

Acyclovir

Zovirax®

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Acyclovir Capsule (Cap 200 mg)

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Classification:

- ▶ **Antiinfective Agents**
 - ▶ Antivirals
- ▶ **Dermatological Agents**
 - ▶ Topical Antiinfectives
 - ▶ *Antivirals*
- ▶ **Oropharyngeal Agents**
 - ▶ Antivirals

Acyclovir is a synthetic deoxyguanosine analog and it is the prototype antiviral agent that is activated by viral thymidine kinase. The antiviral activity of acyclovir is primarily against herpes viruses (e.g., herpes simplex virus [HSV] and varicella-zoster virus [VZV]); although, it has limited efficacy against cytomegalovirus (CMV) and Epstein-Barr virus (EBV). The selective activity of acyclovir is due to its affinity for the thymidine kinase enzyme encoded by HSV and VZV. Acyclovir is approximately 10-times more potent against HSV-1 and -2 than against VZV. It has even less activity against CMV and EBV. The effectiveness of acyclovir against EBV is limited to actively infected cells; latent or persistent EBV infection is not affected. Acyclovir is not effective against the human immunodeficiency virus. Clinically, acyclovir is used in the treatment of herpes simplex, herpes genitalis, and herpes zoster infections. The FDA approved acyclovir in March 1982. It is available as oral, parenteral, and topical formulations.

Mechanism of Action: Acyclovir inhibits viral DNA synthesis. Acyclovir must be phosphorylated intracellularly to be active. Acyclovir is converted to the monophosphate by viral thymidine kinase, then to diphosphate by cellular guanylate kinase, and finally to the triphosphate by various cellular enzymes. Acyclovir triphosphate competitively inhibits viral DNA polymerase, and to a lesser extent human DNA polymerase. Acyclovir triphosphate also competes with the natural substrate, deoxyguanosine triphosphate, for incorporation into viral DNA. Formation of a complex at the end of the DNA strand may lead to irreversible inactivation of viral DNA polymerase. Herpes virus DNA polymerases differ in

sensitivity to acyclovir. Acyclovir is effective only against actively replicating viruses; it does not eliminate the latent herpes virus genome. The range of *in vitro* minimum inhibitory concentrations of acyclovir are as follows: HSV-1, 0.02—0.9 mcg/ml; HSV-2, 0.3—2.2 mcg/ml; VZV, 0.8—4 mcg/ml; CMV 2—57 mcg/ml; and EBV, 1.6 mcg/ml. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral thymidine kinase. Uninfected cells show only minimal phosphorylation of acyclovir, and there is only a small amount of acyclovir taken up into these cells. The concentration of acyclovir triphosphate is 40- to 100- times higher in HSV-infected cells than non-infected cells.

Viral resistance to acyclovir may occur due to loss of thymidine kinase activity, alterations in thymidine kinase substrate specificity, or decreased DNA-polymerase sensitivity. Alterations in these enzymes occur due to point mutations or base insertions or deletions in the specific genes. The most common mechanism of resistance is loss of thymidine kinase activity. These viral variants are also cross resistant to other antiviral agents activated by thymidine kinase (e.g., ganciclovir or penciclovir). Thymidine kinase negative variants of herpes virus may cause severe disease in infants and immunocompromised patients. Acyclovir-resistant herpes simplex virus has been seen in immunocompromised patients, patients with concurrent HIV infection, and immunocompetent patients with genital herpes. Repeated systemic treatment may lead to the development of viral resistance in immunosuppressed patients.

Pharmacokinetics: Acyclovir is administered topically, orally, or intravenously. Acyclovir distributes extensively, with the highest concentrations in the kidneys, liver, and intestines. CSF concentrations are about 50% of plasma, and acyclovir crosses the placenta. Protein binding is 9—33%.

Infected viral cells transform acyclovir to its active triphosphate, and a small proportion may be metabolized extracellularly. Renal elimination via glomerular filtration and tubular secretion of unchanged drug is the major route of elimination accounting for 62—91% of the dose. The only known urinary metabolite is 9-[(carboxy-methoxy)methyl]guanine. Probenecid can inhibit acyclovir renal clearance. The elimination half-life of acyclovir in patients with normal renal function is 2.5—3.3 hours.

•*Route-Specific Pharmacokinetics*

Oral Route

Acyclovir is poorly absorbed from the GI tract following oral administration. The oral bioavailability of acyclovir is 10—20%; bioavailability decreases with increasing dose. Increases in C_{max} are less than dose proportional with increasing dose (e.g., 200 mg C_{max}, 0.83 mcg/ml; 400 mg C_{max}, 1.21 mcg/ml; 800 mg C_{max}, 1.61 mcg/ml). Food does not affect absorption of acyclovir.

Intravenous Route

Following intravenous administration of acyclovir, the mean C_{max} is 9.8 mcg/ml with 5 mg/kg every 8 hours and 22.9 mcg/ml with 10 mg/kg every 8 hours.

Topical Route

Following topical application, there is minimal systemic absorption of acyclovir; no drug is detected in the blood or urine.

•*Special Populations*

Renal Impairment

In anuric patients, the elimination half-life of acyclovir may be as long as 19 hours. Dosage adjustments are required in patients with renal dysfunction. Following peritoneal dosing, the systemic bioavailability of acyclovir is about 61%. Six hours of hemodialysis will remove approximately 60% of the drug.

Pediatrics

In general, the pharmacokinetics of acyclovir in pediatric patients are similar to those of adults. The mean elimination half-life of oral acyclovir 300—600 mg/m² in pediatric patients aged 7 months to 7 years is 2.6 hours (range 1.59—3.74 hours). This is comparable to the elimination half-life of 2.5—3.3 hours seen in adults after oral administration.[\[28977\]](#) In one pharmacokinetic study, the mean elimination half-life of IV acyclovir in 12 patients aged birth to 3 months was 3.8 hours and in 16 patients aged 3 months to 12 years was 2.36 hours.[\[41766\]](#)

References

28977. Zovirax (acyclovir) package insert. Research Triangle Park, NC: GlaxoSmithKline; 2007 Oct.

41766. Zovirax (acyclovir sodium) injection package insert. Research Triangle Park, NC: GlaxoSmithKline; 2003 Nov.

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