the basis of bodyweight.

Neonates and infant up to 3 months with Herpes simplex infections should be given Xovir Injection in doses of 10 mg/kg bodyweight every 8 hours. Treatment for neonatal herpes simplex infections usually lasts 10 days

Dosage in the Elderly: In the elderly total Acyclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Dosage Adjustments for Patients with Renal Impairment: Caution is advised when administering Xovir Injection to patients with impaired renal function.

The following adjustments in dosage are suggested:

Creatinine Clearance	Dosage
25-50 mL/min	The dose recommended above (5 or 10 mg/kg body weight or 500 mg/m^2) should be given every 12 hours.
10-25 mL/min	The dose recommended above (5 or 10 mg/kg bodyweight or 500 mg/m^2) should be given every 24 hours.
0 (anuric)–10 mL/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight or 500 mg/m^2) should be halved and administrated every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight or 500 mg/m^2) should be halved and administered every 24 hours and after dialysis.

Duration of treatment: It is recommended that Xovir can be administered for 5-7 days in the treatment of most infections and for at least 10 days in the treatment of Herpes simplex encephalitis.

Hemodialysis: For patients who require dialysis, the mean plasma half-life of Acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations 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.

Method of preparation
Reconstitution
The required dose of Xovir Injection should be administered by slow intravenous infusion over a one-hour period.

Xovir Injection: Xovir 250 mg vial should be reconstituted by using 10 mL of 0.9% w/v Sodium Chloride Solution (Xenosol) to provide a solution containing 25 mg Acyclovir per mL.

Xovir 500 Injection: Xovir 500 mg vial should be reconstituted by using 20 mL of 0.9% w/v Sodium Chloride Solution (Xenosol) to provide a solution containing 25 mg Acyclovir per mL.

Xovir 1g Injection: Xovir 1g vial should be reconstituted by using 20 mL of 0.9% w/v Sodium Chloride Solution (Xenosol) to provide a solution containing 50 mg Acyclovir per mL.

To reconstitute each vial, shake gently until the contents of the vial have dissolved completely with 0.9% w/v Sodium Chloride Solution (Xenosol). The reconstituted solution should be used within 12 hours.

Administration
After reconstitution Xovir Injection, Xovir 500 Injection & Xovir 1g Injection may be administered into vein over one hour by a controlled rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an Acyclovir concentration of not greater than 5 mg/mL (0.5% w/v) for administration by infusion:-

- Add the required volume of reconstituted solution to 0.9% w/v Sodium Chloride Solution (Xenosol), as recommended below and shake well to ensure proper mixing.
- For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4 mL reconstituted solution of Xovir Injection or Xovir 500 Injection (100 mg Acyclovir) added to 20 mL of infusion fluid.

For intravenous infusion
Powder of Xovir vial should be reconstituted and then, wholly or in part according to the dosage required, added to and mixed with at least 50 mL 0.9% w/v Sodium Chloride Solution (Xenosol). Powder of Xovir 500 vial should be reconstituted and then, wholly or in part according to the dosage required, added to and mixed with at least 100 mL 0.9% w/v Sodium Chloride Solution (Xenosol). Powder of Xovir 1g vial should be reconstituted and then, wholly or in part according to the dosage required, added to and mixed with at least 250 mL 0.9% w/v Sodium Chloride Solution (Xenosol). After addition of reconstituted Xovir Injection, Xovir 500 Injection & Xovir 1g Injection to 0.9% w/v Sodium Chloride Solution (Xenosol), the mixture should be shaken to ensure thorough mixing.

Xovir, Xovir 500 & Xovir 1g Injection is also compatible with the following infusion fluids and stable for up to 12 hours at room temperature (below 25°C) when diluted to a concentration not greater than 0.5% w/v Acyclovir.

- Sodium Chloride Intravenous Infusion (0.45% and 0.9% w/v)
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion
- Compound Sodium Lactate Intravenous Infusion (Hartman's Solution)

Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use and any

unused solution discarded. Reconstituted or diluted solution should not be refrigerated. Should any visible turbidity or crystallization appear in the solution before or during infusion, the preparation should be discarded.

Contraindications: Acyclovir is contraindicated for patients who develop hypersensitivity to Acyclovir or Valacyclovir.

Precautions: Precipitation of Acyclovir crystals in renal tubules can occur if the maximum solubility of free Acyclovir (2.5 mg/mL at 37° C in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure. Abnormal renal function (decreased creatinine clearance) can occur as a result of Acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Concomitant use of other nephro-toxic drugs, pre-existing renal disease, and dehydration make further renal impairment with Acyclovir more likely. Administration of Acyclovir by intravenous infusion must be accompanied by adequate hydration. When dosage adjustments are required they should be based on estimated creatinine clearance.

Overdosage: Overdosage of intravenous Acyclovir has resulted in elevations of serum creatinine, blood urea nitrogen & subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage. Haemodialysis significantly enhances the removal of Acyclovir from the blood and may, therefore, be considered an option in the management of overdose of this medicine.

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

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.

Carcinogenicity: Acyclovir was not found to be 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 & 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 information on the effect of Acyclovir I.V. for Infusion on human female fertility. In a study of 20 male patients with normal sperm count, oral Acyclovir administered at doses of up to 1 g per day for up to 6 months has been shown to have no clinically significant effect on sperm count, motility or morphology.

Side Effects: The side effects listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received Acyclovir at ~ 5 mg/kg (250 mg/m^2) 3 times daily, and approximately 300 patients who received ~ 10 mg/kg (500 mg/m^2) 3 times daily. The most frequent adverse reactions reported during administration of Acyclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received 10 mg/kg). Itching, rash or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients. The following hematologic abnormalities occurred at a frequency of less than 1%: anemia, neutropenia, thrombocytopenia, thrombocytosis, leukocytosis and neutrophilia. In addition, anorexia and hematuria were observed.

PHARMACEUTICAL INFORMATION

Storage condition

Store below 30°C and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Xovir 200 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Xovir 400 Tablet: Each commercial box contains 24 tablets in Alu-Alu blister pack.

Xovir Suspension: Each commercial box contains an amber PET bottle containing 70 mL suspension and a measuring cup.

Xovir Injection: Each combipack contains 1 vial of 250 mg Acyclovir Lyophilized Powder for Solution for Infusion, 1 bottle of 50 mL of 0.9% sodium chloride solution, 1 disposable 10 mL syringe, 1 infusion set and 1 hanger.

Xovir 500 Injection: Each combipack contains 1 vial of 500 mg Acyclovir Lyophilized Powder for Solution for Infusion, 1 bottle of 100 mL of 0.9% sodium chloride solution, 1 disposable 20 mL syringe, 1 infusion set and 1 hanger.

Xovir 1g Injection: Each combipack contains 1 vial of 1 g Acyclovir Lyophilized Powder for Solution for Infusion, 1 bottle of 250 mL of 0.9% sodium chloride solution, 1 disposable 20 mL syringe, 1 infusion set and 1 hanger.

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