

## Acyclovir

Aciclovir  
Acycloguanosine  
ACV

## Acyclovir Sodium

Acyclovir is a synthetic purine nucleoside analog antiviral agent derived from guanine and is active against Herpesviridae.

### Uses

IV acyclovir sodium is used for the treatment of initial and recurrent mucocutaneous herpes simplex virus (HSV-1 and HSV-2) infections and the treatment of varicella-zoster infections in immunocompromised adults and children; for the treatment of severe first episodes of genital herpes infections in immunocompetent individuals; and for the treatment of HSV encephalitis and neonatal HSV infections. Acyclovir is used orally for the treatment of initial and recurrent episodes of genital herpes; for the acute treatment of herpes zoster (shingles, zoster) in immunocompetent individuals; and for the treatment of varicella (chickenpox) in immunocompetent individuals.

For topical uses of acyclovir, see 84:04.06.

### ■ Mucocutaneous, Ocular, and Systemic Herpes Simplex Virus (HSV) Infections

Acyclovir is considered the drug of choice for the treatment of mucocutaneous herpes simplex virus (HSV) infections in immunocompromised adults, adolescents, and children and also is considered the drug of choice for the treatment of severe HSV infections such as HSV encephalitis and neonatal HSV infections.

Controlled studies of initial and recurrent mucocutaneous HSV-1 and HSV-2 infections (e.g., orofacial, esophageal, genital, nasal, labial) in immunocompromised adults and children have shown that IV acyclovir therapy decreases the duration of viral shedding (time from onset of therapy until the last positive culture), the duration of pain and itching, the time required for crusting and healing of lesions, and the duration of positive cultures. In one study, the median duration of viral shedding was 3 days in acyclovir-treated patients compared with 17 days in placebo-treated patients; pain ceased within 10 days of initiating therapy in acyclovir-treated patients compared with 16 days in placebo-treated patients. The time required for crusting and healing of lesions was 7 and 14 days, respectively, in acyclovir-treated patients compared with 14 and 28 days, respectively, in placebo-treated patients. IV acyclovir was not effective in reducing the frequency or delaying the onset of subsequent recurrent infection with HSV-1, HSV-2, or other herpesviruses or in eliminating an established latent infection.

Acyclovir has been used for the treatment of orolabial HSV infections, including gingivostomatitis, in adults and children; the drug is not effective or is minimally effective for the prevention of recurrence of herpes labialis<sup>†</sup> in immunocompetent individuals.

Oral or IV acyclovir has been reported to be effective in the treatment of eczema herpeticum<sup>†</sup> caused by HSV in several patients with a history of atopic dermatitis; the drug decreased fever and/or the appearance of new lesions, and promoted crusting and healing of lesions.

### HIV-Infected Individuals

Acyclovir generally is considered the drug of choice for the treatment of primary or recurrent mucocutaneous HSV infections in individuals with human immunodeficiency virus (HIV) infection. Mucocutaneous HSV infections in HIV-infected individuals can involve severe lesions that persist longer than those in immunocompetent individuals. Infections often progress to visceral disease and CNS or disseminated HSV may occur. HSV oral lesions in HIV-infected individuals generally are erosive, painful ulcerations that persist for several weeks and can extend to the esophagus. While these lesions may heal spontaneously, initiation of oral acyclovir at the onset of symptoms is recommended since severe pain and local tissue destruction may occur; IV acyclovir may be necessary for severe cases.

In patients with advanced HIV infection, reactivation of HSV frequently occurs and can result in chronic, persistent mucocutaneous disease that may be severe. The Prevention of Opportunistic Infections Working Group of the US Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA) has established guidelines for the prevention of opportunistic infections in HIV-infected individuals that include recommendations concerning prevention of exposure to opportunistic pathogens, prevention of first disease episodes, and prevention of disease recurrence. The USPHS/IDSA does *not* currently recommend primary prophylaxis against initial episodes of HSV infection in HIV-infected adults, adolescents, or children. In addition, the USPHS/IDSA does not recommend routine chronic suppressive or maintenance

therapy (secondary prophylaxis) against HSV disease in HIV-infected individuals since acute episodes generally can be treated successfully with acyclovir. However, long-term prophylaxis against recurrence of HSV can be considered for adults, adolescents, and children who have frequent or severe recurrences. If secondary prophylaxis of HSV disease is indicated in HIV-infected adults or adolescents, the USPHS/IDSA and other experts recommend use of oral acyclovir, oral famciclovir, or oral valacyclovir as the regimen of choice. If indicated in infants and children, the USPHS/IDSA and other experts recommend oral acyclovir.

HIV-infected patients receiving acyclovir may develop acyclovir-resistant strains of HSV; these infections have been reported most often in patients with advanced HIV infection or those who have received long-term acyclovir therapy. IV foscarnet or IV cidofovir can be used for the management of HSV infections in HIV-infected patients when the HSV infection is known or suspected of being caused by acyclovir-resistant strains. Additional study is needed to determine whether long-term suppression of HSV reduces or facilitates the emergence of drug-resistant strains of the virus and to determine optimal strategies for suppressive therapy of acyclovir-resistant HSV infections. It has been postulated that alternating the use of antiviral agents (e.g., acyclovir, foscarnet) may prevent emergence and subsequent predominance of drug-resistant isolates.

### Ocular HSV Infections

Oral acyclovir (400 mg 5 times daily) has been used for the treatment of HSV keratitis<sup>†</sup> in HIV-infected patients. Long-term antiviral therapy may be necessary to prevent recurrent ocular HSV disease in these patients. Oral acyclovir (400 mg twice daily for 12 months) has been used for the prevention of recurrent ocular HSV disease<sup>†</sup> in immunocompetent adults and children 12 years of age or older who had an episode of ocular HSV disease (blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, iritis) in one or both eyes within the preceding 12 months. Results of one study in adults indicate that long-term oral acyclovir (400 mg twice daily for up to 18 months) is effective in decreasing the number of HSV recurrences. Oral acyclovir (400 mg twice daily for 6 months) has been used to prevent HSV recurrences in patients undergoing penetrating keratoplasty for herpetic eye disease. The optimum duration of prophylaxis remains to be determined.

### HSV Encephalitis

Controlled studies in adults and children 6 months of age or older have shown that IV acyclovir is effective for the treatment of HSV encephalitis. Many clinicians consider acyclovir the drug of choice for the treatment of HSV encephalitis, and the American Academy of Pediatrics (AAP) and other experts also consider acyclovir the drug of choice for the treatment of neonatal HSV infections involving the CNS.

HSV encephalitis and neonatal HSV infections of the CNS are associated with substantial morbidity and mortality despite antiviral treatment. In one study in patients 6 months to 79 years of age with brain biopsy-proven HSV encephalitis randomized to receive 10 days of IV acyclovir (10 mg/kg every 8 hours) or IV vidarabine (15 mg/kg daily; no longer commercially available in the US), the overall mortality rate at 12 months was 25% in those who received acyclovir versus 59% in those who received vidarabine. Morbidity assessments at 12 months indicated that 32% of patients who received acyclovir were functioning normally or had only mild neurologic sequelae (e.g., decreased attention span); the remaining survivors had moderate (e.g., hemiparesis, speech impediment, seizures) or severe (continuous supportive care required) sequelae. Patients who were younger than 30 years of age and those with less severe neurologic involvement at the time of treatment had the best outcome. Initiation of acyclovir early in the course of the infection (prior to the development of semicoma or coma) may enhance its efficacy.

### Neonatal HSV Infections

The AAP, US Centers for Disease Control and Prevention (CDC), and other experts consider IV acyclovir the drug of choice for the treatment of mucosal, cutaneous, CNS, or disseminated HSV infections in neonates.

Neonatal HSV infection is associated with substantial morbidity and mortality, and approximately 25% of neonates with disseminated HSV disease die despite antiviral therapy. Because the risk of morbidity and mortality increases substantially with systemic (CNS or disseminated) infection compared with mucocutaneous infection, early recognition of neonates with HSV infection confined to the skin, eyes, and mouth and early initiation of antiviral therapy are important. The AAP recommends that IV acyclovir therapy be initiated in all neonates with HSV infection, irrespective of presenting clinical findings. In addition, the AAP states that infants with HSV disease that has ocular involvement should receive a topical ophthalmic antiviral agent (e.g., trifluridine, vidarabine) in addition to parenteral therapy.

In one study in infants with neonatal HSV disease who were randomized to receive a 10-day regimen of IV acyclovir (10 mg/kg every 8 hours) or vidarabine (30 mg/kg daily; no longer commercially available in the US), mortality at 1 year in the acyclovir group was 0/54 in those with localized disease (limited to skin, eye, and/or mouth), 5/35 in those with CNS infections, and 11/18 in

those with visceral organ involvement such as hepatitis or pneumonitis with or without CNS involvement.

Relapse of neonatal HSV disease involving the skin, eyes, mouth, or CNS can occur after acyclovir therapy is discontinued; however, optimal management of these recurrences has not been established. The safety and efficacy of long-term suppressive or intermittent acyclovir therapy for neonates with HSV disease of the skin, eyes, and mouth are being evaluated.

The care of infants exposed to HSV during delivery depends on the status of the mother's infection and mode of delivery; infants exposed to HSV during birth should be monitored carefully in consultation with a specialist. Most experts recommend that women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean section to prevent neonatal herpes. However, cesarean section does not completely eliminate the risk for HSV transmission to the infant. Women without symptoms or signs of genital herpes can deliver vaginally. The AAP states that all neonates born to women with active genital HSV lesions, regardless of whether the child was delivered by vaginal or cesarean delivery, should be observed carefully and viral cultures for HSV should be obtained 24–48 hours after birth. Because the infection rate in infants born by vaginal delivery to mothers with recurrent genital herpes infection is low, most experts recommend that these infants not be given empiric acyclovir therapy. These infants should be observed for signs of infection and undergo surveillance cultures. For neonates whose mothers have presumed or proven primary genital herpes infection, some experts recommend empiric acyclovir treatment at birth (despite the fact that data are not available to support the efficacy of such a strategy) because the risk of infection in these neonates may exceed 50%; other experts would only initiate acyclovir therapy if HSV cultures are positive. All infants with neonatal herpes should be evaluated and treated with acyclovir. Symptoms suggestive of neonatal HSV infection include skin or scalp rash (especially vesicular lesions) and unexplained clinical manifestations (such as respiratory distress, seizures, signs of sepsis). The fact that neonatal HSV infection can occur as late as 4–6 weeks after delivery should be considered.

#### **Hematopoietic Stem Cell Transplant Recipients**

The CDC, the Infectious Diseases Society of America (IDSA), and the American Society of Blood and Marrow Transplantation (ASBMT) have established guidelines for preventing opportunistic infections in hematopoietic stem cell transplant (HSCT) recipients. These guidelines recommend that candidates for HSCT whose screening tests before HSCT are seropositive for HSV receive acyclovir to prevent HSV recurrence<sup>†</sup>. Acyclovir prophylaxis is initiated at the beginning of the conditioning regimen and continued until engraftment occurs or mucositis resolves (approximately 30 days after HSCT). Routine prophylaxis for longer than 30 days is not recommended. Prophylaxis is not indicated for HSCT recipients who are seronegative for HSV.

### ■ Genital Herpes

#### **Treatment of First Episode Infections**

Acyclovir is used in the treatment of initial episodes of genital herpes. First episode genital herpes infections occur in patients experiencing their first vesicular or ulcerative lesion of the genitalia and can be either a true primary infection or a non-primary infection. Primary infections frequently are asymptomatic, in which case the first symptomatic episode actually represents a reactivated recurrent infection. Individuals with true primary HSV infections lack antibody to HSV-1 and/or HSV-2 in their serum.

The severity of first episodes of genital herpes may vary from asymptomatic to disabling; however, untreated primary infections are generally characterized by severe and prolonged symptoms (average duration of 14 days) and a large number of lesions (average duration of 24 days). Symptoms of primary genital herpes usually appear 2–20 days (average: 6 days) following sexual contact with an individual who has a symptomatic or asymptomatic genital herpes infection. Untreated non-primary infections are generally less severe, of shorter duration, and involve fewer systemic complications; lesions of non-primary infections are present for an average of 14 days. Viral shedding occurs in both primary and non-primary infections, and usually lasts about 12 days in untreated primary infections and 7 days in untreated non-primary infections.

Because many patients with first episodes of genital herpes present with mild clinical symptoms but later develop severe or prolonged symptoms, the CDC states that most patients with initial genital herpes should receive antiviral therapy. The CDC and some clinicians recommend that first episodes of genital herpes in immunocompetent adults and adolescents should be treated with a regimen of oral acyclovir (400 mg 3 times daily or 200 mg 5 times daily for 7–10 days), oral famciclovir (250 mg 3 times daily for 7–10 days), or oral valacyclovir (1 g twice daily for 7–10 days). Oral acyclovir also can be used for the treatment of first episodes of genital herpes in pediatric patients. Topical antiviral agents are not recommended for the treatment of genital herpes since these agents offer only minimal clinical benefit.

Controlled studies have shown that oral acyclovir is effective for the treatment of first episodes of genital herpes in immunocompetent patients. Several studies have shown that oral acyclovir therapy decreases viral shedding and the

time required for crusting and healing of lesions; in some patients, the formation of new lesions and the duration of pain, pruritus, or dysuria were decreased.

IV acyclovir should be used for the initial treatment of genital herpes when the infection is severe or when there are complications that necessitate hospitalization, including disseminated infection, pneumonitis, hepatitis, CNS involvement (e.g., meningitis, encephalitis). Controlled studies of severe first episodes of genital herpes in immunocompetent individuals have shown that IV acyclovir decreases viral shedding (time from onset of therapy until last positive culture) from genital and cervical lesions, the time necessary for crusting and healing of lesions, the duration of positive cultures, the formation of new lesions, the duration of dysuria and abnormal vaginal discharge, and the degree and duration of pain and pruritus. In one study, the duration of viral shedding was 2 days in acyclovir-treated patients compared with 8 days in placebo-treated patients; the time required for healing of lesions was 7 days in acyclovir-treated patients compared with 15 days in placebo-treated patients. No substantial reduction in the duration of pain was noted in acyclovir-treated patients compared with placebo-treated patients.

Oral acyclovir has been used at higher dosages (400 mg 5 times daily) for the treatment of first episodes of herpes proctitis<sup>†</sup>.

#### **Episodic Treatment of Recurrent Infections**

Oral acyclovir is used in the treatment of recurrent episodes of genital herpes in immunocompetent adults and adolescents. Antiviral therapy for recurrent genital herpes can be given episodically to ameliorate or shorten the duration of lesions or can be given continuously as suppressive therapy to reduce the frequency of recurrences. For episodic treatment of recurrent genital herpes in immunocompetent adults and adolescents, the CDC and some clinicians recommend oral acyclovir (400 mg 3 times daily for 5 days, 800 mg twice daily for 5 days, or 800 mg 3 times daily for 2 days), oral famciclovir (125 mg twice daily for 5 days or 1 g twice daily for 1 day), or oral valacyclovir (500 mg twice daily for 3 days or 1 g once daily for 5 days). Episodic antiviral therapy should be initiated within 1 day of lesion onset or during the prodrome that precedes some outbreaks.

#### **Suppressive Therapy of Recurrent Infections**

Oral acyclovir is used for chronic suppressive therapy of recurrent genital herpes in immunocompetent adults and adolescents. Data are not available regarding use of acyclovir for suppressive therapy in children. The CDC states that suppressive antiviral therapy can reduce the frequency of genital herpes recurrences by 70–80% in patients who have frequent recurrences (i.e., 6 or more per year) and many patients report no symptomatic outbreaks during such therapy. Quality of life often is improved in patients who receive suppressive therapy rather than episodic treatment for recurrent genital herpes. For chronic suppressive therapy of recurrent genital herpes, the CDC and some clinicians recommend that immunocompetent adults and adolescents receive a regimen of oral acyclovir (400 mg twice daily), oral famciclovir (250 mg twice daily), or oral valacyclovir (500 mg or 1 g once daily). The CDC states that data suggest that famciclovir and valacyclovir are as effective as acyclovir in terms of clinical outcome, although the 500-mg once-daily valacyclovir regimen might be less effective than the acyclovir regimen or other valacyclovir regimens in patients who have very frequent recurrences (i.e., 10 or more episodes per year).

Controlled studies have shown that prophylactic administration of oral acyclovir for suppressive therapy may reduce the frequency and/or severity of subsequent recurrent genital herpes infections or delay the onset of subsequent episodes in immunocompetent patients and can prevent clinical recurrences of genital herpes infections in a substantial proportion of patients. The efficacy of prophylactic administration of oral acyclovir therapy in patients with recurrent herpes proctitis remains to be established. In a study in patients with frequent recurrences of genital herpes infections (6 or more per year) receiving chronic suppressive therapy (400 mg of oral acyclovir twice daily), 45, 52, and 63% of patients were free of recurrences during the first, second, and third years, respectively; serial analyses of 3-month recurrence rates revealed that 71–87% were recurrence free during each quarter, and the annual frequency of recurrences during the third year of therapy relative to the baseline frequency was reduced in 97% of patients. The proportion of these patients (i.e., those receiving chronic suppressive therapy) who remained recurrence free during the first year of the study was substantially higher than that of another group of patients who received intermittent (initiated within 48 hours of onset of a herpes episode) therapy instead; in addition, approximately 25% of patients who received chronic suppressive therapy for 3 years remained recurrence free during the entire period.

Safety and efficacy of oral acyclovir for suppressive therapy of recurrent genital herpes infections have been established in patients receiving daily therapy for up to 5–6 years. Because the frequency of recurrent episodes diminishes over time in many patients, the manufacturer and CDC recommend that suppressive antiviral therapy be discontinued periodically (e.g., once yearly) to assess the need for continued therapy.

### HIV-Infected Individuals

Immunocompromised individuals may have prolonged or severe episodes of genital, perianal, or oral herpes; HSV lesions are common in those with human immunodeficiency virus (HIV) infection and may be severe, painful, and atypical. (See Uses: Mucocutaneous Herpes Simplex Virus Infections.)

The CDC states that episodic treatment or suppressive therapy with oral antiviral agents often is beneficial in HIV-infected individuals with genital herpes. While the drugs of choice for episodic treatment or suppressive therapy of genital herpes in HIV-infected individuals are the same as those in immunocompetent individuals, higher dosages and/or more prolonged therapy may be necessary. For episodic treatment of recurrences of genital herpes in HIV-infected individuals, the CDC recommends a 5- to 10-day regimen of oral acyclovir (400 mg 3 times daily), oral famciclovir (500 mg twice daily), or oral valacyclovir (1 g twice daily). If chronic suppressive therapy of recurrent genital herpes is used in HIV-infected individuals, the CDC recommends oral acyclovir (400–800 mg 2–3 times daily), oral famciclovir (500 mg twice daily), or oral valacyclovir (500 mg twice daily).

Although rare, clinically important resistance to acyclovir is more likely to occur with prolonged or repeated therapy in severely immunocompromised patients with active lesions. Acyclovir-resistant HSV are resistant to valacyclovir and most strains also are resistant to famciclovir. The potential clinical benefits of acyclovir therapy in immunocompromised patients must be weighed against the potential for selecting resistant HSV strains. If presence of acyclovir-resistant HSV are suspected, specimens should be obtained for in vitro susceptibility testing. Patients whose therapy for the prevention or treatment of recurrence fails because of resistance should be managed in consultation with an expert. IV foscarnet can be used for the management of severe HSV infections known or suspected of being caused by acyclovir-resistant strains; IV foscarnet (40 mg/kg every 8 hours given until clinical resolution is attained) often is effective for the treatment of acyclovir-resistant genital herpes.

### Pregnant Women

Although safe use of acyclovir during pregnancy has not been established, the CDC states that oral acyclovir may be used to treat first episodes of genital herpes or severe recurrent genital herpes in pregnant women and that IV acyclovir may be used to treat severe HSV infection in pregnant women.

The risk for transmission of HSV to the neonate from an infected mother during vaginal delivery is high (30–50%) among women who acquire genital herpes near the time of delivery (primary infections) and low (0–5%) among women with histories of recurrent genital herpes at term or women who acquire genital herpes during the first half of pregnancy. Administration of acyclovir late in pregnancy in women who have recurrent genital herpes decreases the frequency of recurrences at term and reduces the frequency of cesarean sections; many clinicians recommend such treatment. There are no data to support administration of acyclovir to HSV-seropositive women who do not have a history of genital herpes. Because the risk of herpes is high in infants of women who acquire genital herpes in late pregnancy, such women should be managed in consultation with an HSV expert. Some experts recommend acyclovir therapy and/or routine cesarean section in these women to decrease the risk of transmission of HSV to the neonate. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation.)

### Patient Counseling and Management of Sexual Partners

Counseling of infected individuals and their sex partners is critical to management of genital herpes. The goals of such counseling are to help patients understand and cope with the infection and to prevent sexual and perinatal transmission of the virus. Antiviral therapy offers clinical benefit to most symptomatic patients and is the mainstay of management; however, genital herpes is a recurrent, lifelong viral infection. Although antiviral therapy can be used to control the symptoms and signs of genital herpes episodes, it cannot eradicate latent HSV or affect the risk, frequency, or severity of recurrences of genital herpes following discontinuance of antiviral therapy.

The majority of genital herpes infections are transmitted by individuals unaware that they have the infection or by individuals who are asymptomatic when transmission occurs. Patients should be advised that acyclovir is not a cure for genital herpes, and there are no data evaluating whether acyclovir prevents transmission of HSV to others. Because genital herpes is a sexually transmitted disease, patients should be advised to avoid sexual contact with uninfected partners when lesions and/or prodromal symptoms are present. In addition, patients should be advised that sexual transmission of the virus can occur during asymptomatic periods and that suppressive antiviral therapy reduces, but does not eliminate, subclinical viral shedding.

Sex partners of individuals with genital herpes should be advised that they may be infected even if they have no symptoms. Asymptomatic partners of patients with genital herpes should be questioned regarding a history of genital lesions, educated to recognize symptoms of genital herpes, and offered type-specific serologic testing to determine whether risk for HSV acquisition exists. Antiviral therapy is not recommended for sex partners who do not have clinical manifestations of infection, but symptomatic sex partners of individuals with genital herpes should be evaluated and treated.

The risk for neonatal HSV infection should be discussed with all genital herpes patients, including men. Pregnant women and women of childbearing potential who have genital herpes should inform their providers who care for them during pregnancy as well as those who will care for their neonate.

Information to assist patients and clinicians in counseling regarding genital herpes is available at <http://www.ashstd.org> and <http://www.ihmf.org>.

## ■ Varicella-Zoster Infections

### Varicella (Chickenpox)

Oral acyclovir is used in the treatment of varicella (chickenpox) in immunocompetent adults and children to reduce the severity and duration of the illness. Use of oral acyclovir therapy (initiated within 24 hours of the onset of rash) in otherwise healthy children, postpubertal adolescents, or adults with varicella can decrease the appearance of new lesions, accelerate vesicle healing (vesicles often progress directly from the maculopapular stage to the crusted or healed stage), reduce new vesicle formation by the second day of treatment, and reduce the frequency, duration, and/or severity of fever, pruritus, and constitutional symptoms (e.g., anorexia, lethargy, coryza). In one study in otherwise healthy children 2–12 years of age, nearly all patients receiving oral acyclovir therapy initiated within 24 hours of the onset of rash developed only mild illness of 3–4 days duration with manifestations characteristic of the infection, whereas untreated children generally developed more severe disease of longer duration and many had progressive cutaneous lesions that persisted for more than 6 days.

Some patients who received oral acyclovir therapy reportedly had decreased numbers of residual hypopigmented lesions 4 weeks after initial appearance of rash, and it has been suggested that this possibly indicates a reduction in cutaneous sequelae. However, the clinical relevance, if any, of this finding remains to be established. There currently is no evidence that acyclovir therapy for acute varicella in immunocompetent patients can affect the frequency and/or severity of early complications associated with the disease, in part because such complications generally are uncommon even in untreated individuals. In addition, there currently is no evidence that such therapy can affect the frequency and/or severity of subsequent herpes zoster (shingles, zoster) later in life. It remains to be established whether acyclovir can affect transmission of varicella within households. Current regimens, in which acyclovir is initiated within 24 hours of the appearance of rash, have not reduced such transmission, possibly because therapy was initiated after the period of greatest infectivity. Many clinicians suggest that amelioration, rather than prevention, of varicella in otherwise healthy household contacts should be the principal goal of therapy since prevention could result in the individual being at ongoing risk of primary infection at an older age when manifestations of the disease generally are more severe.

Oral acyclovir therapy in immunocompetent patients generally does not appear to affect antibody response to varicella-zoster infection when measured 1 month and 1 year following treatment with the drug, although somewhat reduced response occasionally has been observed 1 month following treatment with the drug. However, some theoretical concern persists since use of acyclovir in patients with primary herpes simplex infection may result in decreased humoral and cellular immune responses in some patients. Although these altered responses generally have not been associated with increased rates of recurrence or relapse of herpes simplex, the severity of the first subsequent episode of the disease may be increased. Some clinicians also have raised theoretical concerns that potential pathophysiologic and/or immunologic alterations induced by early treatment of varicella infection may predispose to subsequent development of, or more severe, herpes zoster infection, but such concerns have been questioned and remain to be substantiated. Acyclovir should *not* be used prophylactically in an attempt to prevent infection or illness in otherwise healthy children exposed to varicella.

Because of the usually benign course of varicella, the current lack of evidence of effect of acyclovir therapy on early and delayed complications of the disease, and the lack of established substantial cost-benefit of such therapy, the role of acyclovir in the treatment of varicella in otherwise healthy patients currently is controversial. Therefore, the AAP and other clinicians state that oral acyclovir *should not be used routinely* in otherwise healthy children with uncomplicated varicella since administration within 24 hours of rash results in only a modest decrease in symptoms. However, use of oral acyclovir may be considered in certain individual cases when family or clinical circumstances justify the drug's modest benefit and only when the drug can be initiated within the first 24 hours after the onset of rash. The AAP and other clinicians state that use of acyclovir can be considered for otherwise healthy individuals at increased risk of moderate to severe varicella, including those older than 12 years of age, those who contract the disease from siblings or other household contacts, those with chronic cutaneous or pulmonary disorders, those receiving long-term salicylate therapy, and those receiving short, intermittent, or aerosolized courses of corticosteroids. Although it is not known whether children receiving short, intermittent, or aerosolized courses of corticosteroid therapy are at increased risk of complicated or severe varicella, the AAP states that use of acyclovir to minimize the likelihood of severe disease should be considered

for these children since no data currently exist to confirm their immunocompetence. Because these children are unlikely to have clinically important immunosuppression, oral acyclovir may be used; however, children immunocompromised because of high-dose corticosteroid therapy should receive IV acyclovir therapy. If possible, corticosteroid therapy should be discontinued after known exposure to varicella.

The fact that it may be difficult to recognize varicella and initiate acyclovir therapy soon enough after onset of rash to be of appreciable benefit in many patients, particularly the index case, should be considered. Oral acyclovir provides maximum benefit when initiated as soon as possible after the first manifestation of varicella appears; little if any benefit is apparent if treatment is delayed (e.g., for 48 hours after onset of rash).

IV acyclovir is used for the treatment of varicella in immunocompromised adults and children and many clinicians currently consider IV acyclovir the drug of choice for the treatment of varicella in immunocompromised patients. In immunocompromised adults and children with varicella, IV acyclovir therapy may produce negative viral cultures, decrease the appearance of new lesions, and promote the crusting of lesions; the drug also appears to prevent disseminated, life-threatening infection in some patients. Although limited data suggest that oral acyclovir also may be beneficial in some immunocompromised children with varicella<sup>†</sup>, the AAP states that oral therapy generally is not recommended for these patients because of poor oral bioavailability. However, high dosage of oral acyclovir has been used in highly selected immunocompromised patients perceived to be at lower risk of developing severe varicella, such as HIV-infected patients with relatively normal CD4<sup>+</sup> T-cell counts and children with leukemia in whom careful follow-up is assured. Acyclovir has been used IV in immunocompetent adults for the treatment of complicated varicella (e.g., pneumonia, encephalitis). IV acyclovir therapy appeared to be effective in the treatment of varicella-zoster pneumonia in at least one immunocompetent adult; however, it could not be conclusively determined that the drug was responsible for resolution of infection. In addition, efficacy of the drug may be reduced substantially if initiation of acyclovir is delayed until the disease has advanced to pneumonitis, particularly in immunocompromised patients; therefore, early initiation of therapy is recommended.

#### **Herpes Zoster (Shingles, Zoster)**

Controlled studies have shown that oral acyclovir is effective for the acute treatment of herpes zoster (shingles, zoster) in immunocompetent adults. Oral acyclovir may prevent the appearance of new lesions, decrease viral shedding, decrease the severity and/or duration of pain, promote healing and crusting of lesions, and reduce the prevalence of localized zoster-associated neurologic manifestations (paresthesia, dysesthesia, or hyperesthesia) in immunocompetent adults with localized herpes zoster, at least when given in high dosages within 2 days of the onset of rash. In these studies, acyclovir was particularly effective in adults 50 years of age or older. In immunocompetent adults, high-dose oral acyclovir therapy also may ameliorate cutaneous manifestations, if initiated within 72 hours of rash onset, and acute pain, and may reduce some anterior inflammatory ocular complications (pseudodendritic keratopathy, stromal keratitis, uveitis), if initiated within 7 days of rash onset, but not early cutaneous and external ocular complications (e.g., lid margin vesiculation, conjunctivitis, corneal hypoesthesia, episcleritis). Longer than usual courses of acyclovir (e.g., 21-day therapy) appear to be associated only with marginal additional benefits with regard to the incidence, duration, and severity of pain during the acute phase of the disease in immunocompetent patients when compared with those receiving a 7-day course of therapy. Therefore, because of cost considerations and insufficient evidence of clinical benefits to support such prolonged use, acyclovir therapies longer than 10 days' duration are not recommended for treatment of acute herpes zoster in immunocompetent individuals.

The effect of oral acyclovir on postherpetic neuralgia remains to be clearly determined. In most studies to date, the drug did not appear to prevent postherpetic neuralgia; however, there is some evidence that high-dose therapy may reduce the occurrence of pain in the second and third months after treatment and the associated local neurologic symptoms 3–6 months after treatment. In a limited number of patients with acute herpes zoster, addition of corticosteroids to acyclovir therapy did not appear to influence incidence or severity of postherpetic neuralgia. In one double-blind, placebo-controlled study in immunocompetent adults older than 50 years of age with localized herpes zoster, patients were randomized to receive oral acyclovir (800 mg 5 times daily for 21 days) with oral prednisone (daily dosage of 60 mg for days 1–7, then 30 mg for days 8–14 and 15 mg for days 15–21), oral acyclovir with placebo, oral prednisone with placebo, or 2 placebos. Patients were evaluated for persistence of pain and quality of life (i.e., return to 100% usual activity, return to uninterrupted sleep, cessation of analgesic therapy); acute neuritis was assessed during the first month and chronic pain was assessed for up to 6 months. While patients who received prednisone had a shorter duration of acute pain and improved quality of life during the first month after disease onset compared with those who did not receive the drug, the incidence of pain at 3 or 6 months was similar in all 4 treatment groups.

IV acyclovir is used for the treatment of herpes zoster infections in immunocompromised patients, and some clinicians suggest that IV acyclovir is the preferred antiviral agent for the treatment of primary or disseminated herpes zoster in immunocompromised patients, including HIV-infected patients. IV acyclovir also has been used for the treatment of herpes zoster in immunocompetent patients<sup>†</sup> who have both localized and disseminated infections. In a placebo-controlled study in immunocompromised patients with herpes zoster, reductions in cutaneous and visceral dissemination were greater in those who received IV acyclovir (500 mg/m<sup>2</sup> every 8 hours for 7 days) compared with those who received placebo. In a limited number of immunocompetent adults and immunocompromised adults and children with localized and disseminated herpes zoster infections, IV acyclovir therapy appeared to decrease pain and fever, prevent the appearance of new lesions, produce negative cultures, and promote crusting and healing of lesions; however, the principal therapeutic effect of acyclovir in immunocompromised patients appears to be in preventing progression of disease as manifested by cutaneous or visceral dissemination. IV acyclovir therapy has also produced rapid clinical response in a limited number of immunocompetent and immunocompromised patients with herpes zoster-associated encephalitis. There is no evidence that IV acyclovir prevents postherpetic neuralgia.

Oral acyclovir has been used for the treatment of dermatomal herpes zoster in immunocompromised patients<sup>†</sup>, including transplant recipients and HIV-infected patients.

IV acyclovir (10 mg/kg 3 times daily for 7 days) followed by oral acyclovir (800 mg 3–5 times daily) as maintenance therapy has been used for the treatment of herpes zoster ophthalmicus<sup>†</sup> in HIV-infected patients.

Several cases of acyclovir-resistant varicella-zoster virus infections have been reported in adults and children with acquired immunodeficiency syndrome (AIDS) following chronic suppressive courses of therapy with the drug; because pretreatment isolates were not obtained, it is not known whether the original virus developed resistance or a resistant strain was selected during chronic therapy. Another case of therapeutic failure secondary to resistant varicella-zoster has been reported in an immunocompromised patient; however, limited data to date suggest that resistance of the virus to acyclovir occurs only rarely, but additional study and experience are necessary.

#### **■ Cytomegalovirus Infections**

Acyclovir generally is ineffective in the treatment of cytomegalovirus (CMV) infections<sup>†</sup>. IV acyclovir therapy reportedly reduced fever, improved radiographic findings of pneumonia, and resulted in negative blood cultures in some immunocompromised patients with pneumonia caused by CMV. However, in one randomized study in HIV-infected patients, there was no evidence that oral acyclovir therapy suppressed CMV excretion in these patients. IV acyclovir therapy produced little clinical improvement in several infants with congenital CMV infection.

Oral acyclovir has been used for the prevention of CMV disease in organ transplant recipients<sup>†</sup> considered at risk for the disease. There are conflicting data concerning the effectiveness of the drug for this use, however, and further study is necessary. There is some evidence that IV acyclovir may be effective for suppression of CMV infections in some immunocompromised patients undergoing bone marrow transplantation. Results of a randomized, double-blind study in bone marrow allograft recipients at risk for developing CMV infection (i.e., CMV-seropositive or -seronegative recipients of bone marrow from a CMV-seropositive donor) indicate that in patients who received acyclovir (IV [given 500 mg/m<sup>2</sup> 3 times daily beginning 5 days before bone marrow transplantation until 30 days after transplantation] followed by either placebo or oral acyclovir [800 mg 4 times daily for 6 months]) the probability of developing CMV infection and delaying its onset was reduced compared with those receiving oral acyclovir (200–400 mg 4 times daily beginning 5 days before bone marrow transplantation until 30 days after transplantation) followed by placebo. If acute CMV infection developed in patients receiving oral acyclovir followed by placebo, it occurred at a median time of 41 days after transplantation while if the infection developed in patients receiving IV acyclovir followed by placebo or oral acyclovir, it occurred at a median time of 54 or 57 days, respectively. In addition, survival rate appeared to be increased in patients receiving IV acyclovir followed by oral acyclovir therapy, compared with those receiving oral acyclovir followed by placebo. While IV acyclovir also has been used in an attempt to prevent CMV disease in patients undergoing autologous bone marrow transplantation<sup>†</sup>, the drug does not appear to be effective for this use. In one retrospective study in CMV-seropositive autologous bone marrow recipients, patients who received IV acyclovir (500 mg/m<sup>2</sup> every 8 hours beginning 5 days before transplantation and continued to day 30) did not have a lower incidence of CMV disease and CMV pneumonia during the first 200 days after transplantation than a control group of CMV-seropositive autograft recipients who did not receive the drug.

There is some evidence that high-dose, oral acyclovir therapy may decrease the incidence of CMV disease in certain renal transplant patients, and results of one study indicate that the drug may decrease the incidence of CMV infection in some liver transplant patients. Although some clinicians recommend use of high-dose, oral acyclovir in renal transplant patients, there is little evidence to

date that use of oral acyclovir (with or without concomitant immune globulin IV) is associated with a clinically important effect on CMV infection or disease in patients undergoing heart, lung, liver, or kidney transplantation who are considered at risk. In one randomized study in patients undergoing liver transplantation, acyclovir (10 mg/kg IV every 8 hours from day 1 after transplantation until discharge, then 800 mg orally 4 times daily until day 100) was less effective than ganciclovir (6 mg/kg daily IV from day 1–30 after transplantation, then 6 mg/kg daily 5 days weekly until day 100) in preventing CMV disease in these patients. During the first 120 days after the procedure, CMV infections occurred in 38% of those receiving acyclovir and in only 5% of those receiving ganciclovir.

Acyclovir is not effective in preventing CMV disease in HIV-infected individuals, and the drug is not recommended for this use in such patients.

Acyclovir is not effective in preventing CMV disease in hematopoietic stem cell transplant (HSCT) recipients, and the drug is not recommended for this use in such patients. Ganciclovir is the drug of choice for this indication.

### ■ Epstein-Barr Virus Infections and Disorders

Because acyclovir exhibits *in vitro* activity against Epstein-Barr virus (EBV), the drug has been used in the treatment of uncomplicated or complicated infectious mononucleosis, chronic infectious mononucleosis, and various disorders (e.g., oral hairy leukoplakia) associated with EBV infections†. While the role of acyclovir in EBV infections remains to be more fully elucidated, current evidence suggests that efficacy of the drug is variable and probably depends on the linear or circular state of EBV DNA, clonality of EBV-infected cells, immune responsiveness of the host, and role of ongoing EBV replication in the pathophysiology of the infection.

Although high-dose oral acyclovir or IV acyclovir has transiently inhibited oropharyngeal shedding of EBV in patients with uncomplicated or complicated infectious mononucleosis, therapy with the drug generally has had little clinical benefit in immunocompetent patients with signs and symptoms of infectious mononucleosis† or in immunocompromised patients with EBV infections†. There are some reports that IV acyclovir may decrease fever and interstitial pneumonitis and improve lymphocyte CD4<sup>+</sup>/CD8<sup>+</sup> ratio in patients with chronic infectious mononucleosis; however, these effects do not occur in all patients who receive the drug.

In a limited number of HIV-infected patients, oral acyclovir therapy was effective in producing clinical regression of oral hairy leukoplakia† (apparently caused by EBV), which recurred following discontinuance of the drug; leukoplakia in patients with acquired immunodeficiency syndrome (AIDS) appeared to be less responsive than in patients whose HIV infection had not progressed to this stage. Some clinicians suggest that, because oral hairy leukoplakia is benign and usually asymptomatic, it may not require treatment. If treatment is required, topical therapy (e.g., topical trichloroacetic acid, glycolic acid, podophyllum resin) may be effective; oral acyclovir can be used in severe cases. However, all of these should be considered palliative since the condition recurs when treatment is discontinued. While there is some evidence that oral acyclovir may suppress oral hairy leukoplakia†, the benefit of prolonged suppressive therapy with acyclovir is questionable because such use could promote emergence of acyclovir-resistant HSV in HIV-infected patients.

Acyclovir appeared to produce a beneficial response in several patients with an atypical EBV-associated syndrome manifested as fever, interstitial pneumonitis, pancytopenia, and extremely high titers of antibody to replicative antigens of EBV. IV acyclovir has been reported to be effective in some renal allograft recipients for the treatment of the early stages of posttransplant EBV-associated polyclonal B-cell lymphoproliferative disorders†; however, the drug does not appear to be effective once the tumor progresses into monoclonal lymphoma.

Because Epstein-Barr virus (EBV) has been suggested as a cause of chronic fatigue syndrome (chronic Epstein-Barr virus syndrome), acyclovir has been used in a limited number of patients for the treatment of this condition. However, in a placebo-controlled study in adults with chronic (average duration of 6.8 years), debilitating fatigue, oral acyclovir therapy (3.2 g daily for 30 days) was no more effective than placebo in ameliorating symptoms of the syndrome and there was no correlation between clinical improvement and reduction in EBV antibody levels.

## Dosage and Administration

### ■ Reconstitution and Administration

Acyclovir is administered orally and acyclovir sodium is administered by slow IV infusion at a constant rate over at least 1 hour. Acyclovir sodium should *not* be administered by rapid IV infusion (over less than 10 minutes) or rapid IV injection. (See Cautions: Renal Effects.) Acyclovir sodium also should *not* be administered orally or by IM or subcutaneous injection and should *not* be applied topically or to the eye.

### Oral Administration

Food does not appear to affect oral absorption of acyclovir, and the drug may be administered without regard to meals.

For oral administration, acyclovir is commercially available as capsules, tablets, or an oral suspension. The commercially available capsules and oral suspension are bioequivalent; in addition, one commercially available 800-mg tablet of acyclovir is bioequivalent to four 200-mg capsules of the drug.

### IV Infusion

Prior to IV infusion, commercially available acyclovir sodium powder for injection must be reconstituted and then diluted with a compatible IV solution or the commercially available acyclovir sodium concentrate for injection containing acyclovir 50 mg/mL must be diluted with a compatible IV solution. Infusion concentrations of 7 mg/mL or lower are recommended.

Acyclovir sodium powder for injection is reconstituted by adding 10 or 20 mL of sterile water for injection to a vial labeled as containing 500 mg or 1 g of acyclovir, respectively, to provide a solution containing 50 mg/mL. For use in most patients, the appropriate dose of reconstituted solution should then be withdrawn from the vial and diluted with 50–125 mL of a compatible IV infusion solution. (See Chemistry and Stability: Stability.) Before withdrawing the dose of acyclovir, the vial containing the reconstituted solution should be shaken well to ensure complete dissolution of the drug. For use in fluid-restricted patients, the appropriate dose of reconstituted solution can be diluted in a ratio of about 1 part reconstituted solution of acyclovir to 9 parts infusion solution; however, because of the risk of adverse effects (e.g., phlebitis), concentrations of the infusion generally should not exceed 7 mg/mL. In addition, higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the infusion site if inadvertent extravasation occurs. Reconstituted acyclovir sodium solutions should be used within 12 hours and reconstituted solutions that have been further diluted in a compatible infusion solution should be used within 24 hours. (See Chemistry and Stability: Stability.)

**Rate of Administration.** Acyclovir sodium solutions generally should be given by IV infusion at a constant rate over a 1-hour period. Because of the risk of adverse renal effects (see Cautions: Renal Effects), diluted solutions of acyclovir *should not be infused over a period less than 1 hour*.

### ■ Oral Dosage

#### Mucocutaneous, Ocular, and Systemic Herpes Simplex Virus Infections

**Treatment of Mucocutaneous HSV Infections.** When oral acyclovir is used for the treatment of mucocutaneous HSV infections in immunocompromised adults†, including those infected with human immunodeficiency virus (HIV), some clinicians recommend a dosage of 400 mg every 4 hours while awake (5 times daily) for 7–14 days. For the treatment of these infections in immunocompromised children†, the American Academy of Pediatrics (AAP) recommends an oral dosage of 1 g daily given in 3–5 divided doses for 7–14 days.

For the treatment of orolabial HSV infections in HIV-infected adults, the US Centers for Disease Control and Prevention (CDC) recommends an oral acyclovir dosage of 400 mg 3 times daily for 7–14 days. For the treatment of mild symptomatic HSV gingivostomatitis† in HIV-infected children, CDC recommends a dosage of 20 mg/kg (up to 400 mg) 3 times daily for 7–14 days. A dosage of 15 mg/kg (up to 200 mg) 5 times daily for 7 days has been used for the treatment of HSV gingivostomatitis† in immunocompetent children 1–6 years of age.

**Chronic Suppressive and Maintenance Prophylaxis of HSV.** When oral acyclovir is used for chronic suppressive or maintenance prophylaxis (secondary prophylaxis) of HSV† in HIV-infected adults or adolescents who have frequent or severe recurrences of HSV disease, a dosage of 200 mg 3 times daily or 400 mg twice daily has been recommended by the Prevention of Opportunistic Infections Working Group of the US Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA).

The USPHS/IDSA recommends that HIV-infected infants and children who have frequent or severe recurrences of HSV receive oral acyclovir in a dosage of 80 mg/kg daily given in 3 or 4 divided doses for suppressive therapy.

**Ocular HSV Infections.** For the treatment of HSV keratitis† in HIV-infected patients, oral acyclovir has been given in a dosage of 400 mg 5 times daily; long-term antiviral therapy may be necessary to prevent recurrent ocular HSV disease in these patients. For the prevention of recurrent ocular HSV disease† in immunocompetent adults and children 12 years of age or older, oral acyclovir has been given in a dosage of 400 mg twice daily for 12–18 months. For prevention of recurrent ocular HSV disease† following penetrating keratoplasty for herpetic eye disease, oral acyclovir has been given in a dosage of 400 mg twice daily for 6 months. Optimum duration of prophylaxis remains to be determined.

**Hematopoietic Stem Cell Transplant Recipients.** When oral acyclovir is used for the prevention of recurrent HSV disease† in HSV-seropositive adults and adolescents undergoing hematopoietic stem cell transplantation (HSCT), some clinicians recommend an acyclovir dosage of 200 mg 3 times daily. For

HSV-seropositive children, clinicians recommend an oral acyclovir dosage of 0.6–1 g daily given in 3–5 divided doses.

Acyclovir therapy is initiated at the beginning of the conditioning regimen and continued until engraftment occurs or mucositis resolves (i.e., approximately 30 days after HSCT). Routine prophylaxis for longer than 30 days is not recommended.

### Genital Herpes

**Treatment of Initial Episodes in Immunocompetent Individuals.** For the treatment of initial episodes of genital herpes in immunocompetent individuals, the dosage of oral acyclovir recommended by the manufacturer is 200 mg every 4 hours while awake (5 times daily) for 10 days. The CDC and other clinicians state that the usual dosage of oral acyclovir for the treatment of initial genital herpes in immunocompetent adults or adolescents is 400 mg 3 times daily or 200 mg 5 times daily given for 7–10 days. The CDC states that the duration of therapy may be extended if healing is incomplete after 10 days.

For the treatment of initial episodes of genital herpes in immunocompetent children, the AAP recommends a dosage of 40–80 mg/kg daily (maximum 1 g daily) given in 3 or 4 divided doses for 5–10 days.

If acyclovir is used for the treatment of initial episodes of herpes proctitis† in adults, an oral acyclovir dosage of 400 mg 5 times daily for 10 days or until clinical resolution occurs has been used. Alternatively, some clinicians recommend an oral dosage of 800 mg every 8 hours for 7–10 days for the treatment of initial episodes of herpes proctitis.

**Episodic Treatment of Recurrent Episodes.** For the episodic treatment of recurrent genital herpes in immunocompetent adults, the manufacturer recommends a dosage of 200 mg every 4 hours while awake (5 times daily) for 5 days. The CDC states that the usual dosage of oral acyclovir for the episodic treatment of recurrent genital herpes in immunocompetent adults and adolescents is 400 mg 3 times daily for 5 days, 800 mg twice daily for 5 days, or 800 mg 3 times daily for 2 days.

In HIV-infected adults and children, the CDC recommends a dosage of 400 mg 3 times daily given for 5–10 days for episodic treatment of recurrent episodes; alternatively, acyclovir can be given for 7–14 days. Acyclovir should be initiated at the earliest prodromal sign or symptom of recurrence or within 1 day of the onset of lesions.

**Chronic Suppressive Therapy of Recurrent Episodes.** For chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent adults and adolescents, the usual dosage of oral acyclovir is 400 mg orally twice daily. Alternatively, the manufacturer states that dosages of 200 mg orally 3–5 times daily have been used.

In HIV-infected adults and adolescents, the CDC recommends a dosage of 400–800 mg 2- or 3-times daily for chronic suppressive therapy of recurrent genital herpes. Oral acyclovir has been used for chronic suppressive therapy for up to 5–6 years; however, the manufacturer and CDC recommend that suppressive antiviral therapy be discontinued periodically (e.g., once yearly) to assess the need for continued therapy.

### Varicella-Zoster Infections

**Varicella (Chickenpox).** For the treatment of varicella (chickenpox) in immunocompetent adults and children 2 years of age and older, the recommended oral dosage of acyclovir is 20 mg/kg (maximum 800 mg per dose) 4 times daily for 5 days. The manufacturer recommends that adults and children who weigh more than 40 kg receive 800 mg orally 4 times daily for 5 days and that children 2 years of age and older weighing 40 kg or less receive 20 mg/kg 4 times daily (maximum daily dosage 80 mg/kg) for 5 days. While lower dosages of oral acyclovir also have been used in immunocompetent children with varicella, some evidence indicates that such dosages may be less effective than the currently recommended dosage. Although the manufacturer states that safety and efficacy of oral acyclovir have not been adequately studied for children younger than 2 years of age, the AAP states that certain children older than 12 months of age† may receive the currently recommended oral dosage of the drug but that data are insufficient to make a recommendation for children 12 months of age or younger. For HIV-infected children with mild immunosuppression and mild varicella, CDC recommends oral acyclovir 20 mg/kg (maximum 800 mg per dose) 4 times daily for 7 days or until no new lesions appear for 48 hours.

If oral acyclovir is used for the treatment of varicella, the drug must be initiated at the earliest sign or symptom of infection. Oral acyclovir offers maximum benefit when initiated as soon as possible after the first manifestation of chickenpox appears; little if any benefit is apparent if treatment is delayed (e.g., for 48 hours after onset of rash). AAP recommends that oral acyclovir therapy be initiated within the first 24 hours after the onset of rash.

**Herpes Zoster (Shingles, Zoster).** For the treatment of acute herpes zoster (shingles, zoster) in immunocompetent adults and children 12 years of age or older, the recommended oral dosage of acyclovir is 800 mg every 4 hours 5 times daily (4 g daily) for 5–10 days, preferably initiated within 48 hours of rash onset. Acyclovir also has been used for longer periods (e.g., for 21 days) in the management of acute herpes zoster in immunocompetent patients.

For HIV-infected children with mild immunosuppression and mild zoster, CDC recommends oral acyclovir 20 mg/kg (maximum 800 mg per dose) 4 times daily for 7–10 days.

For the treatment of acute herpes zoster ophthalmicus† in immunocompetent adults, an acyclovir oral dosage of 600 mg every 4 hours 5 times daily (3 g daily) for 10 days, preferably initiated within 72 hours but no later than 7 days of rash onset, has been used.

For the treatment of dermatomal herpes zoster in immunocompromised patients†, including transplant recipients or HIV-infected adults, acyclovir has been given in a dosage of 800 mg orally 5 times daily for 10 days.

### ■ IV Dosage

Dosage of acyclovir sodium is expressed in terms of acyclovir. The manufacturer states that the maximum dosage of IV acyclovir is 20 mg/kg every 8 hours. The manufacturer recommends that obese patients receive IV acyclovir dosages based on ideal body weight.

### Mucocutaneous and Systemic Herpes Simplex Virus Infections

**Treatment of Mucocutaneous HSV Infections.** For the treatment of mucocutaneous HSV infections in immunocompromised patients, including HIV-infected individuals, the usual IV dosage of acyclovir for adults and children 12 years of age or older with normal renal function (i.e., creatinine clearance greater than 50 mL/minute per 1.73 m<sup>2</sup>) is 5 mg/kg every 8 hours (15 mg/kg daily) for 7–14 days; in children younger than 12 years of age, the recommended dosage is 10 mg/kg every 8 hours for 7–14 days.

For the treatment of moderate to severe symptomatic HSV gingivostomatitis† in HIV-infected children, CDC recommends an IV acyclovir dosage of 5–10 mg/kg 3 times daily for 7–14 days.

**Treatment of HSV Encephalitis.** For the treatment of HSV encephalitis, the recommended IV dosage of acyclovir for adults and children 12 years of age or older is 10–15 mg/kg every 8 hours. In children between 3 months and 12 years of age, the recommended IV dosage is 20 mg/kg every 8 hours. The manufacturer recommends 10 days of IV acyclovir therapy for the treatment of HSV encephalitis; however, because relapses have been reported after only 10 days' treatment, some clinicians recommend a longer duration of parenteral treatment (e.g., 14–21 days).

**Treatment of Neonatal HSV Infection.** For the treatment of neonatal HSV infection in infants from birth to 3 months of age, the manufacturer recommends an IV acyclovir dosage of 10 mg/kg every 8 hours for 10 days. The AAP and other clinicians recommend an IV acyclovir dosage of 20 mg/kg every 8 hours for 14–21 days; however, the manufacturer states that safety and efficacy of doses greater than 10 mg/kg for the treatment of neonatal HSV infection have not been established. The AAP states that IV acyclovir should be given for 14 days if disease is limited to the skin, eye, and mouth or for 21 days if disease is disseminated or involves the CNS.

**Hematopoietic Stem Cell Transplant Recipients.** For the prevention of recurrent HSV disease† in HSV-seropositive adults and adolescents undergoing hematopoietic stem cell transplantation (HSCT), some clinicians recommend an IV acyclovir dosage of 250 mg/m<sup>2</sup> every 12 hours. For HSV-seropositive children, some clinicians recommend an IV acyclovir dosage of 250 mg/m<sup>2</sup> every 8 hours or 125 mg/m<sup>2</sup> every 6 hours. Therapy can be switched to oral acyclovir when appropriate. Acyclovir therapy is initiated at the beginning of the conditioning regimen and continued until engraftment occurs or mucositis resolves (i.e., approximately 30 days after HSCT). Routine prophylaxis for longer than 30 days is not recommended.

### Genital Herpes

For the treatment of severe first episodes of genital herpes, the usual IV dosage of acyclovir for immunocompetent adults and children 12 years of age and older is 5–10 mg/kg every 8 hours. The manufacturer and some clinicians states that IV acyclovir should be given for 5–7 days; the CDC states that IV acyclovir should be given for 2–7 days or until clinical improvement occurs and then an oral antiviral agent should be substituted to complete at least 10 days of therapy.

### Varicella-Zoster Infections

For the treatment of varicella (chickenpox) or herpes zoster (shingles, zoster) in immunocompromised adults and children 12 years of age and older with normal renal function, the manufacturer recommends an IV dosage of acyclovir of 10 mg/kg every 8 hours for 7 days. In children younger than 12 years of age, the manufacturer recommends an IV acyclovir dosage of 20 mg/kg every 8 hours for 7 days.

For the treatment of varicella in HIV-infected adults, CDC recommends an IV dosage of 10 mg/kg every 8 hours for 7–10 days. Therapy can be switched to oral acyclovir (800 mg 4 times daily) after defervescence if there is no evidence of visceral involvement.

For the treatment of varicella in immunocompetent children 2 years of age or older, AAP recommends an IV acyclovir dosage of 30 mg/kg daily in divided doses or 500 mg/m<sup>2</sup> every 8 hours for 7–10 days. For the treatment of varicella in immunocompromised children younger than 1 year of age, AAP and

others recommend an IV acyclovir dosage of 10 mg/kg every 8 hours for 7–10 days. For immunocompromised children 1 year of age and older, AAP recommends 500 mg/m<sup>2</sup> every 8 hours for 7–10 days; other experts recommend 30 mg/kg daily in divided doses.

For the treatment of herpes zoster in immunocompromised children younger than 12 years of age, AAP recommends an IV acyclovir dosage of 20 mg/kg every 8 hours for 7–10 days. For immunocompromised children 12 years of age or older, AAP recommends an IV acyclovir dosage of 10 mg/kg every 8 hours for 7 days. For the treatment of herpes zoster in immunocompetent children younger than 1 year of age, AAP recommends an IV acyclovir dosage of 10 mg/kg every 8 hours for 7–10 days. For immunocompetent children 1 year of age and older, AAP recommends 500 mg/m<sup>2</sup> every 8 hours for 7–10 days; other experts recommend 30 mg/kg daily in divided doses.

For the treatment of extensive multidermatomal zoster or zoster with trigeminal nerve involvement in HIV-infected children with severe immunosuppression, CDC recommends an IV acyclovir dosage of 10 mg/kg 3 times daily for 7–10 days.

### ■ Dosage in Renal Impairment

In patients with impaired renal function, doses and/or frequency of administration of acyclovir must be modified in response to the degree of impairment. Generally, the decrease in total body clearance of acyclovir is directly related to the decrease in body-surface-area-corrected creatinine clearance; however, clearance of acyclovir is usually greater than predicted from creatinine clearance, since the drug undergoes some renal tubular secretion.

#### Oral Dosage

Based on pharmacokinetic studies of IV acyclovir in patients with renal impairment, the manufacturer recommends the following oral dosage of acyclovir based on the usual dosage regimen and the patient's creatinine clearance (see Table 1):

**Table 1: Oral Dosage Adjustment in Patients with Renal Impairment.**

Usual Dosage Regimen	Creatinine Clearance (mL/min per 1.73 m <sup>2</sup> )	Adjusted Dosage Regimen
200 mg every 4 h 5 times daily	>10	No adjustment necessary
	0–10	200 mg every 12 h
400 mg every 12 h	>10	No adjustment necessary
	0–10	200 mg every 12 h
800 mg every 4 h 5 times daily	>25	No adjustment necessary
	10–25	800 mg every 8 h
	0–10	800 mg every 12 h

Because acyclovir is removed by hemodialysis, the manufacturer recommends that patients undergoing hemodialysis receive a supplemental oral dose of the drug immediately after each dialysis period. The manufacturer states that supplemental doses of oral acyclovir do not appear to be necessary following peritoneal dialysis.

For HIV-infected patients with impaired renal function, the following oral dosages of acyclovir have been suggested based on a usual dosage regimen of 200–800 mg every 4–6 hours and the patient's creatinine clearance (see Table 2):

**Table 2: Oral Dosage Adjustment in HIV-Infected Patients with Impaired Renal Function.**

Creatinine Clearance (mL/min per 1.73 m <sup>2</sup> )	Adjusted Dosage Regimen
>80	No adjustment necessary
50–80	200–800 mg every 6–8 h
25–50	200–800 mg every 8–12 h
10–25	200–800 mg every 12–24 h
<10	200–400 mg every 24 h
Hemodialysis	supplement usual dose after each hemodialysis

#### Parenteral Dosage

The manufacturer recommends the following IV dosage of acyclovir based on the patient's creatinine clearance (see Table 3):

**Table 3: IV Dosage Adjustment in Patients with Renal Impairment.**

Creatinine Clearance (mL/min per 1.73 m <sup>2</sup> )	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25–50	100%	12
10–25	100%	24
0–10	50%	24

The manufacturer states that patients undergoing hemodialysis may require a supplemental acyclovir dose after each dialysis period. The patient's dosing

schedule should be adjusted so that an additional dose is administered after each dialysis. Alternatively in patients undergoing hemodialysis, some clinicians recommend that 2.5 mg/kg be administered every 24 hours and that an additional 2.5-mg/kg dose be administered after each dialysis period.

Other IV acyclovir dosage regimens have been suggested for patients with end-stage renal disease. In one regimen, an initial loading dose of 93–185 mg/m<sup>2</sup>, a maintenance dosage of 35–70 mg/m<sup>2</sup> every 8 hours, and a dose of 56–185 mg/m<sup>2</sup> immediately after dialysis have been used. Alternatively, an initial loading dose of 250–500 mg/m<sup>2</sup>, a maintenance dosage of 250–500 mg/m<sup>2</sup> every 48 hours, and a dose of 150–500 mg/m<sup>2</sup> immediately after dialysis have been suggested.

Because acyclovir is removed by continuous ambulatory peritoneal dialysis (CAPD) to a lesser extent than by hemodialysis, the manufacturer states that supplemental doses of acyclovir do not appear to be necessary following CAPD.

For HIV-infected patients with impaired renal function, the following IV dosages of acyclovir have been suggested based on a usual dosage regimen of 5 mg/kg every 8 hours and the patient's creatinine clearance:

**Table 4: IV Dosage Adjustment in HIV-Infected Patients with Impaired Renal Function.**

Creatinine Clearance (mL/min per 1.73 m <sup>2</sup> )	Adjusted Dosage Regimen
greater than 80	No adjustment necessary
50–80	No adjustment necessary
25–50	5 mg/kg every 12–24 hours
10–25	5 mg/kg every 12–24 hours
less than 10	2.5 mg/kg every 24 hours
Hemodialysis	administer usual dose after hemodialysis

### Cautions

Adverse reactions generally have been minimal following oral or IV administration of acyclovir. However, potentially serious reactions (e.g., renal failure, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) can occur and fatalities have been reported.

#### ■ Local Effects

The most frequent adverse effects of IV acyclovir are local reactions at the injection site. Inflammation or phlebitis has been reported in approximately 9% of patients. Severe local inflammatory reactions, including tissue necrosis, have occurred following infusion of acyclovir into extravascular tissues.

#### ■ Renal Effects

Increased BUN and/or serum creatinine concentrations, anuria, and hematuria have been reported in patients receiving acyclovir. Abnormal urinalysis (characterized by an increase in formed elements in urine sediment) and pain or pressure on urination have been reported rarely with IV acyclovir.

Transient increases in BUN and/or serum creatinine concentrations and decreases in creatinine clearance occur in about 5–10% of patients receiving IV acyclovir, and have been reported most frequently when the drug was administered by rapid (over less than 10 minutes) IV infusion rather than over the recommended period for IV infusion (at least 1 hour).

Renal failure, resulting in death in some patients, has occurred in patients receiving acyclovir. The risk of adverse renal effects during IV acyclovir therapy depends on the patient's degree of hydration, urine output, concomitant therapy (i.e., other nephrotoxic drugs), preexisting renal disease, and the rate of administration of acyclovir. Precipitation of the drug in the renal tubules can occur when the solubility of free acyclovir in the collecting duct is exceeded or following rapid IV administration of the drug; ensuing renal tubular damage may result in acute renal failure. In some cases, alterations in renal function during IV acyclovir therapy progress to acute renal failure; however, in most cases, alterations in renal function are transient and resolve spontaneously or following improved hydration and electrolyte balance, dosage adjustment, or discontinuance of the drug.

#### ■ Nervous System Effects

Headache is one of the most common nervous system adverse effects of oral acyclovir, occurring in about 2% of patients receiving the drug as chronic suppressive therapy. Aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, delirium, dizziness, encephalopathy, hallucinations, obtundation, paresthesia, psychosis, seizures, somnolence, and tremors have been reported during oral or IV acyclovir therapy and these effects may be marked, particularly in older adults or patients with renal impairment. In patients receiving oral acyclovir for the treatment of herpes zoster (shingles, zoster), malaise was reported in 11.5% of patients receiving the drug and 11.1% of those receiving placebo.

Encephalopathic effects including lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, and coma have occurred in approximately 1% of patients receiving IV acyclovir. Agitation, delirium, diaphoresis,

dizziness, headache, lightheadedness, somnolence, and psychosis have occurred rarely. Coarse tremor and clonus developed in at least one immunocompromised patient during IV acyclovir therapy. Cerebral edema, coma, and death, probably resulting from cerebral anoxia, occurred during IV acyclovir therapy in an immunocompromised bone marrow transplant patient with pneumonitis.

#### ■ GI Effects

Nausea, vomiting, and diarrhea are among the most common adverse effects of oral acyclovir. In a study in patients receiving oral acyclovir for treatment of recurrent genital herpes, nausea occurred in about 5% and diarrhea in about 2% of patients receiving the drug for chronic suppressive therapy and these adverse GI effects occurred in 2.4–2.7% of those receiving episodic treatment of recurrences. In patients receiving oral acyclovir for the treatment of initial episodes of genital herpes, nausea and/or vomiting occurred in 2.7%. Diarrhea was reported in 3.2% of patients receiving the drug for the treatment of varicella (chickenpox). GI distress also has been reported in patients receiving oral acyclovir.

Nausea and/or vomiting have been reported in about 7% of patients receiving IV acyclovir therapy (mainly occurring in nonhospitalized patients receiving acyclovir dosages of 10 mg/kg 3 times daily). Anorexia, diarrhea, and GI distress also have been reported with IV acyclovir.

#### ■ Hematologic Effects

Anemia, leukocytoclastic vasculitis, leukopenia, lymphadenopathy, and thrombocytopenia have been reported in patients receiving oral acyclovir.

Anemia, disseminated intravascular coagulation, hemoglobinemia, hemolysis, leukocytoclastic vasculitis, leukocytosis, leukopenia, lymphadenopathy, neutropenia, neutrophilia, thrombocytopenia, and thrombocytosis have been reported rarely in patients receiving IV acyclovir.

#### ■ Dermatologic and Sensitivity Reactions

Rash, pruritus, or urticaria occasionally occurs during oral or IV acyclovir therapy. Alopecia and angioedema have been reported. At least one case of erythematous rash and vasculitis has been reported following administration of IV acyclovir to an immunocompromised patient exposed to chickenpox; however, this reaction has not been directly attributed to the drug.

Anaphylaxis has been reported rarely in patients receiving oral or IV acyclovir. Stevens-Johnson syndrome, erythema multiforme, photosensitivity rash, and toxic epidermal necrolysis have occurred rarely in patients receiving acyclovir.

#### ■ Other Adverse Effects

Fever and pain have been reported in patients receiving oral or IV acyclovir. Elevated liver function test results, hepatitis, hyperbilirubinemia, jaundice, hypotension, myalgia, peripheral edema, thirst, and visual abnormalities have been reported rarely in patients receiving oral or IV acyclovir.

#### ■ Precautions and Contraindications

Oral and IV acyclovir are contraindicated in patients who develop hypersensitivity to acyclovir or valacyclovir.

Patients receiving acyclovir for the treatment of genital herpes should be advised that the drug is not a cure for genital herpes and that, because genital herpes is a sexually transmitted disease, they should avoid sexual contact while visible lesions are present since there is a risk of infecting their sexual partner. (See Patient Counseling and Management of Sexual Partners under Uses: Genital Herpes.) If acyclovir is used for chronic suppressive therapy of genital herpes, the drug should be discontinued after 1 year of therapy so that the frequency and severity of the patient's genital herpes infection can be reevaluated to determine the need for continuing acyclovir therapy. Oral acyclovir has been used for suppressive therapy of genital herpes in immunocompetent adults for up to 5–6 years without evidence of long-term adverse effects.

All patients receiving oral acyclovir should be instructed to consult their clinician if severe or troublesome adverse effects occur during acyclovir therapy. Female patients receiving the drug should be instructed to consult their physician if they become pregnant or intend to become pregnant or if they intend to breast-feed. (See Cautions: Pregnancy, Fertility, and Lactation.)

The manufacturer states that the recommended dosage and duration of acyclovir therapy should not be exceeded. The manufacturer also cautions that both the dose and dosage interval should be carefully adjusted in patients with renal failure or in patients undergoing hemodialysis to prevent drug accumulation, decrease the risk of toxicity, and maintain adequate plasma concentrations of acyclovir. The manufacturer states that when dosage adjustment is required, they should be based on estimated creatinine clearance. (See Dosage and Administration: Dosage in Renal Impairment.)

Acyclovir should be used with caution in patients receiving other nephrotoxic drugs concurrently since the risk of acyclovir-induced renal impairment and/or reversible CNS symptoms is increased in these patients. Adequate hydration should be maintained in patients receiving acyclovir; however, in patients with encephalitis, the recommended hydration should be balanced by the risk of cerebral edema. Because the risk of acyclovir-induced renal impairment

is increased during rapid IV administration of the drug, acyclovir should be given only by slow IV infusion (over at least 1 hour).

Parenteral acyclovir therapy can cause signs and symptoms of encephalopathy. (See Cautions: Nervous System Effects.) The manufacturer states that acyclovir should be used with caution in patients with underlying neurologic abnormalities and in patients with serious renal, hepatic, or electrolyte abnormalities or substantial hypoxia. The drug also should be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving intrathecal methotrexate or interferon.

#### ■ Pediatric Precautions

The manufacturer states that safety and efficacy of oral acyclovir in children younger than 2 years of age have not been established.

#### ■ Geriatric Precautions

In a clinical study evaluating use of oral acyclovir for the treatment of herpes zoster (shingles, zoster) in immunocompetent adults 50 years of age or older, approximately 65% of patients were 65 years of age or older and more than 30% were 75 years of age or older. There was no overall difference in effectiveness for time to cessation of new lesion formation or time to healing between geriatric patients and younger adults. However, the duration of pain after healing was longer in those 65 years of age and older and nausea, vomiting, and dizziness were reported more frequently in geriatric patients. Clinical studies evaluating IV acyclovir have not included sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger patients.

Geriatric patients are more likely than younger adults to have adverse CNS effects (e.g., coma, confusion, hallucinations, somnolence) during acyclovir therapy. Geriatric patients also are more likely to have adverse renal effects during acyclovir therapy and to have reduced renal function requiring dosage adjustment. Acyclovir dosage should be carefully selected for this age group and it may be useful to monitor renal function.

#### ■ Mutagenicity and Carcinogenicity

Mutagenic changes and chromosomal damage have occurred in vitro in human lymphocytes and mouse lymphoma cells at acyclovir concentrations at least 25 times greater than plasma drug concentrations achievable with usual dosage in humans. In other in vitro microbial and mammalian cell assays, no evidence of mutagenicity or inconclusive results were observed. The manufacturer states that acyclovir was tested in 16 in vitro and in vivo genetic toxicity assays and was positive in 5 of these assays.

In lifetime bioassays in rats and mice receiving single daily dosages of up to 450 mg/kg administered by gastric lavage, there was no statistically significant difference in the incidence of tumors between treated and control animals and no evidence that acyclovir shortened the latency of tumors. Maximum plasma concentrations in the mouse or rat bioassay were 3–6 or 1–2 times, respectively, the usual human concentrations (based on steady-state plasma concentrations observed in humans receiving 200 or 800 mg of acyclovir orally 5 times daily).

Evidence of mutagenicity or carcinogenicity in humans has not been reported to date.

#### ■ Pregnancy, Fertility, and Lactation

##### *Pregnancy*

There are no adequate and controlled studies to date using acyclovir in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Acyclovir administered during organogenesis was not teratogenic in the mouse (450 mg/kg daily orally), rabbit (50 mg/kg daily subcutaneously or IV), or rat (50 mg/kg daily subcutaneously). These dosages resulted in plasma concentrations that were 106, 11, and 22 times, respectively, the steady-state plasma concentrations observed in humans receiving 200 or 800 mg of acyclovir orally 5 times daily. However, in nonstandard tests in rats, fetal abnormalities (e.g., head and tail anomalies) and maternal toxicity were observed with subcutaneous acyclovir. Acyclovir crosses the placenta in humans and the clinical relevance of these animal findings currently is not known.

IV acyclovir has been used during the second or third trimester of pregnancy without apparent adverse effects to the fetus. The US Centers for Disease Control and Prevention (CDC) state that first clinical episodes of genital herpes occurring during pregnancy may be treated with oral acyclovir and that use of IV acyclovir therapy may be indicated for the treatment of severe maternal HSV infections. Preliminary data suggest that acyclovir treatment late in pregnancy might reduce the frequency of cesarean sections among women who have recurrent genital herpes by diminishing the frequency of recurrences at term. The risk for HSV is high in infants born to women who acquired genital herpes in late pregnancy, and such women should be managed in consultation with an HSV specialist. Some experts recommend acyclovir therapy in this circumstance, some recommend routine cesarean section to reduce the risk for neonatal HSV, and others recommend both. (See Pregnant Women under Uses: Genital Herpes.)

Many clinicians do not recommend use of oral acyclovir in pregnant adolescents or women with uncomplicated varicella because the risk or benefit to the fetus currently is not known. However, other clinicians recommend use of oral acyclovir for the treatment of varicella in pregnant women, especially during the second and third trimesters. In addition, use of IV acyclovir is recommended in pregnant women with serious complications of varicella such as extensive cutaneous disease, high fever, or systemic symptoms. It is not known whether acyclovir administered to the mother prevents congenital varicella syndrome (i.e., low birthweight, hypotrophic limbs, ocular abnormalities, brain damage, mental retardation) in the neonate.

To monitor fetal outcomes of pregnant women exposed either inadvertently or intentionally to systemic acyclovir, the manufacturer established a prospective registry of acyclovir use during pregnancy and collected data from 1984 to April 1999. A total of 749 pregnancies were followed over this time period involving 756 outcomes, and comparison of registry data with birth defect surveillance data revealed no evidence of an increased risk for birth defects in infants of mothers treated with acyclovir during the first trimester of pregnancy. However, the sample size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.

### Fertility

Reproduction studies using oral acyclovir dosages of 450 mg/kg daily in mice and subcutaneous dosages of 25 mg/kg daily in rats have not revealed evidence of impaired fertility. Following subcutaneous dosages of 50 mg/kg daily in rats and rabbits, a decrease in implantation efficiency was observed; decreases in the numbers of corpora lutea, implantation sites, and live fetuses were observed in rats. No effect on implantation efficiency was observed in rabbits following IV dosages of 50 mg/kg daily. Although no drug-related reproductive effects were observed in rabbits following IV dosages of 50 mg/kg daily, increases in fetal resorptions and corresponding decreases in litter size were observed following IV dosages of 100 mg/kg daily. Following intraperitoneal acyclovir dosages of 320 or 80 mg/kg daily in male rats for 1 or 6 months, respectively, testicular atrophy was observed; some evidence of recovery of sperm production was apparent 30 days after discontinuance of the drug. Aspermatogenesis was observed in dogs following IV dosages of 100 and 200 mg/kg daily for 31 days. No adverse testicular effects were observed in dogs given IV dosages of 50 mg/kg daily for one month or given 60 mg/kg daily for one year. In a controlled study in men receiving chronic oral acyclovir (400 mg or 1 g daily) therapy, there was no evidence of clinically important effects on sperm count, motility, or morphology during 6 months of therapy and 3 months of posttreatment follow-up.

### Lactation

Limited data indicate that acyclovir is distributed into milk, generally in concentrations greater than concurrent maternal plasma concentrations, and can be absorbed by nursing infants. Acyclovir should be administered to nursing women with caution and only when indicated.

## Drug Interactions

### ■ Antifungal Agents

Amphotericin B has been shown to potentiate the antiviral effect of acyclovir against pseudorabies virus in vitro when both drugs are added to the culture medium. Ketoconazole and acyclovir have shown dose-dependent, synergistic, antiviral activity against herpes simplex virus types 1 and 2 (HSV-1 and -2) in in vitro replication studies. The clinical importance of these interactions has not been established, and additional study is necessary to determine potential antiviral synergy between these antifungal agents and acyclovir.

### ■ Probenecid

Concomitant administration of probenecid and acyclovir has reportedly increased the mean plasma half-life and area under the plasma concentration-time curve (AUC) and decreased urinary excretion and renal clearance of acyclovir. In one study following oral administration of a 1-g dose of probenecid 1 hour prior to a 1-hour IV infusion of acyclovir 5 mg/kg, the half-life and AUC for acyclovir increased by 18% and 40%, respectively, and urinary excretion and renal clearance of acyclovir decreased by 13% and 32%, respectively. This interaction may result from competitive inhibition of the renal secretion of acyclovir by probenecid.

### ■ Interferon

The manufacturer states that IV acyclovir should be used with caution in patients receiving interferon. In vitro, when acyclovir and interferon are both added to cultures of herpes simplex virus type 1 (HSV-1), the drugs have an additive or synergistic antiviral effect; however, the clinical importance of this interaction is not known.

### ■ Methotrexate

The manufacturer states that IV acyclovir should be used with caution in patients receiving intrathecal methotrexate.

### ■ Zidovudine

Acyclovir has been used concomitantly with zidovudine in some patients with human immunodeficiency virus (HIV) infections without evidence of increased toxicity; however, neurotoxicity (profound drowsiness and lethargy), which recurred on rechallenge, has been reported in at least one patient with acquired immunodeficiency syndrome (AIDS) during concomitant therapy with the drugs. Neurotoxicity was evident within 30–60 days after initiation of IV acyclovir therapy, persisted with some improvement when acyclovir was administered orally, and resolved following discontinuance of acyclovir in this patient. Because use of acyclovir for the treatment and prevention of opportunistic infections may be necessary in patients receiving zidovudine, such patients should be monitored closely during combined therapy.

## Acute Toxicity

Acyclovir overdosage involving ingestion of up to 20 g of the drug have been reported. Overdosage of IV acyclovir has been reported following administration of rapid IV injections or inappropriately high doses and in patients with fluid and electrolyte imbalance, resulting in elevations in BUN and serum creatinine concentration and subsequent renal failure. Other adverse effects reported with acyclovir overdosage include agitation, coma, lethargy, and seizures. At renal concentrations exceeding 2.5 mg/mL, acyclovir crystals may precipitate in the renal tubules, possibly causing renal dysfunction and eventual renal failure and anuria. (See Cautions: Renal Effects.)

If acute renal failure and anuria occur, use of hemodialysis should be considered until renal function is restored. A 6-hour period of hemodialysis may result in a 60% decrease in plasma acyclovir concentrations. Data are limited regarding peritoneal dialysis but this method does not appear to appreciably remove the drug.

## Mechanism of Action

Acyclovir exerts its antiviral effect against 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 been fully elucidated.

In cells infected with herpesvirus in vitro, the antiviral activity of acyclovir appears to depend principally on the intracellular conversion of the drug to acyclovir triphosphate. Acyclovir is converted to acyclovir monophosphate principally via virus-coded thymidine kinase (TK); the monophosphate is phosphorylated to the diphosphate via cellular guanylate kinase and then to the triphosphate via other cellular enzymes (e.g., phosphoglycerate kinase, pyruvate kinase, phosphoenolpyruvate carboxykinase). In uninfected cells in vitro, acyclovir is only minimally phosphorylated by cellular (host cell) enzymes. The formation of acyclovir monophosphate appears to be the rate-limiting step in the formation of acyclovir triphosphate. In vitro studies have shown that the extent of formation of acyclovir monophosphate, diphosphate, and triphosphate by both uninfected and virus-infected cells is directly related to the concentration of acyclovir in the culture medium. Acyclovir also is apparently converted to acyclovir triphosphate by other mechanisms since the drug has some activity against several viruses that apparently do not code for viral TK (e.g., Epstein-Barr virus, cytomegalovirus). 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.

In vitro studies with HSV 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. In herpesviruses, acyclovir triphosphate inhibits DNA synthesis by competing with deoxyguanosine triphosphate for viral DNA polymerase and incorporation principally into viral DNA. In vitro in herpesviruses, acyclovir can be incorporated into growing chains of DNA via viral DNA polymerase and to a much lesser extent via cellular  $\alpha$ -DNA polymerase. Viral DNA polymerase exhibits a 10- to 30-fold or greater affinity in vitro for acyclovir triphosphate than does cellular  $\alpha$ -DNA polymerase. Following incorporation of acyclovir triphosphate into the DNA chain, DNA synthesis is terminated. In vitro studies have shown that acyclovir triphosphate also partially inhibits the synthesis of  $\gamma$ -polypeptides within cells that are infected with herpesvirus. Acyclovir has minimal pharmacologic effects in vitro in uninfected cells since uptake of the drug into these cells is poor, phosphorylation of acyclovir and intracellular formation of acyclovir triphosphate are minimal, and cellular  $\alpha$ -DNA polymerase has a low affinity for acyclovir triphosphate.

Non-phosphorylated acyclovir, acyclovir monophosphate, and acyclovir diphosphate are thought to have minimal or no effect on viral or cellular  $\alpha$ -DNA polymerase and therefore have no antiviral activity.

The antiviral activity of acyclovir against Epstein-Barr virus and cytomegalovirus (CMV) appears to differ from that against HSV. The antiviral activity against Epstein-Barr virus may result from increased sensitivity of its viral DNA polymerase to inhibition by low concentrations of acyclovir triphosphate (formed via cellular phosphorylating enzymes). The antiviral activity against human CMV may result from inhibition of virus-specific polypeptide synthesis; such inhibition requires high concentrations of acyclovir or its triphosphate in vitro. In vitro studies indicate that DNA polymerase of murine CMV is substantially more sensitive to inhibition by acyclovir triphosphate than that of human CMV; this difference in sensitivity appears to correlate with the difference in in vitro susceptibility of murine and human CMV to the drug. Further studies are needed to evaluate the antiviral activity of acyclovir against Epstein-Barr virus and CMV.

## Spectrum

Following intracellular conversion to a pharmacologically active triphosphate metabolite, acyclovir is active in vitro against various Herpesviridae including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus, Epstein-Barr virus, herpesvirus simiae (B virus), and cytomegalovirus (CMV).

### ■ In Vitro Susceptibility Testing

Various methods (e.g., cytopathic effect inhibition, plaque inhibition, dye-uptake, disk-agar diffusion) have been used to test the in vitro susceptibility of viruses to acyclovir. The results and interpretations of these tests are method dependent. Although IDs (inhibitory doses) and EDs (effective doses) of acyclovir for various viruses have been reported, a standardized method for determining these values does not currently exist. In addition, the relationship between in vitro susceptibility of viruses to acyclovir and clinical response has not been determined. In viral susceptibility testing, 1 mcg of acyclovir per mL is approximately equivalent to 4.4  $\mu\text{mol/L}$ .

### ■ Herpesviridae

In several studies using a cytopathic effect inhibition assay (CPE-inhibition assay), the ID<sub>50</sub> (concentration of drug required to produce 50% inhibition of viral cytopathic effect or plaque formation) of acyclovir reported for susceptible strains of HSV-1 ranged from 0.02–0.7 mcg/mL; in studies using a plaque inhibition assay, the ID<sub>50</sub> of the drug reported for susceptible HSV-1 was 0.018–0.043 mcg/mL. In several studies using a CPE-inhibition assay, the ID<sub>50</sub> of acyclovir reported for susceptible strains of HSV-2 ranged from 0.01–3.2 mcg/mL; in studies using a plaque inhibition assay, the ID<sub>50</sub> of the drug reported for susceptible HSV-2 was 0.027–0.36 mcg/mL. In several studies using a plaque inhibition assay, the ID<sub>50</sub> of acyclovir for susceptible strains of varicella-zoster ranged from 0.34–1.43 mcg/mL.

In several studies using a cytohybridization assay, the ID<sub>50</sub> of acyclovir for susceptible strains of Epstein-Barr virus ranged from 1.4–1.6 mcg/mL. In several studies using a plaque inhibition assay, the ID<sub>50</sub> of acyclovir for susceptible strains of herpes simiae ranged from 5–10 mcg/mL.

Acyclovir is much less active against CMV than against many other Herpesviridae. This may occur because CMV does not produce thymidine kinase (TK) and therefore is less able than other viruses to phosphorylate acyclovir to its pharmacologically active triphosphate derivative. In several studies using a plaque inhibition assay, the ID<sub>50</sub> of acyclovir for susceptible strains of CMV ranged from 2 to greater than 50 mcg/mL.

Acyclovir is inactive against vaccinia virus, adenovirus type 5, and several RNA viruses. Preliminary data indicate that acyclovir may inhibit replication of hepatitis B virus; however, additional study of the susceptibility of this virus to acyclovir is needed.

## Resistance

Resistance to acyclovir in Herpesviridae can result from qualitative and quantitative changes in viral thymidine kinase (TK) and/or DNA polymerase. Since the antiviral activity of acyclovir generally appears to depend on phosphorylation of the drug to acyclovir triphosphate (see Mechanism of Action), resistance to the drug may result from low concentrations or absence of virus-coded TK in infected cells or from alterations in substrate specificity of virus-coded TK. Other mechanisms of resistance to acyclovir may also exist.

Acyclovir resistance in HSV-1 and HSV-2 may result from production of a virus-coded TK with altered substrate specificity or from an impaired ability to produce active virus-coded TK; either of these mechanisms may result in minimal amounts or absence of phosphorylated drug. Resistance to acyclovir in varicella-zoster may result from production of a virus-coded TK or DNA polymerase with altered substrate specificity or from an impaired ability to produce active virus-coded TK or DNA polymerase. The relative resistance of Epstein-Barr virus and cytomegalovirus (CMV) compared with HSV-1 and HSV-2 is thought to result from the inability of Epstein-Barr virus and CMV to code for virus-specific TK. In addition, although cellular TK may be present, its low af-

finity for acyclovir may result in concentrations of acyclovir triphosphate that are insufficient to effectively inhibit the DNA polymerase of Epstein-Barr virus or CMV. Presence of virus-coded TK is not the only determinant of susceptibility to acyclovir. Cells infected with vaccinia virus produce virus-coded TK, but the enzyme does not phosphorylate acyclovir and the drug does not inhibit replication of the virus. In addition to qualitative or quantitative alterations in virus-coded TK, resistance of herpesviruses to acyclovir may result from production of an altered DNA polymerase capable of synthesizing DNA in the presence of acyclovir triphosphate.

Clinical isolates of HSV or varicella-zoster with reduced susceptibility to acyclovir have been obtained from immunocompromised individuals, especially those with advanced human immunodeficiency virus (HIV) infection. It has been suggested that repeated treatment of recurrent viral infections with acyclovir may favor the selection of preexisting, or development of drug-resistant strains. While most of the acyclovir-resistant mutants isolated from immunocompromised individuals have been found to be TK-deficient, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults, and the possibility of acyclovir resistance should be considered in patients who show poor clinical response to the drug.

Although lack of virus-coded TK is apparently responsible for resistance in some strains of viruses, this lack has also been associated with a loss of or decrease in virulence in some strains. In addition, in one study, inoculation of mice with acyclovir-resistant HSV-1 mutants afforded protection against infection with virulent acyclovir-susceptible HSV-1 strains.

During the course of an acute or asymptomatic herpesvirus infection, the virus usually leaves the initial site of infection and invades other cells and tissues where it establishes a site of latent infection. HSV-1, HSV-2, and varicella-zoster are thought to establish latent infections principally within the ganglia. Animal studies indicate that colonization of sensory neurons by HSV-1 may occur as soon as 24–48 hours after initial infection and latency may develop within 2–3 weeks. Epstein-Barr virus and CMV are thought to establish latent infections within B cells and leukocytes, respectively. The exact nature of the virus during the latent state is not well understood; however, current evidence suggests that the virus is not actively replicating and, therefore, would not be susceptible to the antiviral action of drugs such as acyclovir. Despite the host's immunity, latency usually persists for life and the virus can be periodically reactivated by various stimuli (e.g., fever, stress, trauma, exposure to sunlight, menstruation, sexual intercourse, immunosuppression). Once reactivated, the virus usually reinfects the site(s) of initial infection. Acyclovir is apparently unable to eliminate an established latent infection. Acyclovir-resistant HSV mutants appear to be less capable of establishing latent infections than susceptible strains.

## Pharmacokinetics

In the studies described in the Pharmacokinetics section involving IV administration of the drug, acyclovir was administered as the sodium salt; dosages and concentrations of the drug are expressed in terms of acyclovir. A concentration of 1 mcg of acyclovir per mL is approximately equivalent to 4.4  $\mu\text{mol/L}$ .

The pharmacokinetics of acyclovir in children generally are similar to that reported in adults.

Acyclovir plasma concentrations are higher in geriatric patients than in younger adults, in part due to age-related changes in renal function.

### ■ Absorption

#### Oral Administration

Absorption of acyclovir from the GI tract is variable and incomplete. It is estimated that 10–30% of an oral dose of the drug is absorbed. Some data suggest that GI absorption of acyclovir may be saturable; in a crossover study in which acyclovir was administered orally to healthy adults as 200-mg capsules, 400-mg tablets, or 800-mg tablets 6 times daily, the extent of absorption decreased with increasing dose, resulting in bioavailabilities of 20, 15, or 10%, respectively. The manufacturer states that this decrease in bioavailability appears to be a function of increasing dose, not differences in dosage forms. In addition, steady-state peak and trough plasma acyclovir concentrations were not dose proportional over the oral dosing range of 200–800 mg 6 times daily, averaging 0.83 and 0.46, 1.21 and 0.63, or 1.61 and 0.83 mcg/mL for the 200-, 400-, or 800-mg dosing regimens, respectively.

Peak plasma concentrations of acyclovir usually occur within 1.5–2.5 hours after oral administration.

In immunocompromised individuals, steady-state peak and trough plasma acyclovir concentrations averaged 0.49–0.56 and 0.29–0.31 mcg/mL, respectively, following oral administration of 200 mg every 4 hours, 1.2 and 0.62 mcg/mL, respectively, following oral administration of 400 mg every 4 hours, and 2.8 and 1.8 mcg/mL, respectively, following oral administration of 800 mg (as capsules) every 4 hours. In another study in immunocompromised individuals, steady-state peak and trough plasma acyclovir concentrations averaged 1.4

and 0.55 mcg/mL, respectively, following oral administration of 800 mg (as capsules) every 6 hours.

Food does not appear to affect absorption of acyclovir.

The commercially available capsules and oral suspension are bioequivalent; in addition, one commercially available 800-mg tablet of acyclovir is bioequivalent to four 200-mg capsules of the drug.

#### IV Infusion

Results of studies in adults with normal renal function receiving single acyclovir doses ranging from 0.5- to 15-mg/kg or multiple doses ranging from 2.5- to 15-mg/kg every 8 hours indicate that plasma concentrations of the drug are dose proportional.

In adults with normal renal function receiving 5 or 10 mg/kg of acyclovir IV over 1 hour every 8 hours, mean steady-state peak plasma concentrations were 9.8 or 22.9 mcg/mL, respectively, and trough plasma concentrations were 0.7 or 1.9 mcg/mL. In a multiple-dose study in adults with malignancies and normal renal and liver function, 1-hour IV infusions of 2.5, 5, 10, or 15 mg/kg of acyclovir every 8 hours resulted in mean steady-state peak serum concentrations of 5.1, 9.8, 20.7, and 23.6 mcg/mL, respectively, and mean steady-state trough serum concentrations of 0.5, 0.7, 2.3, and 2 mcg/mL, respectively.

In several studies in adults with malignancies and normal renal and hepatic function, IV infusion over 1 hour of a single acyclovir dose of 0.5, 1, 2.5, or 5 mg/kg resulted in serum concentrations of the drug that averaged 0.7–1.4, 1.4–2.5, 3.4–4.9, or 7.7 mcg/mL, respectively, at the end of the infusion and 0.14, 0.27, 0.34, or 0.93 mcg/mL, respectively, 6 hours after the end of the infusion.

Serum concentrations in children 3 months to 16 years of age receiving IV acyclovir 10 mg/kg or 20 mg/kg every 8 hours are similar to those achieved in adults receiving IV acyclovir 5 mg/kg or 10 mg/kg every 8 hours. In a multiple-dose study in neonates up to 3 months of age, IV infusion over 1 hour of 5, 10, or 15 mg/kg of acyclovir every 8 hours resulted in mean steady-state peak serum concentrations of 6.8, 13.9, or 19.6 mcg/mL, respectively, and mean steady-state trough serum concentrations of 1.2, 2.3, or 3.1 mcg/mL, respectively. In another multiple-dose study in pediatric patients, IV infusion over 1 hour of 250 or 500 mg/m<sup>2</sup> of acyclovir every 8 hours resulted in mean steady-state peak serum concentrations of 10.3 or 20.7 mcg/mL, respectively.

In a single-dose study in adults with end-stage renal disease, a 1-hour IV infusion of 2.5 mg/kg of acyclovir resulted in serum concentrations of the drug that averaged 8.5, 4, 2.3, 2, and 1.5 mcg/mL at 1, 2, 8, 12, and 24 hours after the start of infusion, respectively. When these patients underwent hemodialysis, predialysis (48 hours after the start of drug infusion) and postdialysis (54.5 hours after the start of drug infusion) plasma acyclovir concentrations were 0.6 and 0.3 mcg/mL, respectively.

#### ■ Distribution

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 also is 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.

The apparent volume of distribution of acyclovir is reported to be 32.4–61.8 L/1.73 m<sup>2</sup> in adults and 28.8, 31.6, 42, or 51.2–53.6 L/1.73 m<sup>2</sup> in neonates up to 3 months of age, children 1–2 years, 2–7 years, or 7–12 years of age, respectively.

In vitro, acyclovir is approximately 9–33% bound to plasma proteins at plasma concentrations of 0.41–5.2 mcg/mL.

Following IV infusion, acyclovir generally diffuses well into CSF. In patients with uninfamed meninges, CSF concentrations of acyclovir are reported to be approximately 50% of concurrent serum acyclovir concentrations.

Acyclovir crosses the placenta. Limited data indicate that the drug is distributed into milk, generally in concentrations greater than concurrent maternal plasma concentrations, possibly via an active transport mechanism.

#### ■ Elimination

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 ( $t_{1/2\alpha}^1$ ) averages 0.34 hours and the half-life in the terminal phase ( $t_{1/2\beta}^1$ ) averages 2.1–3.5 hours. In adults with renal impairment, both  $t_{1/2\alpha}^1$  and  $t_{1/2\beta}^1$  may be prolonged, depending on the degree of renal impairment. In a study in adults with anuria, the  $t_{1/2\alpha}^1$  of acyclovir averaged 0.71 hours. In several studies, the  $t_{1/2\beta}^1$  of acyclovir averaged 3, 3.5, or 19.5 hours in adults with creatinine clearances of 50–80 or 15–50 mL/minute per 1.73 m<sup>2</sup> or with anuria, respectively. In patients undergoing hemodialysis, the  $t_{1/2\beta}^1$  of acyclovir during hemodialysis averaged 5.4–5.7 hours.

In neonates, the half-life of acyclovir depends principally on the maturity of renal mechanisms for excretion as determined by gestational age, chronological age, and weight. In children older than 1 year of age, the half-life of the drug appears to be similar to that of adults. The  $t_{1/2\beta}^1$  averages 3.8–4.1, 1.9, 2.2–2.8, or 3.6 hours in neonates up to 3 months of age, children 1–2 years, 2–12 years, or 12–17 years of age, respectively.

Acyclovir is metabolized partially to 9-carboxymethoxymethylguanine (CMMG) and minimally to 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine. In vitro, acyclovir also is metabolized to acyclovir monophosphate, diphosphate, and triphosphate in cells infected with herpesviruses, principally by intracellular phosphorylation of the drug by virus-coded thymidine kinase (TK) and several cellular enzymes. (See Mechanism of Action.)

Acyclovir is excreted principally in urine via glomerular filtration and tubular secretion. Most of a single IV dose of acyclovir is excreted in urine as unchanged drug within 24 hours after administration. In adults with normal renal function, approximately 30–90% of a single IV dose is excreted unchanged in urine within 72 hours; approximately 8–14% and less than 0.2% are excreted in urine as CMMG and 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine, respectively, within 72 hours. In a study in neonates up to 2 months of age, 62–72% of a single dose was excreted in urine unchanged. Less than 2% of a single IV dose of acyclovir is recovered in feces and only trace amounts in expired CO<sub>2</sub>; the drug apparently does not accumulate in tissues.

Total body clearance of acyclovir is reported to be 327, 248, 190, or 29 mL/minute per 1.73 m<sup>2</sup> in patients with creatinine clearances of greater than 80, 50–80, 15–50, or 0 mL/minute per 1.73 m<sup>2</sup>, respectively.

Oral administration of 1 g of probenecid 1 hour before a single 1-hour IV infusion of 5 mg/kg of acyclovir increased the plasma half-life and the area under the plasma concentration-time curve, produced higher and more prolonged plasma concentrations, and decreases the renal clearance of acyclovir. The volume of distribution of acyclovir does not appear to be affected by concomitant administration of oral probenecid. (See Drug Interactions: Probenecid.)

Acyclovir is removed by hemodialysis. The amount of acyclovir removed during hemodialysis depends on several factors (e.g., type of coil used, dialysis flow-rate); a 6-hour period of hemodialysis in one study removed into the dialysate approximately 60% of a single 2.5-mg/kg dose of acyclovir when the dose was given by a 60-minute IV infusion 48 hours prior to dialysis. Data are limited, but peritoneal dialysis and blood exchange transfusions do not appear to appreciably remove the drug.

## Chemistry and Stability

### ■ Chemistry

Acyclovir is a synthetic purine nucleoside analog derived from guanine. The drug differs structurally from guanine by the presence of an acyclic side chain. Acyclovir is commercially available for parenteral use as the sodium salt and for oral use as the base. Potency of commercially available acyclovir sodium powder or concentrate for injection is expressed in terms of acyclovir.

Acyclovir occurs as a white, crystalline powder and has a maximum solubility of 2.5 mg/mL in water at 25°C. The drug has pK<sub>a</sub>s of 2.27 and 9.25. Commercially available acyclovir sodium powder for injection occurs as a white, crystalline, lyophilized powder. 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 un-ionized and has a maximum solubility of 2.5 mg/mL. The sodium salt of acyclovir contains 4.2 mEq of sodium per gram of acyclovir. Following reconstitution with sterile water for injection, acyclovir sodium solutions containing 50 mg of acyclovir per mL have a pH of approximately 11 and are clear and colorless.

### ■ Stability

Acyclovir capsules and tablets should be stored in tight, light-resistant containers at 15–25°C. Acyclovir suspension should be stored at 15–25°C.

Commercially available acyclovir sodium powder for injection should be stored at 15–25°C. Following reconstitution with sterile water for injection, acyclovir sodium solutions containing 50 mg of acyclovir per mL are stable for 12 hours. Refrigeration of the reconstituted solution may result in formation of a precipitate which will redissolve at room temperature; potency of the drug does not appear to be affected by precipitation and subsequent redissolution. Acyclovir sodium also is compatible with bacteriostatic water for injection containing *benzyl alcohol*, exhibiting the stability noted above for sterile water for injection; however, use of this diluent is not recommended because of the potential risk of benzyl alcohol exposure if such reconstituted drug were administered to a neonate. Bacteriostatic water for injection containing *parabens* should *not* be used to reconstitute acyclovir sodium powder for injection since this diluent is incompatible with the drug and may cause precipitation.

The manufacturer states that acyclovir sodium is physically and chemically compatible for 24 hours at 25°C when diluted with 50–100 mL of a standard, commercially available electrolyte and/or dextrose solution. Although yellowish discoloration may occur when acyclovir sodium is diluted with greater than 10% dextrose, potency of the drug is not affected. The manufacturer states that acyclovir sodium is incompatible with biologic and/or colloidal fluids (e.g., blood products, protein-containing solutions).

## Preparations

**Acyclovir****Oral**

<b>Capsules</b>	200 mg*	<b>Acyclovir Capsules</b> <sup>®</sup> , ActavisRanbaxyTevaWatson <b>Zovirax</b> <sup>®</sup> (with parabens), GlaxoSmithKline
<b>Suspension</b>	200 mg/5 mL*	<b>Acyclovir Suspension</b> (with parabens), ActavisHi-Tech <b>Zovirax</b> <sup>®</sup> (with glycerin, parabens, and sorbitol), GlaxoSmithKline
<b>Tablets</b>	400 mg*	<b>Acyclovir Tablets</b> <sup>®</sup> , ActavisRanbaxyTevaWatson
	800 mg*	<b>Zovirax</b> <sup>®</sup> (with povidone), GlaxoSmithKline <b>Acyclovir Tablets</b> <sup>®</sup> , ActavisRanbaxyTevaWatson <b>Zovirax</b> <sup>®</sup> (with povidone), GlaxoSmithKline

\*available by nonproprietary name

**Acyclovir Sodium****Parenteral**

<b>For injection, concentrate, for IV infusion only</b>	50 mg (of acyclovir) per mL (500 mg, 1 g)	<b>Acyclovir Sodium Injection</b> , Abraxis
<b>For injection, for IV infusion only</b>	500 mg (of acyclovir)  1 g (of acyclovir)	<b>Acyclovir Sodium for Injection</b> , AbraxisBedfordSicor <b>Zovirax</b> <sup>®</sup> , GlaxoSmithKline <b>Acyclovir Sodium for Injection</b> , AbraxisBedfordSicor <b>Zovirax</b> <sup>®</sup> , GlaxoSmithKline

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

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