***Therapeutic Class Overview***
***Oral Antivirals: Herpes***

**Therapeutic Class**

- **Overview/Summary:** Acyclovir (Zovirax®), famciclovir (Famvir®) and valacyclovir (Valtrex®) are Food and Drug Administration-approved for the treatment of various herpes viruses.[1-4] Herpes simplex virus (HSV)-1 and -2 cause a variety of illnesses, including mucocutaneous infections, central nervous system infections and infections of the visceral organs. They are widely associated as the causative agent in orolabial and genital lesions, commonly referred to as cold sores and genital herpes, respectively. Both viral subtypes can cause orolabial or genital infections and are clinically indistinguishable; however, cold sores are most often caused by HSV-1, and genital herpes is most often caused by HSV-2. After inoculation and initial infection, HSV settles into nerves near the spine and becomes latent. The virus can travel along the nerves, back to the skin and either reactivate (i.e., new blisters or lesions are formed) or shed (i.e., no new blisters or lesions are formed). In contrast to initial infections, associated symptoms, signs and anatomic sites of recurrent infections are typically localized to a defined mucocutaneous site. Recurrent infections may also be associated with prodromal symptoms, which can occur in the absence of lesions, and vary from mild tingling sensations to shooting pains in the buttocks, legs or hips.[5] Varicella-zoster virus (VZV) causes chickenpox and herpes zoster, commonly known as shingles. Chickenpox is the primary infection following exposure to VZV. Chickenpox is a common and highly contagious disease, but is generally benign in children and is characterized by an exanthematous rash. Following resolution of the rash, the virus remains dormant in the dorsal root ganglia until reactivation. Reactivation of the virus leads to herpes zoster, or shingles, which is characterized as a sporadic disease. Herpes zoster is also associated with acute neuritis and postherpetic neuralgia.[6]

  The oral antiviral agents exert their antiviral effect against HSV and VZV by interfering with DNA and inhibiting viral replication.[4,8] Acyclovir and famciclovir are synthetic purine and acyclic purine nucleoside analogs. Valacyclovir is a prodrug and after oral administration is rapidly converted to acyclovir. The bioavailability of oral acyclovir is relatively low (15 to 21%); however, the relative bioavailability of acyclovir is three to five times greater after ingestion of valacyclovir (54 to 70%). Acyclovir is typically dosed five times daily compared to one to three times daily with famciclovir and valacyclovir. Acyclovir is available as a capsule and oral solution, famciclovir is available as a tablet and valacyclovir is available as a caplet.[1-3] All formulations of all agents are available generically.

**Table 1. Current Medications Available in the Therapeutic Class[1-3]**

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Acyclovir (Zovirax®***) | Acute treatment of herpes zoster (shingles), management of recurrent episodes of genital herpes, treatment of chickenpox (varicella), treatment of initial episodes of genital herpes | Capsule:<br>200 mg<br><br>Suspension:<br>200 mg/5 mL<br><br>Tablet:<br>400 mg<br>800 mg | ✔ |
| Famciclovir (Famvir®***) | Chronic suppressive therapy of recurrent episodes of genital herpes†,‡, management of recurrent episodes of genital herpes†,¶, treatment of herpes zoster (shingles) †,‖‖, treatment of recurrent episodes of orolabial or genital herpes in human immunodeficiency virus infected adults##, treatment of recurrent herpes labialis† | Tablet:<br>125 mg<br>250 mg<br>500 mg | ✔ |
| Valacyclovir | Chronic suppressive therapy of recurrent | Caplet: | ✔ |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| (Valtrex®***) | episodes of genital herpes§,‖, management of recurrent episodes of genital herpes†,#, reduction of transmission of genital herpes†,**, treatment of chickenpox (varicella)*, treatment of herpes zoster (shingles) †,¶¶, treatment of initial episodes of genital herpes†,††, treatment of cold sores‡‡,§§ | 500 mg<br>1,000 mg | |

*In immunocompetent pediatric patients aged two to <18 years. Based on efficacy data from clinical trials with oral acyclovir, treatment with valacyclovir should be initiated within 24 hours after onset of rash.
†In immunocompetent adults.
‡The efficacy and safety of famciclovir for the suppression of recurrent genital herpes beyond one year have not been established.
§In immunocompetent and in human immunodeficiency virus (HIV) 1 infected adults.
‖The efficacy and safety of valacyclovir for the suppression of recurrent genital herpes beyond one year in immunocompetent patients and beyond six months in HIV 1 infected patients have not been established.
¶The efficacy of famciclovir when initiated more than six hours after onset of symptoms or lesions has not been established.
#The efficacy of valacyclovir when initiated more than 24 hours after the onset of signs and symptoms has not been established.
**The efficacy of valacyclovir for the reduction of transmission of genital herpes beyond eight months in discordant couples has not been established. The efficacy of valacyclovir for the reduction of transmission of genital herpes in individuals with multiple partners and non-heterosexual couples has not been established.
††The efficacy of valacyclovir when initiated more than 72 hours after the onset of signs and symptoms has not been established.
‡‡In patients 12 years of age or older.
§§The efficacy of valacyclovir initiated after the development of clinical signs of a cold sore has not been established.
‖‖The efficacy of famciclovir when initiated more than 72 hours after onset of rash has not been established.
¶¶The efficacy of valacyclovir when initiated more than 72 hours after the onset of rash and the efficacy and safety of valacyclovir for treatment of disseminated herpes zoster have not been established.
##The efficacy of famciclovir when initiated more than 48 hours after onset of symptoms or lesions has not been established.
****Generic available in at least one dosage form or strength.

**Evidence-based Medicine**

- Overall, several head-to-head trials have demonstrated comparable efficacy and safety among acyclovir, famciclovir and valacyclovir in the treatment of herpes simplex and zoster infections.
- For the treatment of genital herpes, no differences among the agents with regard to the time to complete healing, viral shedding and resolution of all symptoms were noted.[8-12]
- For the treatment of herpes zoster; there were minimal differences between the agents with regards to time to complete healing and resolution of zoster-associated pain and/or abnormal sensation. While one agent may have achieved "superiority" over another for one particular outcome in one clinical trial, "superiority" of any agent was not consistently demonstrated.[13-18]
- The results of a systematic review of 12 trials demonstrated that both famciclovir and valacyclovir reduced the risk of pain compared to acyclovir in patients with herpes zoster who presented within 72 hours of symptom onset.[18]
- In addition, with regard to ocular manifestations in patients with herpes zoster infection, two head-to-head trials of acyclovir and famciclovir demonstrated no difference between the treatments in the proportion of patients with at least one ocular manifestation.[15] Various dosing regimens of antiviral therapy were evaluated and results demonstrated that no one dosing regimen is consistently "superior" to another.[16-29]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
    - For the treatment of genital herpes specifically, antiviral therapy offers clinical benefits to active infections, but does not eradicate latent virus or affect the risk, frequency or severity of recurrences after therapy is discontinued.
    - All primary or initial infections should be treated with antiviral therapy, and therapy for recurrent infections can be administered as either suppressive therapy, to reduce the frequency of recurrences, or episodically, to ameliorate or shorten the duration of lesions.
    - Suppressive therapy decreases the risk of transmission to susceptible sexual partners.
    - Systemic antiviral therapy is preferred and topical antiviral therapy is discouraged as it offers minimal clinical benefit.[8-18]

- Other Key Facts:
    - Generic products are available.

## References


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# *Therapeutic Class Review*
# *Oral Antivirals: Herpes*

**Overview/Summary**

Acyclovir (Zovirax®), famciclovir (Famvir®) and valacyclovir (Valtrex®) are nucleosides that are Food and Drug Administration-approved for the treatment of various herpes viruses.[1-4] While hundreds of herpes viruses have been identified that can infect nearly all animals, eight of them naturally infect humans. Herpes viruses contain double-stranded deoxyribonucleic acid (DNA) and human herpes viruses are subdivided into three subfamilies: α, β and γ herpes viruses. Specifically, α herpes viruses include herpes simplex virus (HSV)-1 and -2, varicella-zoster virus (VZV) and herpes B virus.[5]

HSV-1 and -2 cause a variety of illnesses, including mucocutaneous infections, central nervous system infections and infections of the visceral organs. They are widely associated as the causative agent in orolabial and genital lesions, commonly referred to as cold sores and genital herpes, respectively. Both viral subtypes can cause orolabial or genital infections and are clinically indistinguishable; however, cold sores are most often caused by HSV-1, and genital herpes is most often caused by HSV-2. Herpes simplex is typically transmitted through close contact with a person who is shedding virus at a peripheral site, mucosal surface or in genital or oral secretions. Following transmission, the initial infection may not demonstrate any lesions; however, most are associated with systemic signs and symptoms and involve both mucosal and extramucosal sites. Initial infections are also associated with higher complication rates and have a longer duration of symptoms and viral shedding from lesions. After inoculation and initial infection, HSV settles into nerves near the spine and becomes latent. The virus can travel along the nerves, back to the skin and either reactivate (i.e., new blisters or lesions are formed) or shed (i.e., no new blisters or lesions are formed). In contrast to initial infections, associated symptoms, signs and anatomic sites of recurrent infections are typically localized to a defined mucocutaneous site. Recurrent infections may also be associated with prodromal symptoms, which can occur in the absence of lesions, and vary from mild tingling sensations to shooting pains in the buttocks, legs or hips.[6]

VZV causes two diseases: chickenpox and herpes zoster, commonly known as shingles. Chickenpox is the primary infection following exposure to VZV. Chickenpox is a common and highly contagious disease, but is generally benign in children and is characterized by an exanthematous rash. Following resolution of the rash, the virus remains dormant in the dorsal root ganglia until reactivation. Reactivation of the virus leads to herpes zoster, or shingles, which is characterized as a sporadic disease. Factors leading to reactivation are unknown and herpes zoster may occur in people previously exposed to VZV at any age; however, the elderly and immunocompromised are most often afflicted. Herpes zoster is characterized by unilateral vesicular eruptions with a dermatomal distribution, but may have ophthalmic involvement that is sight-threatening. Herpes zoster is also associated with acute neuritis and postherpetic neuralgia.[7]

The oral antivirals acyclovir, famciclovir and valacyclovir are well established treatment options for both HSV and VZV infections. All of the agents have demonstrated comparable efficacy for the treatment of primary or initial genital herpes and for the suppression of recurrent infection. In addition, comparable efficacy among the agents have been demonstrated for the treatment of herpes zoster in immunocompetent patients.[8,9] For the treatment of genital herpes specifically, antiviral therapy offers clinical benefits to active infections, but does not eradicate latent virus or affect the risk, frequency or severity of recurrences after therapy is discontinued. All primary or initial infections should be treated with antiviral therapy, and therapy for recurrent infections can be administered as either suppressive therapy, to reduce the frequency of recurrences, or episodically, to ameliorate or shorten the duration of lesions. Suppressive therapy decreases the risk of transmission to susceptible sexual partners. Systemic antiviral therapy is preferred and topical antiviral therapy is discouraged as it offers minimal clinical benefit.[8-13]

The oral antiviral agents exert their antiviral effect against HSV and VZV by interfering with DNA and inhibiting viral replication.[4,14] Acyclovir and famciclovir are synthetic purine and acyclic purine nucleoside analogs. Valacyclovir is a prodrug and after oral administration is rapidly converted to acyclovir. The bioavailability of oral acyclovir is relatively low (15 to 21%); however, the relative bioavailability of

acyclovir is three to five times greater after ingestion of valacyclovir (54 to 70%). Acyclovir is typically dosed five times daily compared to one to three times daily with famciclovir and valacyclovir. Acyclovir is available as a capsule and oral solution, famciclovir is available as a tablet and valacyclovir is available as a caplet.[1-3] All formulations of all agents are available generically.

## Medications

**Table 1. Medications Included Within Class Review**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Acyclovir (Zovirax®*) | Antiviral herpes | ✔ |
| Famciclovir (Famvir®*) | Antiviral herpes | ✔ |
| Valacyclovir (Valtrex®*) | Antiviral herpes | ✔ |

*Generic is available in at least one dosage form or strength.

## Indications

**Table 2. Food and Drug Administration-Approved Indications**[1-3]

| Indication(s) | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| **Chickenpox** | | | |
| Treatment of chickenpox (varicella) | ✔ | | ✔ * |
| **Genital Herpes** | | | |
| Chronic suppressive therapy of recurrent episodes of genital herpes | | ✔ †,‡ | ✔ §,‖ |
| Management of recurrent episodes of genital herpes | ✔ | ✔ †,¶ | ✔ †,# |
| Reduction of transmission of genital herpes | | | ✔ †,** |
| Treatment of initial episodes of genital herpes | ✔ | | ✔ †,†† |
| **Herpes Labialis (cold sores)** | | | |
| Treatment of cold sores | | | ✔ ‡‡,§§ |
| Treatment of recurrent herpes labialis | | ✔ † | |
| **Herpes Zoster** | | | |
| Acute treatment of herpes zoster (shingles) | ✔ | | |
| Treatment of herpes zoster (shingles) | | ✔ †,‖‖ | ✔ †,¶¶ |
| **Orolabial or Genital Herpes** | | | |
| Treatment of recurrent episodes of orolabial or genital herpes in human immunodeficiency virus infected adults | | ✔ ## | |

*In immunocompetent pediatric patients aged two to <18 years. Based on efficacy data from clinical trials with oral acyclovir, treatment with valacyclovir should be initiated within 24 hours after onset of rash.
†In immunocompetent adults.
‡The efficacy and safety of famciclovir for the suppression of recurrent genital herpes beyond one year have not been established.
§In immunocompetent and in human immunodeficiency virus (HIV) 1 infected adults.
‖The efficacy and safety of valacyclovir for the suppression of recurrent genital herpes beyond one year in immunocompetent patients and beyond six months in HIV 1 infected patients have not been established.
¶The efficacy of famciclovir when initiated more than six hours after onset of symptoms or lesions has not been established.
#The efficacy of valacyclovir when initiated more than 24 hours after the onset of signs and symptoms has not been established.
**The efficacy of valacyclovir for the reduction of transmission of genital herpes beyond eight months in discordant couples has not been established. The efficacy of valacyclovir for the reduction of transmission of genital herpes in individuals with multiple partners and non-heterosexual couples has not been established.
††The efficacy of valacyclovir when initiated more than 72 hours after the onset of signs and symptoms has not been established.
‡‡In patients 12 years of age or older.
§§The efficacy of valacyclovir initiated after the development of clinical signs of a cold sore has not been established.
‖‖The efficacy of famciclovir when initiated more than 72 hours after onset of rash has not been established.
¶¶The efficacy of valacyclovir when initiated more than 72 hours after the onset of rash and the efficacy and safety of valacyclovir for treatment of disseminated herpes zoster have not been established.
##The efficacy of famciclovir when initiated more than 48 hours after onset of symptoms or lesions has not been established.

Acyclovir has the potential to be used off-label for the treatment of acute retinal necrosis, chickenpox pneumonia, eczema herpeticum, human immunodeficiency virus (HIV)-associated genital herpes simplex; herpes labialis; varicella and herpes zoster, herpes zoster auricularis and ophthalmic herpes simplex. In addition, acyclovir has the potential to be used off-label as prophylaxis treatment of herpes zoster in immunocompromised patients and varicella-zoster virus infection. Famciclovir has the potential to be used off-label in the treatment of acute retinal necrosis, initial episodes of genital herpes simplex, hepatitis B and HIV-associated initial episode of herpes labialis; herpes zoster and varicella. In addition, valacyclovir has the potential to be used off-label for the treatment of acute retinal necrosis, non-genital herpes simplex, HIV-associated initial and recurrent genital herpes simplex; herpes labialis; herpes zoster and varicella and for prophylaxis treatment of cytomegalovirus infection in transplant patients.[4]

## Pharmacokinetics

**Table 3. Pharmacokinetics**[15]

| Generic Name | Bioavailability (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|
| Acyclovir | 10 to 20 | 14 | None | 2.5 to 19.5 |
| Famciclovir | 77 | 73 | Penciclovir | 2.3 |
| Valacyclovir | 54.5 | 46 | Acyclovir | 2.5 to 3.3 |

## Clinical Trials

Clinical trials for the antiviral herpes in their Food and Drug Administration (FDA)-approved indications are outlined in table 4.[15-30]

Several head-to-head trials have demonstrated comparable efficacy and safety among acyclovir, famciclovir and valacyclovir in the treatment of herpes simplex and zoster infections. For the treatment of genital herpes, no differences among the agents with regard to the time to complete healing, viral shedding and resolution of all symptoms were noted.[19-23] For the treatment of herpes zoster, there were minimal differences between the agents with regard to time to complete healing and resolution of zoster-associated pain and/or abnormal sensation. While one agent may have achieved “superiority” over another for one particular outcome in one clinical trial, “superiority” of any agent was not consistently demonstrated.[25-29] In addition, with regard to ocular manifestations in patients with herpes zoster infection, two head-to-head trials of acyclovir and famciclovir demonstrated no difference between the treatments in the proportion of patients with at least one ocular manifestation.[26] The results of a systematic review of 12 trials demonstrated that both famciclovir and valacyclovir reduced the risk of pain compared to acyclovir in patients with herpes zoster who presented within 72 hours of symptom onset.[30] Various dosing regimens of antiviral therapy were evaluated and results demonstrated that no one dosing regimen is consistently “superior” to another.[16-29] The FDA approved dosing for the individual agents should be consulted when determining appropriate dosing for a particular patient and infection.[1-3]

**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Herpes Labialis** | | | | |
| Spruance et al[15]<br><br>Famciclovir 1,500 mg QD for 1 day<br><br>vs<br><br>famciclovir 750 mg BID for 1 day<br><br>vs<br><br>placebo<br><br>Patients were instructed to initiate therapy within 1 hour of onset of prodromal symptoms and before the appearance of any signs of herpes labialis lesions. | DB, MC, PC, RCT<br><br>Immuno-competent adults ≥18 years of age with recurrent herpes simplex labialis (≥3 episodes of cold sores within previous 12 months) | N=701<br><br>Up to 14 days | Primary:<br>Time to healing of the primary vesicular lesions<br><br>Secondary:<br>Time to healing of all vesicular lesions, time to return to normal skin (loss of crust, swelling and dry flaking) for all lesions (vesicular and aborted) and duration of lesion tenderness and pain | Primary:<br>The time to healing of primary vesicular lesions in the mITT group was significantly shorter in patients treated with famciclovir 1,500 mg QD (4.4 days; 95% CI, 3.9 to 5.0) or 750 mg BID (4.0 days; 95% CI, 3.8 to 4.8) compared to 6.2 days (95% CI, 5.7 to 7.0) with placebo (*P*<0.001 for both dosing regimens). Similar results were reported in the PP population.<br><br>There were no significant differences between the famciclovir treatment groups with regard to the time to healing of primary vesicular lesions (*P* values not reported).<br><br>Secondary:<br>The time to healing of all vesicular lesions in the mITT group was significantly shorter in patients treated with famciclovir 1,500 mg QD (5.5 days; 95% CI, 4.0 to 5.0) or 750 mg BID (4.1 days; 95% CI, 3.8 to 5.0) compared to 6.6 days (95% CI, 5.9 to 7.3) with placebo (*P*<0.001 for both dosing regimens). Similar results were reported in the PP population.<br><br>There were no significant differences between the famciclovir treatment groups in time to healing of all vesicular lesions (*P* values not reported).<br><br>Treatment with famciclovir 1,500 mg QD significantly improved the time to return to normal skin of all lesions (vesicular and aborted) compared to placebo (4.5 vs 7.0 days; HR, 1.50; 95% CI, 1.18 to 1.90). The time to return to normal skin did not differ significantly (*P*=0.067) between patients treated with famciclovir 750 mg BID and placebo (5.7 vs 7.0 days; HR, 1.26; 95% CI, 0.98 to 1.62).<br><br>There was no significant difference between the two famciclovir regimens in the time to return to normal skin.<br><br>Treatment with 1,500 mg of famciclovir QD reduced the time to resolution of pain and tenderness (1.7 vs 2.9 days; HR, 1.56; 95% CI, 1.25 to 1.94) |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | compared to placebo (*P*<0.001) and was more effective than famciclovir 750 mg BID (*P*=0.046). The time to resolution of pain and tenderness was not significantly different between the famciclovir 750 mg BID group and placebo (2.1 vs 2.9 days; HR, 1.25; 95% CI, 1.00 to 1.56). |
| Hull et al[16]<br><br>Valacyclovir 2,000 mg BID for 1 day plus clobetasol gel 0.05% BID for 3 days<br><br>vs<br><br>placebo | RCT<br><br>Patients ≥18 years of age with recurrent herpes simplex labialis | N=81<br><br>14 days | Primary:<br>Change in maximum size of the primary lesion complex<br><br>Secondary:<br>Frequency of primary lesions that were aborted, mean time to healing of classical primary lesions, frequency and mean duration of lesion pain among primary lesions, frequency of secondary lesions, frequency of post-treatment lesions and safety | Primary:<br>Valacyclovir plus clobetasol gel significantly reduced the mean maximum lesion size compared to placebo (9.7 vs 54.0 $mm^2$; *P*=0.002).<br><br>Secondary:<br>There were significantly more aborted lesions with combination therapy compared to placebo (50.0 vs 15.8%; *P*=0.04).<br><br>Combination therapy significantly reduced the mean healing time of classical lesions compared to placebo (5.8 vs 9.3 days; *P*=0.002).<br><br>There were no differences between the two treatments in pain. The mean maximum lesion pain was 1.6±1.0 vs 1.7±1.3 with combination therapy and placebo (*P* value not reported). The proportions of patients reporting pain at any time were also not different (85 vs 80%; *P* value not reported).<br><br>Secondary and post-treatment recurrences were not increased with combination therapy compared to placebo.<br><br>Adverse events were similar between the two treatments. Overall, adverse events were infrequent and mild and there were no serious adverse events reported. Headache occurred most commonly. |
| **Herpes Simplex** | | | | |
| Bartlett et al (abstract)[17]<br>RELIEF<br><br>Famciclovir 125 mg BID for 5 days (episodic dosing)<br><br>vs | MC, OL, RCT<br><br>Patients with recurrent genital herpes | N=384<br><br>6 months | Primary:<br>Time to first recurrence of genital herpes, change in total RGHQoL questionnaire score | Primary:<br>There was a significant difference between the two treatments in the time to first recurrence of symptoms in favor of suppressive dosing (*P*<0.0001).<br><br>There were no differences between the two treatments in RGHQoL total score or in patient satisfaction with treatment (*P* values not reported).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| famciclovir 250 mg BID (suppressive dosing) | | | Secondary:<br>Not reported | Not reported |
| Bodsworth et al (abstract)[18]<br>FaST<br><br>Famciclovir 500 mg once, followed by 250 mg BID for 2 days<br><br>vs<br><br>famciclovir 125 mg BID for 5 days | RCT<br><br>Patients with recurrent genital herpes | N=873<br><br>5.5 days | Primary:<br>Proportion of recurrences, safety, proportion of lesions aborted, time to next recurrence, patient reported symptoms, impact on daily functioning<br><br>Secondary:<br>Not reported | Primary:<br>The proportion of evaluable recurrences with lesions present at 5.5 days was less with two vs five days of famciclovir treatment (24 vs 28%). The difference demonstrated non inferiority between the two treatment regimens (*P* value not reported).<br><br>Both treatments had similar adverse events, proportion of lesions aborted, time to next recurrence, patient reported symptoms and impact on daily functioning (*P* values not reported).<br><br>Secondary:<br>Not reported |
| Chosidow et al[19]<br><br>Acyclovir 200 mg 5 times daily for 5 days<br><br>vs<br><br>famciclovir 125 mg BID for 5 days | DB, PG, RCT<br><br>Adult patients with genital herpes who had ≥3 occurrences within the past 12 months | N=204<br><br>10 days | Primary:<br>Mean lesion healing time<br><br>Secondary:<br>Proportion of healed lesions at the different days of clinical evaluation and duration of symptoms | Primary:<br>Mean healing times (re-epithelialization of lesions) were 5.13 and 5.38 days with famciclovir and acyclovir (difference, 0.25 days; 95% CI, -0.32 to 0.82). Famciclovir was considered statistically equivalent to acyclovir.<br><br>Secondary:<br>There were no differences between the two treatments in the proportion of patients having complete healing at the different days of evaluation (*P* values not reported).<br><br>Duration of symptoms was comparable between the two treatments (*P* value not reported). Drug-related adverse events also did not differ between the two treatments in severity or frequency. The most common reported adverse events included headache, nausea, gastrointestinal disorder and sore throat. |
| Romanowski et al[20]<br><br>Acyclovir 400 mg 5 times daily for 7 days<br><br>vs | DB, PG, RCT<br><br>Adult patients with HIV, clinically diagnosed with | N=293<br><br>7 days | Primary:<br>Proportion of patients developing new lesions during treatment | Primary:<br>The proportions of patients developing new lesions were 16.7 and 13.3% with famciclovir and acyclovir, respectively (95% CI, -4.8 to 11.5).<br><br>Secondary:<br>Median time to complete healing was seven days with both treatments (HR, |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| famciclovir 500 mg BID for 7 days | mucocutaneous herpes simplex virus infection (orolabial or genital) and prior history of lesions | | Secondary:<br>Time to complete healing, time to cessation of viral shedding, duration of lesion-associated symptoms and number of withdrawals due to treatment failure | 1.01; 95% CI, 0.79 to 1.29; *P*=0.95).<br><br>Median time to cessation of viral shedding was two days with both treatments (HR, 0.93; 95% CI, 0.68 to 1.27; *P*=0.64).<br><br>Median time to loss of lesion-associated symptoms was four days with both treatments (HR, 0.99; 95% CI, 0.75 to 1.30; *P*=0.93).<br><br>Two patients receiving acyclovir and one patient receiving famciclovir withdrew due to treatment failure (*P* value not reported). The occurrence of drug-related adverse events was comparable between the two treatments. The most common reported adverse events were headache, nausea and diarrhea. |
| Abudalu et al[21]<br><br>Famciclovir 1,000 mg BID for 1 day<br><br>vs<br><br>valacyclovir 500 mg BID for 3 days | DB, MC, PG, RCT<br><br>Immuno-competent adult patients with a history of recurrent genital herpes | N=1,179<br><br>Duration not reported | Primary:<br>Time to healing of all nonaborted lesions<br><br>Secondary:<br>Time to healing of all nonaborted and aborted lesions, proportion of patients experiencing aborted lesions, time to resolution of symptoms, safety | Primary:<br>Time to healing of nonaborted lesions in the ITT population was similar between the two treatments (4.25 vs 4.08 days). A median treatment difference (0.16 days) and its 95% CI demonstrated that famciclovir was non inferior to valacyclovir with respect to time to healing of all nonaborted genital herpes lesions. Consistent results were obtained for the PP population.<br><br>Secondary:<br>The time to healing of all lesions (nonaborted and aborted) in the ITT population was similar with famciclovir and valacyclovir (3.07 vs 3.01 days; median difference, 0.00; 95% CI, 0.00 to 0.00; HR, 1.07; 95% CI, 0.91 to 1.25; *P*=0.42).<br><br>A similar proportion of patients within the ITT population experienced aborted lesions (32.7 vs 33.6%; *P* value not reported).<br><br>Within the ITT population, patients receiving famciclovir and valacyclovir had similar median times to resolution of all symptoms associated with recurrent genital herpes (72.9 vs 72.0 hours; HR, 1.03; 95% CI, 0.86 to 1.24; *P*=0.75), as well as similar median times to resolution of each individual symptom (pain [18.0 vs 20.1 hours; HR, 1.00; 95% CI, 0.85 to 1.17; *P*=0.96], itching [43.9 vs 42.3 hours; HR, 1.02; 95% CI, 0.86 to 1.20; *P*=0.84], tingling [23.8 vs 23.0 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | hours; HR, 1.13; 95% CI, 0.96 to 1.33; *P*=0.13], burning [16.1 vs 12.6 hours; HR, 1.08; 95% CI, 0.92 to 1.26; *P*=0.35] and tenderness [55.2 vs 47.9 hours; HR, 1.06; 95% CI, 0.90 to 1.26; *P*=0.47]).<br><br>Adherence to study medication as prescribed was excellent. Regardless of medication, the overall incidence of adverse events was 23.2 and 22.3% with famciclovir and valacyclovir. The most commonly reported adverse events with either treatment were headache (7.8 vs 4.4%), nausea (6.2 vs 4.7%), diarrhea (2.2 vs 1.3%), vomiting (1.3 vs 0.8%) and abdominal pain (0.3 vs 1.0%). Most were mild or moderate intensity. |
| Wald et al[22]<br><br>Famciclovir 250 mg BID<br><br>vs<br><br>valacyclovir 500 mg QD | 2 DB, RCT<br><br>Adult patients with recurrent genital herpes with ≥6 recurrences in the past year | N=390<br><br>10 to 16 weeks | Primary:<br>Time to recurrence, proportion of days with herpes simplex virus detected by polymerase chain reaction<br><br>Secondary:<br>Time to first virologically confirmed recurrence, proportion of days with subclinical shedding | Primary:<br>Time to recurrence was comparable between the two treatments (HR, 1.17; 95% CI, 0.78 to 1.76; *P*=0.45).<br><br>Herpes simplex virus was detected by polymerase chain reaction on 3.2 and 1.3% of days with famciclovir and valacyclovir (HR, 2.33; 95% CI, 1.18 to 4.89; *P*=0.014).<br><br>Secondary:<br>Time to virologically confirmed recurrence was significantly shorter with famciclovir (HR, 2.15; 95% CI, 1.00 to 4.60; *P*=0.049).<br><br>Herpes simplex virus shedding was detected on 32.4 and 1.1% of days with famciclovir and valacyclovir (HR, 2.05; 95% CI, 1.07 to 4.11; *P*=0.031).<br><br>Drug-related adverse events were mild and comparable between the two treatments. The most common reported adverse event was headache. |
| Warkentin et al[23]<br><br>Acyclovir 400 mg TID<br><br>vs<br><br>valacyclovir 500 mg BID | RCT, SB<br><br>Patients ≥16 years old with a hematologic malignancy receiving chemotherapy or | N=151<br><br>35 days (median duration of treatment) | Primary:<br>Incidence of herpes simplex virus infection<br><br>Secondary:<br>Evidence of CMV infection or | Primary:<br>The incidence of herpes simplex virus infection was similar between all treatments (*P*=0.08).<br><br>Secondary:<br>No patient developed CMV infection or disease, varicella zoster virus infection or genital or disseminated herpes simplex virus infection. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>valacyclovir 250 mg BID | undergoing stem cell transplant positive for herpes simplex virus antibody | | disease, varicella zoster virus infection and genital or disseminated herpes simplex virus | Overall rates of adverse events were comparable between the three treatments (*P*=0.53). Gastrointestinal adverse events were most commonly reported (48%), followed by nephrotoxicity (30%). |
| **Herpes Zoster** | | | | |
| Arora et al[24]<br><br>Valacyclovir 1,000 mg TID for 7 days<br><br>vs<br><br>valacyclovir 2,000 mg TID for 7 days | DB, RCT<br><br>Immuno compromised patients ≥18 years of age with clinical evidence of localized uncomplicated herpes zoster | N=87<br><br>Up to 24 weeks | Primary:<br>Time to complete cessation of zoster-associated pain<br><br>Secondary:<br>Time to cessation of zoster-associated abnormal sensation, proportion of days one to 28 with zoster-associated pain and/or abnormal sensation, proportion of weeks one to 24 with zoster-associated pain and/or abnormal sensation, days to complete healing of zoster-associated rash, proportion of patients with | Primary:<br>There was no difference in time to complete cessation of zoster-associated pain between the two treatments (HR, 1.279; *P*=0.44).<br><br>Secondary:<br>There was no difference between the two treatments in the time to complete cessation of zoster-associated abnormal sensation between the two treatments (HR, 0.837; *P*=0.568).<br><br>There was no difference between the two treatments in the proportion of days one to 28 with zoster-associated pain (85.00 vs 75.95%; *P*=0.122) and/or abnormal sensation (58.04 vs 65.62%; *P*=0.453).<br><br>There was no difference between the two treatments in the proportion of weeks one to 24 with zoster-associated pain (56.0 vs 45.2%; *P*=0.092) and/or abnormal sensation (43.9 vs 46.3%; *P*=0.655).<br><br>There was no difference between the two treatments in the time from treatment initiation to full crusting; median times to healing were eight days with both treatments (*P* value not reported).<br><br>Zoster-associated complications were experienced by similar proportions of patients receiving either treatment (4 vs 7%; *P* value not reported).<br><br>Adverse events were reported by 49 and 60% of patients receiving valacyclovir 1,000 and 2,000 mg (*P* value not reported). The most common drug-related adverse events were headache, pain, nausea, vomiting and |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | zoster-associated complications, safety | constipation. |
| Tyring et al[25]<br><br>Acyclovir 800 mg 5 times daily for 10 days<br><br>vs<br><br>famciclovir 500 mg TID for 10 days | DB, MC, RCT<br><br>Patients ≥12 years of age with immune-suppression with clinical evidence of herpes zoster | N=148<br><br>10 days | Primary:<br>Proportion of patients with new lesions while on medication, time to complete healing of lesions, time to resolution of acute phase pain<br><br>Secondary:<br>Safety | Primary:<br>New lesion formation was reported in 77 and 73% of patients receiving famciclovir and acyclovir, respectively (95% CI, -9.2 to 18.6).<br><br>Median time to complete healing was 20 and 21 days with famciclovir and acyclovir, respectively (HR, 0.98; 95% CI, 0.67 to 1.42).<br><br>Median time to loss of acute phase pain was 14 and 17 days with famciclovir and acyclovir, respectively (HR, 1.11; 95% CI, 0.71 to 1.75).<br><br>Secondary:<br>Reported drug-related adverse events were comparable between the two treatments. The most commonly reported adverse events were nausea, headache and vomiting. |
| Tyring et al[26]<br><br>Acyclovir 800 mg 5 times daily for 7 days<br><br>vs<br><br>famciclovir 500 mg TID for 7 days | 2 DB, MC, RCT<br><br>Adult patients diagnosed with herpes zoster infection involving primarily the ophthalmic branch of the trigeminal nerve | N=454<br><br>6 months | Primary:<br>Proportion of patients that experienced a severe ocular manifestation (e.g., glaucoma, anterior uveitis, iridocyclitis) and nonsevere manifestations (e.g., conjunctivitis, punctate epithelial keratopathy, episcleritis)<br><br>Secondary:<br>Proportions of patients that | Primary:<br>After six months, one or more ocular manifestations occurred in 58.0 and 58.2% of patients receiving famciclovir and acyclovir. There was no difference between the two treatments (*P* value not reported).<br><br>Secondary:<br>The proportion of patients who experienced one or more severe ocular manifestation was 41.2 and 39.8% with famciclovir and acyclovir, respectively (95% CI, 0.72 to 1.56).<br><br>The proportion of patients who experienced one or more non-severe ocular manifestation was 44.9 and 43.4% with famciclovir and acyclovir, respectively (95% CI, 0.73 to 1.55).<br><br>The proportion of patients who experienced visual acuity loss was 2.6 and 6.3% with famciclovir and acyclovir, respectively (OR, 0.4; 95% CI, 0.15 to 1.08). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | experienced a severe and non-severe ocular manifestation, proportions of patients with loss of visual acuity, safety | Drug-related adverse events were comparable between the two treatments. The most common reported adverse events were nausea (10%), headache (5%) and vomiting (5%). |
| Shafran et al[27]<br><br>Acyclovir 800 mg 5 times daily<br><br>vs<br><br>famciclovir 750 mg QD<br><br>vs<br><br>famciclovir 500 mg BID<br><br>vs<br><br>famciclovir 250 mg TID | DB, MC, RCT<br><br>Adult patients with herpes zoster lesions for <72 hours | N=559<br><br>7 days | Primary:<br>Healing rates<br><br>Secondary:<br>Safety | Primary:<br>There were no differences between any of the treatments with respect to healing rates (*P* values not reported).<br><br>Secondary:<br>The frequency of drug-related adverse reactions was comparable between all treatments. |
| Beutner et al[28]<br><br>Acyclovir 800 mg 5 times daily for 7 days<br><br>vs<br><br>valacyclovir 1,000 mg TID for 7 days<br><br>vs | RCT<br><br>Immuno-competent patients ≥50 years old with herpes zoster | N=1,141<br><br>6 months | Primary:<br>Time to resolution of zoster-associated pain, time to cessation of new lesion formation and/or lesion area increase, time to ≥50% healed rash<br><br>Secondary: | Primary:<br>Median time to resolution of zoster-associated pain was 38 days with seven days of valacyclovir (*P*=0.001 vs acyclovir) and 44 days with 14 days of valacyclovir (*P*=0.03 vs acyclovir) compared to 51 days with acyclovir.<br><br>Time to cessation of new lesion and time to ≥50% healed rash was five days with all treatments.<br><br>Secondary:<br>Median time to resolution of zoster-associated abnormal sensations was 45 days with seven days of valacyclovir (HR, 1.18; 95% CI, 0.99 to 1.41 vs acyclovir) and 38 days with 14 days of valacyclovir (HR, 1.27; 95% CI, 1.07 to |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| valacyclovir 1,000 mg TID for 14 days | | | Time to resolution of zoster-associated abnormal sensations, pain intensity, safety | 1.52 vs acyclovir) compared to 57 days with acyclovir.<br><br>Rates of rash healing were comparable between the three treatments (HR, 1.01; 95% CI, 0.93 to 1.30; *P*=0.26).<br><br>Pain intensity did not differ among the three treatments (*P* value not reported).<br><br>Drug-related adverse events were comparable among the three treatments and mild in severity. The most common reported adverse events were headache, nausea, vomiting, diarrhea and constipation. |
| Tyring et al[29]<br><br>Famciclovir 500 mg TID for 7 days<br><br>vs<br><br>valacyclovir 1,000 mg TID for 7 days | DB, MC, RCT<br><br>Immuno-competent patients ≥50 years old with herpes zoster | N=597<br><br>24 weeks | Primary:<br>Time to resolution of zoster-associated pain<br><br>Secondary:<br>Time to resolution of zoster-associated abnormal sensations, rash healing, lesion dissemination, safety | Primary:<br>Median time to resolution of zoster-associated pain was 42 and 49 days with valacyclovir and famciclovir, respectively (HR, 1.02; 95% CI, 0.84 to 1.23; *P*=0.84).<br><br>Secondary:<br>Median time to resolution of zoster-associated abnormal sensation was 42 and 35 days with valacyclovir and famciclovir, respectively (HR, 1.00; 95% CI, 0.82 to 1.21; *P*=0.98).<br><br>Rates of rash healing were comparable between the two treatments (HR, 1.01; 95% CI, 0.93 to 1.30; *P*=0.26).<br><br>No cases of lesion dissemination were reported.<br><br>Drug-related adverse events were reported in 34 and 38% of patients receiving valacyclovir and famciclovir (*P* value not reported). The most commonly reported adverse events were headache, nausea and constipation. |
| McDonald et al (abstract)[30]<br><br>Acyclovir 5 times daily for ≥7 days | SR<br><br>Immuno-competent patients >18 | N=7,277<br><br>≥7 days | Primary:<br>Proportion of patients with a reduction in pain | Primary:<br>Compared to treatment with acyclovir, patients treated with valacyclovir experienced a significant reduction in herpes zoster-associated pain for up to 112 days. The largest risk reduction in pain (36%) was seen at 21 to 30 days (RR, 0.64; 95% CI, 0.59 to 0.70) with a NNT of (95% CI, 2.7 to 3.8). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>brivudin* 125 mg QD for ≥7 days<br><br>vs<br><br>famciclovir QD to TID for ≥7 days (depending on study)<br><br>vs<br><br>valacyclovir 1,000 mg TID for ≥7 days | years of age who were diagnosed with herpes zoster within 72 hours of symptom onset | | Secondary:<br>Rate of lesion healing and adverse events | Famciclovir treatment was also more efficacious compared to acyclovir treatment, with a 46% reduction in risk of pain at 28 to 30 days (RR, 0.54; 95% CI, 0.48, 0.68) and NNT of three (95% CI, 2 to 5).<br><br>Secondary:<br>The time to lesion healing and adverse events were comparable between the treatment groups. |

*Agent not available in the United States
Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, ITT=intention-to-treat, MC=multicenter, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel-group, PP=per protocol, RCT=randomized controlled trial, RR=relative risk, SB=single blind, SR=systematic review
Miscellaneous abbreviations: CI=confidence interval, CMV=cytomegalovirus, HIV=human immunodeficiency virus, mITT=modified intent to treat, NNT=number needed to treat, RGHQoL=Recurrent Genital Herpes Quality of Life

## Special Populations

**Table 5. Special Populations**[1-3,]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Acyclovir | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>FDA-approved for the treatment of chickenpox in children two to 18 years of age.<br><br>Safety and efficacy in children have not been established for the treatment of genital herpes. | Renal dose adjustment is required. | No dosage adjustment required. | B | Yes (% not reported). |
| Famciclovir | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | Renal dose adjustment is required. | No dosage adjustment required. | B | Unknown; do not use. |
| Valacyclovir | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>FDA-approved for the treatment of chickenpox in children two to <18 years of age.<br><br>FDA approved for the treatment of herpes labialis in children ≥12 years of age. | Renal dose adjustment is required. | No dosage adjustment required. | B | Yes (<2%); use with caution. |

FDA=Food and Drug Administration

## Adverse Drug Events

**Table 6. Adverse Drug Events (%)**[1-3]

| Adverse Events | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| **Central Nervous System** | | | |
| Aggressive behavior | ✔ | - | ✔ |

| Adverse Events | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| Agitation | ✔ | - | ✔ |
| Ataxia | ✔ | - | ✔ |
| Coma | ✔ | - | ✔ |
| Confusion | ✔ | ✔ | ✔ |
| Decreased consciousness | ✔ | - | ✔ |
| Delirium | ✔ | - | - |
| Depression | - | - | 5 to 7 |
| Dizziness | ✔ | ✔ | 2 to 4 |
| Dysarthria | ✔ | - | ✔ |
| Encephalopathy | ✔ | - | ✔ |
| Hallucinations | ✔ | ✔ | ✔ |
| Headache | 2.2 | 8.5 to 39.3 | 10 to 38 |
| Mania | - | - | ✔ |
| Migraine | - | 0.7 to 3.1 | - |
| Paresthesia | ✔ | 0 to 2.6 | - |
| Psychosis | ✔ | - | ✔ |
| Seizure | ✔ | - | ✔ |
| Somnolence | ✔ | ✔ | - |
| Tremors | ✔ | - | ✔ |
| **Gastrointestinal** | | | |
| Abdominal pain | - | 0 to 7.9 | 3 to 11 |
| Diarrhea | 2.4 to 3.2 | 1.6 to 9.0 | ✔ |
| Flatulence | - | 0.2 to 4.8 | - |
| Gastrointestinal distress | ✔ | - | - |
| Nausea/vomiting | 2.4 to 4.8 | 2.2 to 12.5 | 4 to 15 |
| Vomiting | 2.7 | 0.7 to 4.8 | 3 to 6 |
| **General** | | | |
| Anaphylaxis | ✔ | - | ✔ |
| Angioedema | ✔ | - | ✔ |
| Dysmenorrhea | - | 0 to 7.6 | 5 to 8 |
| Dyspnea | - | - | ✔ |
| Facial edema | - | - | ✔ |
| Fatigue | - | 0.6 to 4.8 | 8 |
| Fever | ✔ | - | - |
| Hypertension | - | - | ✔ |
| Malaise | 11.5 | - | - |
| Nasopharyngitis | - | - | 16 |
| Pain | ✔ | - | - |
| Peripheral pain | ✔ | - | - |
| Tachycardia | - | - | ✔ |
| Upper respiratory tract infection | - | - | 9 |
| **Hematologic and Lymphatic** | | | |
| Anemia | ✔ | 0.1 | 0.2 to 0.8 |
| Leukocytoclastic vasculitis | ✔ | - | ✔ |
| Leukopenia | ✔ | 1.3 | 0.6 to 1.3 |
| Neutropenia | - | 3.2 | - |
| Thrombocytopenia | ✔ | ✔ | 0.4 to 1.0 |
| Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome | ✔ | - | ✔ |
| **Hepatobiliary Tract and Pancreas** | | | |
| Cholestatic jaundice | - | ✔ | - |

| Adverse Events | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| Elevated amylase | - | 1.5 | - |
| Elevated liver function tests | ✔ | 2.3 to 3.2 | 1.8 to 16.0 |
| Hepatitis | ✔ | - | ✔ |
| Hyperbilirubinemia | ✔ | 1.9 | - |
| Jaundice | ✔ | - | - |
| **Musculoskeletal** | | | |
| Arthralgia | - | - | 5 to 6 |
| Myalgia | ✔ | - | - |
| **Skin** | | | |
| Alopecia | ✔ | - | ✔ |
| Erythema multiforme | ✔ | ✔ | ✔ |
| Photosensitive rash | ✔ | - | ✔ |
| Pruritus | ✔ | 0 to 3.7 | ✔ |
| Rash | ✔ | 0 to 3.3 | 8 |
| Stevens-Johnson syndrome | ✔ | ✔ | - |
| Toxic epidermal necrolysis | ✔ | ✔ | - |
| Urticaria | ✔ | ✔ | ✔ |
| **Special Senses** | | | |
| Visual abnormalities | ✔ | - | ✔ |
| **Urogenital** | | | |
| Elevated blood urea nitrogen | ✔ | - | - |
| Elevated creatinine | ✔ | 0.2 | 0.2 to 0.7 |
| Hematuria | ✔ | - | - |
| Renal failure | ✔ | - | ✔ |
| Renal pain | ✔ | - | ✔ |

✔ Percent not specified.
-Event not reported.

## Contraindications

**Table 7. Contraindications**[1-3]

| Contraindication | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| Clinically significant hypersensitivity reaction (e.g., anaphylaxis) to valacyclovir, acyclovir or any component of the formulation. | ✔ | - | ✔ |
| Known hypersensitivity to the product, its components, or penciclovir cream. | - | ✔ | - |

## Warnings/Precautions

**Table 8. Warnings and Precautions**[1-3]

| Warning/Precaution | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| Acute renal failure; reported in patients with reduced renal function, underlying renal disease, concomitant nephrotoxic drug therapy or in patients who are dehydrated. | ✔ | ✔ | ✔ |
| Central nervous system effects; reported in patients receiving higher than recommended doses of for their level of renal function. | - | - | ✔ |
| Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; cases have occurred in patients with advanced human immunodeficiency virus-1 disease and | ✔ | - | ✔ |

| Warning/Precaution | Acyclovir | Famciclovir | Valacyclovir |
|---|---|---|---|
| also in allogeneic bone marrow transplant and renal transplant recipients. Discontinue treatment immediately if clinical signs, symptoms, and laboratory abnormalities occur. | | | |

## Drug Interactions

**Table 9. Drug Interactions**[1]

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Antivirals, herpes (acyclovir) | Theophyllines | Plasma theophylline concentrations may be elevated, increasing the pharmacologic and adverse effects. |

## Dosage and Administration

**Table 10. Dosing and Administration**[1-3]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Acyclovir | Treatment of chickenpox (varicella) in adults and children >40 kg:<br>Capsule, suspension, tablet: 800 mg QID for five days<br><br>Management of recurrent episodes of genital herpes:<br>Capsule, suspension, tablet: suppressive therapy, 400 mg BID or 200 mg TID to five times daily for up to 12 months<br><br>Capsule, suspension, tablet: episodic treatment, 200 mg five times daily for five days initiated at the earliest sign or symptom of recurrence<br><br>Treatment of initial episodes and the management of recurrent episodes of genital herpes:<br>Capsule, suspension, tablet: 200 mg five times daily for 10 days<br><br>Acute treatment of herpes zoster (shingles):<br>Capsule, suspension, tablet: 800 mg five times daily for seven to 10 days | Treatment of chickenpox (varicella) in children two years of age and older:<br>Capsule, suspension, tablet: 20 mg/kg/dose QID for five days<br><br>Safety and efficacy in children have not been established for the treatment of genital herpes. | Capsule:<br>200 mg<br><br>Suspension:<br>200 mg/5 mL<br><br>Tablet:<br>400 mg<br>800 mg |
| Famciclovir | Chronic suppressive therapy of recurrent episodes of genital herpes (immunocompetent patients):<br>Tablet: 250 mg BID<br><br>Management of recurrent episodes of genital herpes (immunocompetent patients):<br>Tablet: 1,000 mg BID for one day initiated at the earliest sign or symptoms of recurrence<br><br>Treatment of recurrent herpes labialis | Safety and efficacy in children have not been established. | Tablet:<br>125 mg<br>250 mg<br>500 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | (immunocompetent patients):<br>Tablet: 1,500 mg as a single dose initiated at earliest sign or symptoms of recurrence<br><br>Treatment of herpes zoster (immunocompetent patients):<br>Tablet: 500 mg TID for seven days at the earliest sign of diagnosis<br><br>Treatment of recurrent episodes of orolabial or genital herpes in HIV infected adults:<br>Tablet: 500 mg BID for seven days initiated at the earliest sign or symptoms of recurrence | | |
| Valacyclovir | Chronic suppressive therapy of recurrent episodes of genital herpes:<br>Caplet: immunocompetent patients, 500 or 1,000 mg once daily; HIV 1 infected patients, 500 mg BID<br><br>Management of recurrent episodes of genital herpes (immunocompetent patients):<br>Caplet: 500 mg BID for three days initiated at the first sign or symptom of an episode<br><br>Reduction of transmission of genital herpes (immunocompetent patients):<br>Caplet: 500 mg once daily for the source partner<br><br>Treatment of initial episodes of genital herpes (immunocompetent patients):<br>Caplet: 1,000 mg BID for 10 days<br><br>Treatment of cold sores in patients ≥12 years of age:<br>Caplet: 2,000 mg BID for one day initiated at the earliest symptoms of a cold sore<br><br>Treatment of herpes zoster (immunocompetent patients):<br>Caplet: 1,000 mg TID for seven days initiated at the earliest sign or symptoms of herpes zoster | Treatment of chickenpox in children two to <18 years of age (immunocompetent patients):<br>Caplet: 20 mg/kg TID for five days initiated at the earliest sign or symptoms; maximum, 1,000 mg TID | Caplet:<br>500 mg<br>1,000 mg |

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily
HIV=human immunodeficiency virus

## Clinical Guidelines

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendations |
|---|---|
| Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment** | Management of genital herpes<br>• Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management.<br>• Systemic antiviral drugs can partially control the signs and symptoms of |

| Clinical Guideline | Recommendations |
|---|---|
| **Guidelines (2010)**[10] | herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy.<br>• Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued.<br>• Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes.<br>• Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability.<br>• Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged.<br>• Newly acquired genital herpes can cause prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even patients with first episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy.<br>• Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir 200 mg orally five times daily for seven to 10 days, famciclovir 250 mg orally three times daily for seven to 10 days or valacyclovir 1,000 mg orally twice daily for seven to 10 days. Treatment can be extended if healing is incomplete after 10 days of therapy.<br>• Almost all patients with symptomatic first episode genital herpes simplex virus (HSV)-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection.<br>• Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Suppressive therapy may be preferred because of the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners.<br>• The safety and efficacy of suppressive therapy have been documented among patients receiving daily therapy with acyclovir for as long as six years and with famciclovir or valacyclovir for one year.<br>• Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.<br>• Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy.<br>• Recommended regimens for suppressive therapy of genital herpes include acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily or valacyclovir 1,000 mg orally once daily.<br>• Acyclovir, famciclovir and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding. Ease of administration and cost also are important to consider when deciding on prolonged treatment.<br>• Effective episodic treatment of recurrent herpes requires initiation of therapy within one day of lesion onset or during the prodrome that precedes some outbreaks. Patients should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms being. |

| Clinical Guideline | Recommendations |
|---|---|
| | • Recommended regimens for episodic treatment of genital herpes include acyclovir 400 mg orally three times daily for five days, acyclovir 800 mg orally twice daily for five days, acyclovir 800 mg orally three times daily for two days, famciclovir 125 mg orally twice daily for five days, famciclovir 1,000 mg orally twice daily for one day, famciclovir 500 mg orally once; followed by 250 mg orally twice daily for two days, valacyclovir 500 mg orally twice daily for three days or valacyclovir 1,000 mg orally once daily for five days.<br>• Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications.<br>• The sex partners of patients who have genital herpes can benefit from evaluation and counseling.<br>• Recommended regimens for daily suppressive therapy of genital herpes in patients infected with human immunodeficiency virus (HIV) include acyclovir 400 to 800 mg orally twice daily, famciclovir 500 mg orally twice daily or valacyclovir 500 mg orally twice daily.<br>• Recommended regimens for episodic treatment of genital herpes in patients infected with HIV include acyclovir 400 mg orally three times daily for five to 10 days, famciclovir 500 mg orally twice daily for five to 10 days or valacyclovir 1,000 mg orally twice daily for five to 10 days.<br>• The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established.<br>• Infants exposed to HSV during birth should be followed carefully in consultation with a pediatric infectious disease specialist. |
| American College of Obstetricians and Gynecologists: **American College of Obstetricians and Gynecologists Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Gynecologic Herpes Simplex Virus Infections (2004)**[11] | • Acyclovir, famciclovir and valacyclovir are antiviral drugs approved for treatment of genital herpes.<br>• Comparative trials of these medications suggest they have compatible clinical efficacy and result in comparable decrease in viral shedding.<br>• Treatment should be offered for first episode, even if they appear to be mild initially.<br>• Treatment decreases lesions, viral shedding and symptoms, but does not affect the long term natural history of infection.<br>• Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral intake or has prominent neurologic involvement.<br>• Intravenous acyclovir should be used for severe cases.<br>• Topical antiviral medications are not an effective therapy and do not add to the benefit of oral medication; their use is discouraged. |
| American Academy of Pediatrics Committee on Infectious Diseases: **The Use of Oral Acyclovir in Otherwise Healthy Children With Varicella (1993)**[12] | • The use of oral acyclovir for treatment in otherwise healthy children is not recommended.<br>• Oral acyclovir may be considered in the following children at an increased risk for moderate to severe varicella infection:<br>o >12 years old.<br>o Chronic cutaneous or pulmonary disorders.<br>o Receiving long term salicylate therapy.<br>o Receiving corticosteroids.<br>• Intravenous acyclovir is recommended for immunocompromised patients. |
| Center for Disease Control and Prevention, the National Institutes of | HSV disease<br>• The dose, duration and efficacy of antiviral prophylaxis after exposure to HSV have not been evaluated. |

| Clinical Guideline | Recommendations |
|---|---|
| Health and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for the Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-Infected Adults and Adolescents (2009)**[13] | • Patients with HSV infections can be treated with episodic therapy when lesions occur or with daily therapy to prevent recurrences.<br>• Patients with orolabial lesions can be treated with oral acyclovir, famciclovir or valacyclovir for five to 10 days. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous acyclovir.<br>• Genital HSV infection should be treated with oral acyclovir, famciclovir or valacyclovir for five to 14 days. Short course therapy (one, two or three days) should not be used in patients with HIV infection.<br>• Treatment failure related to resistance to anti-HSV drugs should be suspected if lesions do not begin to resolve within seven to 10 days after initiation of therapy.<br>• The treatment of choice for acyclovir-resistant HSV is intravenous foscarnet. Topical trifluridine, cidofovir and imiquimod also have been successfully used for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.<br>• Most recurrences of genital herpes can be prevented using daily anti-HSV therapy, and this is recommended for persons who have frequent or severe recurrences. Suppressive therapy with oral acyclovir, famciclovir or valacyclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily with HIV infected patients, or twice daily regimens with acyclovir or famciclovir should be used.<br>• Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for nonpregnant women.<br><br><u>Varicella zoster virus diseases</u><br>• No controlled prospective clinical trials of antiviral therapy for chickenpox in HIV infected adults have been reported.<br>• For uncomplicated varicella, recommended treatment options are oral acyclovir (20 mg/kg body weight, up to a maximum dose of 800 mg five times daily), oral famciclovir (500 mg three times daily) or oral valacyclovir (1,000 mg three times daily) for five to seven days.<br>• Intravenous acyclovir for seven to 10 days is recommended as initial therapy for HIV infected patients with severe chickenpox.<br>• Prompt antiviral therapy should be instituted in all immunocompromised herpes zoster patients within one week of rash onset or any time before full crusting of lesions.<br>• Recommended treatment options for acute localized dermatomal herpes zoster in HIV infected patients are oral acyclovir, famciclovir or valacyclovir for seven to 10 days, although longer durations should be considered if lesions resolve slowly. Famciclovir or valacyclovir are preferred due to improved pharmacokinetic properties and simplified dosing schedule. Intravenous acyclovir should be initiated if cutaneous lesions are extensive or if visceral involvement is suspected.<br>• Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. A treatment regimen recommended by certain specialists is a combination of intravenous ganciclovir and foscarnet, plus intravitreal injections of ganciclovir and/or foscarnet.<br>• Treatment failure caused by resistance of varicella zoster virus to acyclovir (and related drugs) should be suspected if lesions do not improve within 10 days of initiation of therapy or if they have an atypical appearance. Among patients with suspected or proven acyclovir-resistant infections, treatment with intravenous foscarnet is |

| Clinical Guideline | Recommendations |
|---|---|
| | recommended.<br>• No intervention has been recognized as preventing the recurrence of herpes zoster among HIV infected patients.<br>• Oral acyclovir or valacyclovir are the preferred treatments for HIV infected pregnant women who have uncomplicated chickenpox during pregnancy. |

## Conclusions

Acyclovir (Zovirax®), famciclovir (Famvir®) and valacyclovir (Valtrex®) are antiviral agents Food and Drug Administration (FDA)-approved for the treatment of the herpes viruses herpes simplex virus (HSV) and varicella-zoster virus (VZV).[1-3] These agents exert their antiviral effect against HSV and VZV by interfering with deoxyribonucleic acid and inhibiting viral replication.[1-4] Valacyclovir is a prodrug and after oral administration is rapidly converted to acyclovir. The bioavailability of oral acyclovir is relatively low (15 to 21%); however, the relative bioavailability of acyclovir is three to five times greater after ingestion of valacyclovir (54 to 70%). Acyclovir is typically dosed five times daily compared to one to three times daily with famciclovir and valacyclovir. Acyclovir is available as a capsule, oral suspension and tablet, famciclovir is available as a tablet and valacyclovir is available as a caplet.[1-3] All formulations of all agents are available generically.

Acyclovir, famciclovir and valacyclovir are all well-established treatment options for both HSV and VZV infections and have demonstrated comparable efficacy.[8,9] Head-to-head clinical trials support treatment guidelines in that acyclovir, famciclovir and valacyclovir all provide clinical benefit to patients with HSV or VZV infection, and no one agent is preferred over another.[19-23,24-29] Furthermore, various dosing regimens of antiviral therapy have been evaluated in clinical trials and results demonstrate that no one dosing regimen is consistently “superior” to another.[16-29] FDA-approved dosing for the individual agents should be consulted when determining appropriate dosing for a particular patient and infection.[1-3] For the treatment of genital herpes, antiviral therapy should be used to treat all initial episodes, as well as recurrent episodes. For recurrent episodes, antiviral therapy can be administered as either suppressive therapy or episodically. Suppressive therapy has the advantage over episodic treatment in decreasing the risk of transmission to susceptible sexual partners. Systemic antiviral therapy is preferred and topical antiviral therapy is discouraged as it offers minimal clinical benefit.[8-13]

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