

Therapeutic Class Overview

Antivirals, Herpes

INTRODUCTION

- Famvir (famciclovir), Sitavig (acyclovir), Valtrex (valacyclovir), and Zovirax (acyclovir) are nucleoside analogues that are Food and Drug Administration (FDA)-approved for the treatment of various herpes viruses.
- Herpes viruses contain double-stranded deoxyribonucleic acid (DNA), and human herpes viruses are subdivided into three subfamilies: α , β and γ herpes viruses. Specifically, the herpes viruses include herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), and herpes B virus (*Cohen 2015*).
- HSV-1 and -2 cause a variety of illnesses, including mucocutaneous infections, central nervous system infections, and infections of the visceral organs. They are 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 (*Schiffer et al 2015*).
- 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 (ie, new blisters or lesions are formed) or shed (ie, no new blisters or lesions are formed) (*Schiffer et al 2015*).
 - 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 pain in the buttocks, legs or hips (*Schiffer et al 2015*).
- 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 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. 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 (*Whitley 2015*).
- 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, suppression of recurrent infection, and herpes zoster in immunocompetent patients (*Schiffer et al 2015, Whitley 2015*). In 2013, a buccal formulation of acyclovir, Sitavig, for recurrent herpes labialis was approved via the 505(b)(2) pathway.
- For the treatment of genital herpes, 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 (*Centers for Disease Control and Prevention [CDC] 2015*).
- The oral antiviral agents exert their effect against HSV and VZV by interfering with DNA and inhibiting viral replication. Acyclovir and famciclovir are synthetic purine and acyclic purine nucleoside analogs. Valacyclovir is a prodrug that is rapidly converted to acyclovir after oral administration. The bioavailability of oral acyclovir is relatively low compared to valacyclovir and famciclovir. Acyclovir is typically dosed 5 times daily, while famciclovir and valacyclovir are typically dosed 1 to 3 times daily.
- Oral acyclovir is available as a capsule, tablet, buccal tablet, and suspension for oral administration. Acyclovir is also available in intravenous, cream, and ointment formulations; the topical acyclovir products are included in the "Antivirals, topical" review. Famciclovir and valacyclovir are available as tablets. While brand Famvir is no longer marketed, generic famciclovir remains commercially available.
- Medispan class: Antivirals; Herpes agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
famciclovir*	✓
Sitavig (acyclovir) buccal tablet	-
Valtrex (valacyclovir)	✓
Zovirax (acyclovir)	✓

* Branded product, Famvir, is no longer marketed.

(Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018)

INDICATIONS

Table 2. FDA Approved Indications

Indication(s)	famciclovir	Valtrex (valacyclovir)	Zovirax, Sitavig (acyclovir)
Chickenpox			
Treatment of chickenpox (VZV)	-	✓ *	✓ *
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	✓ †	-	✓ † (Sitavig only)
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 2 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 1 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 1 year in immunocompetent patients and beyond 6 months in HIV 1 infected patients have not been established.

¶ The efficacy of famciclovir when initiated more than 6 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 8 months in discordant 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.

§§ 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

(Prescribing information: famciclovir 2016, Sitavig 2015, Valtrex 2013, Zovirax 2013)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Chickenpox

- A Cochrane review of 3 randomized controlled trials (RCTs) of acyclovir in healthy children with chickenpox found that acyclovir was associated with a reduction in the number of fever days (–1.1 days; 95% confidence interval [CI], –1.3 to –0.9) and the maximum number of lesions (–76 lesions; 95% CI, –145 to –8) compared to placebo. No differences were observed between acyclovir and placebo with respect to complications associated with chickenpox and adverse effects associated with treatment (*Klassen et al 2005*).
- The approval of valacyclovir for chickenpox was based on an open-label trial with single-dose pharmacokinetic and multiple-dose safety data, along with extrapolated data from the 3 acyclovir RCTs (*Valtrex prescribing information 2013*).

Genital Herpes

- A Cochrane review of 26 trials (N = 2084) was conducted to assess the safety and efficacy of existing treatments for the first episode of genital herpes. There was low quality evidence from 2 studies that oral acyclovir reduced the duration of symptoms in the primary treatment of genital herpes compared to placebo (–3.22; 95% CI, –5.91 to –0.54). Oral valacyclovir demonstrated similar efficacy to acyclovir when compared directly in 2 studies (*Heslop et al 2016*).
- A systematic review found high-quality evidence based on 1 RCT (N = 643) that oral acyclovir and valacyclovir were equally effective in reducing time to healing, time to resolution of all symptoms, and duration of viral shedding for first episodes of genital herpes in HIV-negative patients (*Hollier and Eppes 2015*).
- For the episodic treatment of genital herpes, acyclovir, famciclovir, and valacyclovir have demonstrated comparable efficacy to each other and superior efficacy to placebo (*Abudalu et al 2008, Chosidow et al 2001, Romanowski et al 2000, Warkentin et al 2002*).
- For chronic suppressive therapy of genital herpes, a systematic review of 22 trials with oral antivirals in immunocompetent and nonpregnant patients showed inconsistent and low quality evidence that suppressive therapy with acyclovir, famciclovir, and valacyclovir in patients with at least 4 recurrences per year decreased the number of patients with at least one recurrence compared to placebo. Based on indirect comparisons in a network meta-analysis, no oral antiviral was shown to be superior (*Le Cleach et al 2014*).

Herpes Labialis

- The efficacy of Sitavig (acyclovir) buccal tablets was established in a randomized, double-blind (DB), placebo-controlled, patient-initiated, multicenter (MC) trial comparing a single dose to placebo (N = 771). Enrolled patients had at least 4 recurrent herpes labialis episodes in the preceding 12 months. Median time to healing of primary vesicular lesion was reduced in the treatment group (7 days vs 7.3 days; p = 0.015). In a 9-month follow-up of 537 patients, a benefit was suggested in delaying and reducing frequency of herpes labialis lesion recurrence (*Bieber et al 2014*).
- A Cochrane review showed that oral acyclovir or oral valacyclovir may prevent herpes simplex labialis when used prophylactically for greater than 1 month. However, the clinical benefit was small, and it was not seen with short-term or long-term use of topical antivirals (*Chi et al 2015*). For the treatment of recurrent herpes labialis, a meta-analysis of 25 RCTs found that oral valacyclovir was more effective than oral acyclovir in reducing the time to healing of all lesions and time to resolution of pain. Both acyclovir and valacyclovir increased the percentage of aborted lesions, but the same benefit was not observed with famciclovir (*Chen et al 2017*).

Herpes Zoster

- There is conflicting evidence with respect to the comparative efficacy of the oral antivirals for herpes zoster treatment. In general, there were minimal differences between the agents with regard to time to complete healing and resolution of zoster-associated pain. While the results from some studies suggest within-class differences for certain outcomes, superiority of any agent was not consistently demonstrated (*Beutner et al 1995, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b*).
 - In a DB, MC, RCT, famciclovir was directly compared with acyclovir in 559 immunocompetent adults with herpes zoster. Both antivirals resulted in similar efficacy with respect to the cutaneous healing of herpes zoster (eg, cessation of new lesion formation, 50% reduction in affected area, loss of acute pain) (*Shafran et al 2004*).

- In another DB, MC, RCT, famciclovir was directly compared with valacyclovir in 597 immunocompetent adults with herpes zoster. No statistically significant differences were detected between groups in the resolution of zoster-associated pain, rash healing, or postherpetic neuralgia (*Tyring et al 2000*).
- In a DB, MC, RCT, valacyclovir was directly compared with acyclovir in 1141 patients with herpes zoster. Valacyclovir for 7 days significantly accelerated the resolution of herpes zoster-associated pain vs acyclovir ($p = 0.001$). Valacyclovir also significantly reduced the duration of postherpetic neuralgia and the proportion of patients with pain persisting for 6 months. No differences were observed in pain intensity or quality-of-life measures (*Beutner et al 1995*).
- The results of a systematic review of 12 trials demonstrated that both famciclovir and valacyclovir reduced pain compared to acyclovir in patients with herpes zoster who presented within 72 hours of symptom onset (*McDonald et al 2012*). However, data are limited for the use of these agents for prevention of postherpetic neuralgia (*Chen et al 2014*).
- With regard to ocular manifestations in patients with herpes zoster infection, a head-to-head trial of acyclovir and famciclovir demonstrated no difference between treatments in the proportion of patients with at least one ocular manifestation (*Tyring et al 2001b*). Additionally, a Cochrane review comparing oral valacyclovir and acyclovir for the treatment of herpes zoster ophthalmicus found similar rates of ocular complications regardless of the agent utilized. The incidence of post-herpetic pain, tolerability of the medication, and side-effect profiles were also similar between both treatments (*Schuster et al 2016*).
- While various dosing regimens of antiviral therapy in genital herpes, herpes zoster, and herpes labialis were evaluated, no dosing regimen has consistently demonstrated better outcomes than another (*Abudalu et al 2008, Arora et al 2008, Bartlett et al 2008, Beutner et al, 1995, Bodsworth et al 2008, Chosidow et al 2001, Hull et al 2009, Romanowski et al 2000, Shafran et al 2004, Tyring et al 2000, Tyring et al 2001a, Tyring et al 2001b, Wald et al 2006, Warkentin et al 2002*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics recommends against the routine use of oral acyclovir or valacyclovir for the treatment of chickenpox in otherwise healthy children, for whom antiviral therapy results in only a modest decrease in symptoms. For healthy patients with risk factors for moderate to severe varicella (ie, unvaccinated patients > 12 years old, chronic cutaneous or pulmonary disorders, long term salicylate therapy, patients receiving short or intermittent courses of oral or aerosolized corticosteroids), oral acyclovir or valacyclovir should be considered. Intravenous acyclovir is recommended for immunocompromised patients (*American Academy of Pediatrics 2015*).
 - Administration of oral acyclovir for post-exposure prophylaxis in healthy children may prevent or attenuate varicella. For exposed immunocompromised patients, varicella zoster immune globulin is the treatment of choice. There is limited data on the effectiveness of prophylactic oral acyclovir (*American Academy of Pediatrics 2015*).
- 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 an advantage over episodic treatment in that it reduces 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 (*CDC 2015, Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2017*).
 - Acyclovir, famciclovir, and valacyclovir appear equally effective in the episodic treatment of genital herpes, but famciclovir may be less effective for suppression of viral shedding (*CDC 2015*).
- For the management of herpes zoster infection, acyclovir, valacyclovir, and famciclovir are all effective. Treatment should be initiated within 72 hours of the appearance of the rash to decrease the duration of symptoms and severity of pain (*Saguil et al 2017*).

SAFETY SUMMARY

- Acyclovir buccal tablets are contraindicated in patients with known hypersensitivity to milk protein concentrate.
- In patients with reduced renal function, underlying renal disease, concomitant nephrotoxic drug therapy, or in patients who are dehydrated, the development of acute renal failure has been reported with acyclovir, famciclovir, and valacyclovir. Dosage reductions are recommended for patients with renal impairment.
- Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have been reported with acyclovir and valacyclovir in patients with advanced HIV-1 disease, allogeneic bone marrow transplant, and renal transplant recipients. Discontinue treatment immediately if clinical signs, symptoms, and laboratory abnormalities occur.

- Central nervous system adverse reactions (eg, agitation, hallucinations, confusion, and encephalopathy) have been reported with valacyclovir.
- The most common adverse events are nausea/vomiting, headache, and dizziness.
 - Application site reactions are associated with acyclovir buccal tablets.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
famciclovir	Tablet	Oral	1 to 3 times daily	
Sitavig (acyclovir) buccal tablet	Buccal tablet	Oral	Single dose	Apply within one hour of the onset of prodromal symptoms and before signs of lesions to the upper gum on the same side as the symptoms.
Valtrex (valacyclovir)	Tablet	Oral	1 to 3 times daily	
Zovirax (acyclovir)	Capsule, suspension, tablet Cream, ointment Injection	Oral Topical IV	2 to 5 times daily	Topical acyclovir products are included in the "Antivirals, topical" review. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

See the current prescribing information for full details

CONCLUSION

- Famciclovir, Sitavig (acyclovir), Valtrex (valacyclovir), and Zovirax (acyclovir) are antiviral agents FDA-approved for the treatment of the herpes viruses, HSV and/or VZV.
 - These agents exert their antiviral effect against HSV and VZV by interfering with DNA and inhibiting viral replication.
- The bioavailability of oral acyclovir is relatively low compared to valacyclovir and famciclovir. Acyclovir is typically dosed 5 times daily, compared to 1 to 3 times daily with famciclovir and valacyclovir. Oral acyclovir is available as a capsule, oral suspension, tablet and buccal tablet; famciclovir and valacyclovir are available as tablets.
- Acyclovir, famciclovir, and valacyclovir are all well-established treatment options for their FDA-approved indications. Comparative trials, meta-analyses, and treatment guidelines suggest acyclovir, famciclovir, and valacyclovir all provide clinical benefit to patients with HSV or VZV infection, and no one agent is preferred over another (*Abudalu et al 2008, Arora et al 2008, Bartlett et al 2008, Beutner et al, 1995, Bodsworth et al 2008, Chosidow et al 2001, Hull et al 2009, Romanowski et al 2000, Shafran et al 2004, Tying et al 2000, Tying et al 2001a, Tying et al 2001b, Wald et al 2006, Warkentin et al 2002*). 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 (*Arora et al 2008, Beutner et al, 1995, Shafran et al 2004, Tying et al 2000, Tying et al 2001a, Tying et al 2001b*).
- 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 (*Centers for Disease Control and Prevention 2015, Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2017*).

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