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Drug Class Update: Antivirals for HSV

Date of Review: August 2026

Date of Last Review: September 2019
Dates of Literature Search: 07/01/2019 - 04/13/2026

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class review is to identify new literature for the herpes simplex virus (HSV) class. Additionally, in anticipation of funding line changes in 2027, coverage parameters will be reviewed to determine oral and/or topical options as it relates to disease severity.

Plain Language Summary:
- Herpes simplex virus (HSV) is a common, lifelong infection that can cause painful blisters or sores. The most common form of herpes is herpes simplex virus type 1 (HSV-1), which usually appears around the mouth and lips. The other type of virus is herpes simplex virus type 2 (HSV-2), which occurs around the genitalia.
- Both HSV-1 and HSV-2 can be passed from person to person when there are symptoms and when there are no symptoms.
- Certain antiviral medicines like acyclovir and valacyclorvir can treat HSV infections. They shorten the time the sores are present, may decrease symptoms and spreading of the infection. There is no cure for HSV.
- Antiviral medicines taken by mouth, like tablets, are more effective than topical antiviral medicines applied to the skin.
- This review found no new high-quality guidelines or systematic reviews for the treatment of HSV.
- There is one new antiviral formulation that was approved by the Food and Drug Administration (FDA) for acyclovir. It is used to treat HSV in the eye, which can occur but is not very common.
- There are two new safety warnings for the drugs acyclovir and valacyclovir. These drugs have been associated with severe skin reactions in rare cases.
- The Drug Research and Management (DURM) group does not recommend changes to the Preferred Drug List of antiviral medicines for HSV.

Research Questions:
1. What is the comparative evidence for efficacy of antivirals used to treat HSV?
2. What is the comparative evidence for the safety of antivirals used to treat HSV?
3. Are there groups of patients based on specific demographic characteristicss (e.g., age, racial or ethnic groups, gender, disease severity), for which antivirals are more effective or associated with less harm for the treatment of HSV?

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Conclusions:

- No new high quality systematic reviews or clinical practice guidelines for HSV were identified.
- A new formulation of acyclovir ophthalmic ointment (AVACLYR) was approved for the treatment of acute herpetic keratitis in patients with herpes simples (HSV-1 and HSV-2) virus.[1] Acyclovir was not previously available in an ophthalmic preparation.
- Two new safety alerts regarding risk of hypersensitivity for both acyclovir and valacyclovir were identified (**Table 2**). The same contraindication and warning were added to both drug's labeling.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- There was no new evidence identified in the previous review done in September of 2019.
- Preferred drugs include acyclovir capsules, tablets and oral suspension. Valacyclovir tablets and VALTREX tablets are also preferred.

Background:

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are common infections with an incidence of 520 million for HSV-1 and 3.8 billion for HSV-2 worldwide.[2] High-income countries have reported declining rates of HSV. Primary oral and genital herpes occurs at an increased incidence in adolescents and young adults. Children attending day care, adolescents and athletes involved in contact sports may be at increased risk for HSV-1.[3] The incidence of genital herpes increases with the number of sexual partners in women and in non-Hispanic Black patients.[4] Oral herpes is mainly caused by HSV-1 and is spread by oral contact. Genital herpes can be caused by HSV-1 but is more commonly due to HSV-2 and is spread by sexual contact.[2] The herpes virus is a chronic infection in the sensory ganglia. Infections can alternate between active symptoms and inactivity.[5] Most infections are asymptomatic (subclinical) but some present with painful blisters or ulcers, fever, local lymphadenopathy and headache that can often reoccur.[5] Initial infections usually last 2 to 12 days after exposure.[3] Recurrence of HSV-1 is rarely associated with systemic symptoms.[3] In rare cases HSV can cause severe disease such as encephalitis, meningitis, hepatitis, respiratory tract infections, and esophagitis.[5] Transmission can occur during asymptomatic viral shedding as well as with active infections.[3] Recurrent infections are more common with HSV-2 compared to HSV-1.[4] Reactivation of the virus from the latent state to active replication can be triggered by illness or fever, sun exposure, menstrual period, injury, emotional stress and surgery.[2]

Individuals that are immunocompromised are at increased risk of reactivation of HSV, including those with:[3]

- Human immunodeficiency virus (HIV) with advanced disease (CD4 count <200 cells/microL)
- Transplant recipients with history of previous HSV-1 infection
- Burns or other skin disorders
- Pregnancy

There is no cure for HSV-1 and HSV-2; however, antivirals are effective for decreasing symptom duration, severity of symptoms and virus transmission.[6] They are most effective when given within 48 hours of an outbreak. Primary treatment of a genital HSV infection should include antiviral therapy, ideally within 72 hours

of lesion appearance.[6] Oral acyclovir is appropriate for most infections; intravenous (IV) therapy indicated for complicated infections such as central nervous system disease or disseminated disease.

Considerations for when to treat HSV-1 include if it is the primary infection, recurrent infection, severity of symptoms, site of infection, frequency of recurrence and if there is a well-defined prodrome.[3] In immunocompetent patients, oral treatment is recommended for primary gingivostomatitis (mouth infection) who present within 72 hours of symptom onset (**Table 1**).[3] Treatment is commonly 7-10 days; however, treatment can be extended if the lesion is not healed. If the patient presents outside of the 72 hours and still has significant pain or new lesions, antiviral therapy should still be offered.[3] Topical antivirals are not recommended for HSV due to less efficacy compared to oral antiviral therapies and multiple times a day application.

Treatment of genital herpes is the same as for HSV-1 (**Table 1**). Oral antivirals recommended by the Centers for Disease Control and Prevention (CDC) for genital herpes (HSV-1 and HSV-2) are acyclovir, famciclovir, and valacyclovir.[6] For patients who have HSV recurrence, episodic or chronic suppressive therapy can be considered. Chronic suppressive therapy options for ongoing genital HSV include acyclovir, famciclovir or valacyclovir.[6]

Individuals with severe disease may be candidates for episodic or chronic suppressive therapy (**Table 1).**[3] Episodic therapy, given for 5 days, is considered for patients with occasional recurrence with mild to moderate symptoms with well-defined prodrome.[3] Daily suppressive therapy is recommended for patients with severe disease to reduce HSV episodes, symptoms, pain, and complications.[6] Suppressive therapy has been shown to decrease risk for transmitting HSV and decreasing recurrent episodes. Topical therapy is not indicated for genital HSV.

Table 1. Oral Medication Recommendations for the Treatment of HSV in Adolescents and Adults [3,6]

Indication	Medication and Dose
Primary HSV-1 Infection	Acyclovir 400 mg three times daily or 200 mg five times daily
	Famciclovir 250 mg three times daily or 500 mg twice daily
	Valacyclovir 1 gm twice daily
Genital HSV	Acyclovir 400 mg three times daily
	Famciclovir 250 mg three times daily
	Valacyclovir 1 gm twice daily
Recurrent HSV-1 infections	Acyclovir 400 mg three times daily for 5 days
	Famciclovir 750 mg twice daily for 1 day or 1500 mg as a single dose
	Valacyclovir 2 gm twice daily for 1 day
Episodic therapy for HSV-1 and HSV-2	Acyclovir 400 mg three times daily
	Famciclovir 750 mg twice a day for one day or 1500 mg as a single dose
	Valacyclovir 2 gm twice daily for one day
Chronic Suppressive Therapy for HSV-1 and HSV-2	Acyclovir 400 mg twice daily
	Valacyclovir 500 mg orally once daily

All antivirals used for HSV should have doses adjusted in patients with moderate to severe renal insufficiency.[3] Adverse reactions are usually mild and may include headache, diarrhea, vomiting , pain and dizziness.

The Antiviral for HSV drug class represents a small quarterly spend to the Oregon Health Plan for fee-for-service (FFS) patients of about $2500. Ninety-nine percent of claims were for preferred products prescribed to 267 patients.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
None identified.

After review, 9 systematic reviews were excluded due to poor quality (e.g., indirect network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[7–15]

New Guidelines:
No high-quality clinical practice guidelines were identified.

After review, one guideline was excluded due to poor quality.[16]

New Formulations or Indications:

AVACLYR (acyclovir ophthalmic ointment 3%): Topical acyclovir ophthalmic ointment was approved in March 2019.[1] Acyclovir ophthalmic ointment is an antiviral approved for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2) virus. Acyclovir is a herpes simplex virus nucleoside analog deoxyribonucleic acid (DNA) polymerase inhibitor.[1] Acyclovir ointment is applied in a 1 cm ribbon in the lower cul-de-sac of the affected eye 5 times daily till healed and then 3 times daily for 7 days. The approval of acyclovir ointment was based on 5 double-blind, RCTs (n=238) which enrolled patients with dendritic herpetic keratitis. Safey and efficacy in pediatric patients less than 2 years of age was not studied.[1] Evidence from 5 randomized trials demonstrated clinical resolution of healed ulcers. At day 7 resolution averaged 83% for acyclovir ophthalmic ointment 3% compared to 50% for idoxuridine ophthalmic ointment 0.5% and 1%.[1] Idoxuridine was the standard of care for treating ophthalmic herpes prior to the approval of acyclovir making it an appropriate compartor. In July 2021, labeling was updated to include a warning that patients should not wear contact lenses during treatment with acyclovir ophthalmic ointment if they have signs or symptoms of herpetic keratitis or during the course of therapy with treatment.[1]

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles
Acyclovir[17] and Valacyclovir[18]	ZOVIRAX VALTREX	November 2025	Contraindications	Acyclovir is contraindicated in patients who have had demonstrated clinically significant hypersensitivity reaction (e.g., anaphylaxis, severe cutaneous adverse reaction [SCARs]) to valacyclovir, acyclovir or any component of the formulation.
			Warnings and Precautions	Severe cutaneous adverse reactions (SCARs), including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported during postmarketing experience with valacyclovir. Discontinue immediately if painful rash with mucosal involvement or a progressive severe rash develops.

Randomized Controlled Trials:

A total of 62 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

References:

1. Avaclyr (acyclovir ophthalmic ointment 3%) [prescribing information]. Locust Valley, NY; Fera Pharmaceuticals, LLC. July 2021.

2. World Health Organization. Herpes Simplex Virus. May 2025. Available at: https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus. Accessed April 14, 2026.

3. Wald A. Treatment and prevention of herpes simplex virus type 1 in immunocompetent adolescents and adults. UpToDate. March 2026. Available by subscription. Accessed April 14, 2026.

4. Albrecht M. Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection. UpToDate. March 2026. Available by subscription. Accessed April 13, 2026.

5. Johnston C, Wald A. Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection. UpToDate. March 2026. Available by subscription. Accessed April 14, 2026.

6. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1. Epub 2021.

7. Chang ST, Wu H, Chiu YL, Chuang YF. Anti-herpetic treatment reduces dementia risk: A systematic review and meta-analysis. J Alzheimer's Dis. 109(4):1590-1602.

8. Chatzakis C, Bourgon N, Fourgeaud J, et al. The effect of valacyclovir on secondary prevention of congenital cytomegalovirus infection. Best Pract Res Clin Obstet Gynaecol. 2025;103:102679.

9. Putera I, Ridwan AS, Dewi A, et al. Antiviral treatment for acute retinal necrosis: A systematic review and meta-analysis. Surv Opthalmol. 2024;69(1):67-84.

10. Putera I, La Distia N, Dewi AC, et al. Antiviral therapy for cytomegalovirus retinitis: A systematic review and meta-analysis. Surv Opthalmol. 2025;70(2):215-231.

11. Fujiwara T, Uraguchi K. Antiviral treatment for Ramsay Hunt syndrome: A systematic review and meta-analysis. Auris, Nasus, Larynx. 2024;51(3):488-491.

12. Rybak-Krzyszkowska M, Gorecka J, Huras H, et al. Cytomegalovirus Infection in Pregnancy Prevention and Treatment Options: A Systematic Review and Meta-Analysis. Viruses. 2023;15(11):1024.

13. D'Antonio, Marinceu D, Prasad S, Khalil A. Effectiveness and safety of prenatal valacyclovir for congenital cytomegalovirus infection: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2023;61(4):436-444.

14. Vernooij RWM, Michael M, Colombijn JMT, Owers DS, Webster AC, Strippoli GFM, Hodson EM. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2025, Issue 1. Art. No.: CD005133.

15. Vernooij RWM, Michael M, Ladhani M, Webster AC, Strippoli GFM, Craig JC, Hodson EM. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2024, Issue 5. Art. No.: CD003774.

16. Kim W, Lee S, Bae S, et al. Korean sexually transmitted infection guidelines 2023 revision, guideline update of viral infections: Genital herpes and anogenital warts. Investig Clin Urol. 2023;65(1):9-15.

17. Food and Drug Administration. Drug safety-related labeling changes - Zovirax. November 12, 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=3209. Accessed April 9, 2026.

18. Food and Drug Administration. Drug safety-related labeling changes - Valtrex. November 11, 2025. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2144. Accessed April 9, 2026.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
acyclovir	ACYCLOVIR	CAPSULE	Y
acyclovir	ACYCLOVIR	ORAL SUSP	Y
acyclovir	ACYCLOVIR	TABLET	Y
valacyclovir HCl	VALACYCLOVIR	TABLET	Y
valacyclovir HCl	VALTREX	TABLET	Y
acyclovir	ACYCLOVIR	CREAM (G)	N
acyclovir	SITAVIG	MA BUC TAB	N
acyclovir	ACYCLOVIR	OINT. (G)	N
docosanol	DOCOSANOL	CREAM (G)	N
famciclovir	FAMCICLOVIR	TABLET	N
penciclovir	DENAVIR	CREAM (G)	N
penciclovir	PENCICLOVIR	CREAM (G)	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 07, 2026

Search Strategy:

#	Searches	Results
1	acyclovir.mp. or Acyclovir/	13887
2	Valacyclovir/ or valacyclovir.mp.	1982
3	docosanol.mp.	123
4	Famciclovir/ or famciclovir.mp.	942
5	penciclovir.mp.	477
6	1 or 2 or 3 or 4 or 5	15066
7	limit 6 to (english language and humans and yr="2019 -Current")	1623
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	62

Appendix 3: Key Inclusion Criteria

Population	Patients diagnosed with herpes simplex virus (HSV)-1 or HSV-2
Intervention	Oral or topical antiviral used for the treatment of HSV
Comparator	Placebo or active treatment
Outcomes	Symptom improvement
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Antivirals for Herpes Simplex Virus

Goal(s):

- Cover oral and/or topical antivirals only for funded diagnoses. HSV infections are funded only when complicated by an immunocompromised host.
- Support individual review under the EPSDT benefit.

Length of Authorization:

- Up to 12 months (criteria specific)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Immunocompromised Conditions

Cancer and undergoing chemotherapy or radiation
Solid organ transplant or an islet transplant
Advance or untreated HIV with CD4 cell counts <200/mm3, history of AIDs-defining illness without reconstitution or clinical manifestations of symptomatic HIV
Moderate or primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)

Centers for Disease Control and Prevention. People who are immunocompromised. May 2023. Available at: https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html. Accessed April 13, 2026.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
~~1.~~ Has the patient tried and failed or have contraindications to preferred products?~~Will the prescriber consider a change to a preferred product?~~ ~~2.~~ ~~3. Message:~~ ~~4. Preferred products do not require a PA.~~ ~~5.~~2. ~~Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.~~	**Yes:** ~~Inform prescriber of covered alternatives in class.~~Go to #3	**No:** Deny; inform provider of preferred antiviralsGo to #3
~~2.~~3. Is the diagnosis uncomplicated herpes simplex virus infection (HSV-1 or HSV-2)?	**Yes:** Go to #4	**No:** Go to #6
~~3.~~ Pass to RPh: Is the patient immunocompromised as listed in Table 1 (document ICD10 code)? ~~Examples:~~ ~~1. Diagnosis of cancer AND currently undergoing chemotherapy or radiation. Document therapy and length of treatment.~~ ~~2. Solid organ transplant~~ ~~3.~~4. ~~HIV/AIDS~~	**Yes:** Approve for up to 12 months. ICD10 code:_____	**No:** Go to #5

Approval Criteria		
~~4.~~ 5. Is the patient currently taking an immunosuppressive drug similar to the examples described below? ~~5.~~ Document name of drug. If is drug not in the list below, pass to RPh for evaluation. ~~6. Immunosuppressive drugs include, but are not limited to:~~	**Yes:** Approve for up to 90 days	**No:** Pass to RPh. Go to #6.

~~Immunosuppressants~~	
~~Abatacept~~	~~Infliximab~~
~~Adalimumab~~	~~Leflunomide~~
~~Anakinra~~	~~Methotrexate~~
~~Apremilast~~	~~Natalizumab~~
~~Azathioprine~~	~~Rituximab~~
~~Basiliximab~~	~~Secukinumab~~
~~Certolizumab pegol~~	~~Sirolimus~~
~~Cyclosporine~~	~~Tacrolimus~~
~~Etanercept~~	~~Tocilizumab~~
~~Golimumab~~	~~Tofacitinib~~
~~Hydroxychloroquine~~	~~Ustekinumab~~
	~~Vedolizumab~~

Active treatment with high-dose corticosteroids (20 mg or more of prednisone or equivalent per day when administered for 2 weeks or more)
Alkylating agents
Antimetabolites
Transplant-related immunosuppressive drugs
Cancer chemotherapeutic agents
Tumor necrosis factor (TNF) blockers
Other biologic agents that are immunosuppressive or immunomodulatory

Approval Criteria		
6. RPh only: All other indications need to be evaluated as to whether they are an OHP-funded condition. Note: Viral ICD-10 codes that do not appear on the OHP funding list pending a more specific diagnosis code should be treated as not funded by the OHP.	If funded and clinic provides supporting literature, approve for length of therapy or 3 months whichever is less. Note: deny non-viral diagnoses (medical appropriateness)	Non-funded and not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #7.
7. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** If clinic provides supporting literature, approve for length of therapy or 3 months whichever is less. Note: deny non-viral diagnoses (medical appropriateness)	**No:** Pass to RPh. Deny; medical necessity.

P&T Review: *8/26 (KS), 9/19 (KS), 7/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *8/16; 1/1/11*