

# Acyclovir

**Brand Name:** Zovirax

**Drug Class:** Opportunistic Infection and Other Drugs



## Drug Description

Acyclovir is a synthetic purine nucleoside analogue with activity against herpesviruses. [1]

## HIV/AIDS-Related Uses

Oral acyclovir is approved by the FDA for the treatment of initial and recurring episodes of herpes simplex virus (HSV-1) and genital herpes virus (HSV-2) infections in immunocompromised patients. Parenteral acyclovir is approved for the treatment of initial or recurrent HSV infections and herpes zoster infection (shingles) caused by varicella-zoster virus (VZV) in immunocompromised patients.[2] Topical acyclovir is approved for the treatment of initial episodes of genital herpes and HSV infections in immunocompromised patients; however, systemic acyclovir is more effective and may be preferred.[3]

## Non-HIV/AIDS-Related Uses

Oral acyclovir was approved by the FDA on December 10, 1997, for treatment of initial and recurrent genital herpes infection, herpes zoster infection, and adult varicella infection (chickenpox) caused by VZV. It is not recommended for use in the treatment of uncomplicated chickenpox in healthy children. Parenteral acyclovir is approved for severe initial episodes of genital herpes infection, neonatal HSV infection, and herpes simplex encephalitis in immunocompetent patients.[4]

## Pharmacology

Acyclovir inhibits HSV and VZV both in vitro and in vivo by interfering with DNA synthesis and inhibiting viral replication. Acyclovir is converted to acyclovir triphosphate by cellular kinases and is highly specific for thymidine kinase (TK) encoded by HSV and VZV. The activated phosphorylated form of acyclovir stops replication of viral DNA by competitive inhibition of viral DNA polymerase, incorporation into and termination of the viral DNA chain, and inactivation of viral DNA polymerase.[5] [6]

Acyclovir's absorption from the gastrointestinal (GI) tract is variable and incomplete; an estimated 10% to 30% of an oral dose is absorbed. Some data suggest that GI absorption of acyclovir may be saturable; in healthy adults, the extent of absorption decreases with increasing dose. Less than dose-proportional plasma concentration increases do not appear to be a function of the dosage form. Food does not appear to affect acyclovir's absorption. Peak plasma concentration of acyclovir usually occurs within 1.7 hours after oral administration and at the end of a 1-hour infusion with IV administration.[7] [8]

Acyclovir is widely distributed into body tissues and fluids, including the brain, kidney, saliva, lung, liver, muscle, spleen, uterus, vaginal mucosa and secretions, cerebrospinal fluid (CSF), herpetic vesicular fluid, and semen. The reported apparent volume of distribution of acyclovir is 32.4 to 61.8 l/1.73 m<sup>2</sup> in adults. Following IV infusion, acyclovir generally diffuses well into CSF; in patients with uninflamed meninges, reported CSF concentrations of acyclovir are approximately 50% of concurrent serum acyclovir concentrations.[9]

Acyclovir is in FDA Pregnancy Category B. There are no adequate and well-controlled studies of acyclovir in pregnant women. When administered to mice, rabbits, and rats during organogenesis at doses up to 22 times normal human plasma levels, acyclovir was not teratogenic. Acyclovir did not impair fertility or reproduction in mice or rats, though at higher doses implantation efficacy decreased in rats and rabbits. Acyclovir crosses the placenta. Limited data indicate that the drug is distributed into milk at concentrations up to 4.1 times greater than concurrent maternal plasma concentrations. As a result, acyclovir should be administered to nursing mothers with caution and only when indicated.[10]

In vitro, acyclovir is approximately 9% to 33% bound to plasma proteins at drug concentrations of 0.41 to 52 mcg/ml. In adults with normal renal function, the half-life of oral acyclovir ranges from 2.5 to 3.3 hours, and the half-life of parenteral acyclovir is approximately 2.5 hours. Acyclovir is excreted principally in urine via glomerular

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## Pharmacology (cont.)

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filtration and tubular secretion; most of a single IV dose of the drug is excreted unchanged in urine within 24 hours of administration. Limited data suggest that peritoneal dialysis and blood exchange transfusions do not appreciably remove the drug. Hemodialysis reduces plasma concentrations of acyclovir by about 60%. Doses and frequency of administration of the drug should be modified according to creatinine clearance and age.[11] [12]

Resistance to acyclovir can result from qualitative and quantitative changes in viral TK or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially those with advanced HIV infection. Most acyclovir-resistant mutants are TK-deficient; these TK-negative mutants may cause severe disease in infants and immunocompromised adults. Although acyclovir is apparently unable to eliminate an established latent infection, acyclovir-resistant mutants appear less able of establishing a latent infection. The possibility of viral resistance to acyclovir should only be considered in patients who show poor clinical response during therapy.[13] [14]

## Adverse Events/Toxicity

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Adverse reactions after oral or IV administration of acyclovir have generally been minimal. However, potentially serious reactions (e.g., renal failure, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in immunocompromised patients) can occur and may be fatal.[15]

The most frequent adverse effects observed with acyclovir use are phlebitis (inflammation at the parenteral injection site), symptoms of acute renal failure, headache, malaise, and GI disturbances (e.g., nausea, vomiting, diarrhea). Rare but serious adverse effects include encephalopathy, urticaria, and hematologic abnormalities such as thrombocytopenia or thrombocytosis, hematuria, or anemia.[16] [17]

Adverse effects observed with topical acyclovir use include mild pain, burning, and stinging; itching, rash, and vulvitis may occur less frequently.[18]

## Drug and Food Interactions

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Dosage adjustment is recommended when administering acyclovir to patients with renal impairment or to patients receiving potentially nephrotoxic agents; acyclovir may increase the risk of renal dysfunction and of reversible central nervous system symptoms, such as those reported in patients treated with IV acyclovir.[19]

Amphotericin B has strengthened the antiviral effect of acyclovir against pseudorabies virus in vitro. Interferon has also shown additive or synergistic antiviral effects with acyclovir in vitro against HSV-1 cultures. The clinical importance of these interactions is not known. Drugs with the potential for clinically significant interactions with acyclovir include antifungal agents (e.g., ketoconazole), probenecid, interferon, intrathecal methotrexate, and zidovudine. Neurotoxicity has been reported in one case of concurrent acyclovir and zidovudine administration.[20]

Food does not appear to affect acyclovir's absorption; oral dosage forms may be given with or without food.[21]

## Contraindications

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Acyclovir is contraindicated in patients with hypersensitivity to acyclovir or valacyclovir.[22]

Acyclovir use should be carefully considered in patients with pre-existing renal function impairment or dehydration.[23]

## Clinical Trials

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For information on clinical trials that involve Acyclovir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Acyclovir AND HIV Infections.

## Dosing Information

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Mode of Delivery: Oral; intravenous infusion: topical.[24]

Dosage Form: Capsules containing acyclovir 200 mg.[25]

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## Dosing Information (cont.)

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Tablets containing acyclovir 400 mg and 800 mg.[26]

Oral banana-flavored suspension containing acyclovir 200 mg per 5 ml sorbitol with preservative.[27]

Acyclovir sodium for injection (preservative-free) in 10 ml sterile vials containing the equivalent of acyclovir 500 mg and in 20 ml sterile vials containing the equivalent of acyclovir 1,000 mg.[28]

5% topical ointment in 3 g and 15 g tubes containing acyclovir 50 mg in a polyethylene glycol base. Acyclovir 5% topical cream is available in Canada.[29] [30]

Storage: Store capsules, tablets, and suspension at temperatures between 15 C and 25 C (59 F and 77 F). Protect tablets and suspension from light; protect capsules from light and moisture.[31]

Store acyclovir sodium for injection at temperatures between 15 C and 25 C (59 F and 77 F).[32]

Store 5% topical ointment at temperatures between 15 C and 25 C (59 F and 77 F) in a dry place.[33]

## Chemistry

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CAS Name: 6H-Purin-6-one,2-amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-[34]

CAS Number: 59277-89-3[35]

Molecular formula: C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>[36]

C42.67%, H4.92%, N31.10%, O21.31%[37]

Molecular weight: 225.20[38]

Melting point: 256.5 C to 257 C, crystals from methanol.[39]

Physical Description: White crystalline powder; lyophilized monosodium salt.[40]

Stability: After reconstitution with sterile water, each injectable vial of acyclovir 50 mg/ml is stable

for 12 hours; after further dilution for administration, each dose of acyclovir sodium for injection should be used within 24 hours.[41]

Prior to reconstitution, acyclovir suspension is stable without refrigeration for 24 months. Refrigeration causes formation of a precipitate, which redissolves when the suspension is returned to room temperature. The oral suspension requires shaking before administering a dose.[42]

Solubility: Maximum solubility of 2.5 mg/ml in water at 37 C in a neutral pH.[43]

Acyclovir sodium has a maximum solubility of greater than 100 mg/ml in water at 25 C, but at physiologic pH and 37 C, the drug is almost completely unionized and has a maximum solubility of 2.5 mg/ml.[44]

## Other Names

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Aciclovir[45]

ACV[46]

Acyclovir sodium[47]

## Further Reading

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Celum CL, Robinson NJ, Cohen MS. Potential effect of HIV type 1 antiretroviral and herpes simplex virus type 2 antiviral therapy on transmission and acquisition of HIV type 1 infection. *J Infect Dis.* 2005 Feb 1;191 Suppl 1:S107-14. Review.

Corey L. Challenges in genital herpes simplex virus management. *J Infect Dis.* 2002 Oct 15;186 Suppl 1:S29-33. Review.

Strick LB, Wald A, Celum C. Management of herpes simplex virus type 2 infection in HIV type 1-infected persons. *Clin Infect Dis.* 2006 Aug 1;43(3):347-56. Epub 2006 Jun 15.

Villarreal EC. Current and potential therapies for the treatment of herpes-virus infections. *Prog Drug Res.* 2003;60:263-307.

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## **Manufacturer Information**

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(201) 947-7774

Acyclovir  
Mylan Laboratories Inc  
1030 Century Building / 130 Seventh St  
Pittsburgh, PA 15222  
(800) 796-9526

Zovirax  
GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27709  
(888) 825-5249

## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

## **References**

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1. AHFS Drug Information - 2007; p. 777
2. USP DI - 2005; pp. 24-5
3. USP DI - 2005; p. 30
4. FDA - Acyclovir Approval Information, December 10, 1997. Available at: [http://www.fda.gov/cder/foi/anda/97/074897\\_acyclovir\\_toc.htm](http://www.fda.gov/cder/foi/anda/97/074897_acyclovir_toc.htm). Accessed 06/08/07.
5. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, p. 2. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/07/07.
6. AHFS Drug Information - 2007; p. 785
7. AHFS Drug Information - 2007; p. 786
8. USP DI - 2005; p. 25

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9. AHFS Drug Information - 2007; p. 786
10. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, pp. 5-6. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/07/07.
11. USP DI - 2005; p. 25
12. AHFS Drug Information - 2007; pp. 786-7
13. AHFS Drug Information - 2007; p. 786
14. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, p. 2. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/07/07.
15. AHFS Drug Information - 2005; pp. 775-6
16. USP DI - 2005; pp. 26-7
17. GlaxoSmithKline - Zovirax Prescribing Information, June 2005, pp. 6-7. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/15/07.
18. USP DI - 2005; p. 31
19. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, p. 4. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/07/07.
20. AHFS Drug Information - Zovirax Capsules, Tablets, and Suspension Prescribing Information, 2007; p. 785
21. USP DI - 2005; p. 25
22. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, p. 4. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/07/07.
23. USP DI - 2005; p. 26
24. USP DI - 2005; pp. 28-9, 31
25. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, pp. 8-9. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/08/07.
26. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, pp. 8-9. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/08/07.
27. GlaxoSmithKline - Zovirax Capsules, Tablets, and Suspension Prescribing Information, June 2005, pp. 8-9. Available at: [http://us.gsk.com/products/assets/us\\_zovirax.pdf](http://us.gsk.com/products/assets/us_zovirax.pdf). Accessed 06/08/07.
28. GlaxoSmithKline - Zovirax for Injection Prescribing Information, November 2003, p. 10. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_injection.pdf](http://us.gsk.com/products/assets/us_zovirax_injection.pdf). Accessed 06/08/07.
29. GlaxoSmithKline - Zovirax Ointment 5% Prescribing Information, May 2001, p. 4. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_ointment.pdf](http://us.gsk.com/products/assets/us_zovirax_ointment.pdf). Accessed 06/08/07.
30. USP DI - 2005; pp. 31-2
31. USP DI - 2005; pp. 28-9
32. GlaxoSmithKline - Zovirax for Injection Prescribing Information, November 2003, p. 11. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_injection.pdf](http://us.gsk.com/products/assets/us_zovirax_injection.pdf). Accessed 06/08/07.
33. GlaxoSmithKline - Zovirax Ointment 5% Prescribing Information, May 2001, p. 4. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_ointment.pdf](http://us.gsk.com/products/assets/us_zovirax_ointment.pdf). Accessed 06/08/07.
34. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 06/08/07.
35. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 06/08/07.
36. Merck Index - 2006; p. 26
37. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 06/08/07.
38. Merck Index - 2006; p. 26
39. Merck Index - 2006; p. 26

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40. AHFS Drug Information - 2007; p. 787
41. GlaxoSmithKline - Zovirax for Injection Prescribing Information, November 2003, pp. 10-1. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_injection.pdf](http://us.gsk.com/products/assets/us_zovirax_injection.pdf). Accessed 06/07/07.
42. USP DI - 2005; pp. 28-9
43. GlaxoSmithKline - Zovirax for Injection Prescribing Information, November 2003, p. 1. Available at: [http://us.gsk.com/products/assets/us\\_zovirax\\_injection.pdf](http://us.gsk.com/products/assets/us_zovirax_injection.pdf). Accessed 06/07/07.
44. AHFS Drug Information - 2007; p. 787
45. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 06/07/07.
46. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 06/07/07.
47. MeSH - Available at: <http://www.nlm.nih.gov/mesh/MBrowser.html>. Accessed 06/07/07.