Therapeutic Class Overview
Antivirals, Topical

INTRODUCTION

- Herpes simplex virus 1 (HSV-1) and HSV-2 cause a wide variety of illnesses, including mucocutaneous infections, central nervous system infections, and infections of the visceral organs. The 2 most common cutaneous manifestations of HSV infection are orolabial and genital herpes (*Cernik et al 2008)*. The Centers for Disease Control and Prevention (CDC) estimated a prevalence of HSV-1 and HSV-2 of 47.8% and 11.9%, respectively, in 2015 to 2016 among adolescents and adults 14 to 49 years of age (*CDC 2018*). 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 (*Corey 2018*).
- Herpes simplex is typically transmitted through close contact with a person who is shedding virus at a peripheral site, at a mucosal surface, or in genital or oral secretions. Contact must involve mucous membranes or open or abraded skin. Following transmission, the initial infection is associated with systemic signs and symptoms and involves 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. From there, 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). The exact mechanism of reactivation is not completely understood; however, the frequency depends on the severity and duration of the initial episode, the infecting serotype (ie, HSV-1 or -2), and the host. 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. Recurrent labial herpes infection affects approximately one-third of the US population. Typically, patients experience 1 to 6 episodes per year (*Cernik et al 2008*).
- Genital herpes is one of the most common viral sexually transmitted infections (STIs) in the world. In the US, between the periods of 1988 to 1994 and 1999 to 2004, the overall prevalence of HSV-2, the most common cause of genital herpes, had a relative decline of 19.0%, from 21.0% of males and females infected with the virus to 17.0%. The prevalence in men declined most dramatically, from 17.0% to 11.2%, a 34.1% decrease (*Xu et al 2006*). Overall HSV-2 seroprevalence in 2005 to 2010 was 15.7%, suggesting a plateau in infection rates (*Bradley et al 2014*). More recent data from a period between 1999 and 2016 showed that seroprevalence continued to decline, with the odds of HSV-2 infection declining by 2.23% and 2.89% per year among men and women, respectively (*Chemaitelly et al 2019*). Most people infected with HSV-2 have not been diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. After resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, causing recurrent (often less severe) outbreaks.
- Before the introduction of acyclovir as an antiviral drug in the early 1980s, cutaneous HSV infection was managed with drying agents and other local care. Today, treatment options include multiple oral, intravenous, and topical antiviral agents. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection (*Corey 2018*). Topical antivirals have minimal clinical benefit in genital herpes, and use should be discouraged (*CDC 2015*). No antiviral agent currently available will eradicate HSV, and thus treatment is aimed at managing rather than curing the disease. This review will focus on the topical agents for HSV.
- Medispan class: Antivirals, Topical and Antivirals, Topical Combinations

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Denavir (penciclovir)	-
Xerese (acyclovir/hydrocortisone)	-
Zovirax (acyclovir cream)	✔
Zovirax (acyclovir ointment)	✔

*In addition to the prescription products listed in the table, Abreva (docosanol) cream is available as an over-the-counter product (brand and generic).

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications†

Indication	Denavir (penciclovir)	Xerese (acyclovir/ hydrocortisone)	Zovirax (acyclovir cream)	Zovirax (acyclovir ointment)
Early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time (age ≥ 6 years)		✔		
Management of initial genital herpes				✔
Management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients				✔
Treatment of recurrent herpes labialis (cold sores) (age ≥ 12 years)	✔		✔ *	

* In immunocompetent patients

† Indication for Abreva (docosanol): Treatment of cold sores/fever blisters on face or lips to shorten healing time and duration of symptoms (age ≥ 12 years)

(*Prescribing information: Abreva 2018, Denavir 2018, Xerese 2019, Zovirax cream 2018, Zovirax ointment 2017*)

- 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

- Conflicting results have been observed among clinical trials with topical antivirals.
- In 2 placebo-controlled studies evaluating the efficacy of a 5-day treatment regimen of acyclovir 5% ointment for the treatment of genital herpes, viral shedding was reduced in acyclovir-treated patients, but no difference in healing time was demonstrated between groups (*Luby et al 1984, Reichman et al 1983*). Studies evaluating the efficacy of a regimen with duration greater than 5 days showed that acyclovir 5% ointment significantly reduced the duration of viral shedding from genital lesions, mean duration of local pain or itching, mean time to healing of lesions, and duration of new lesion formation when compared to placebo (*Corey et al 1982, Kinghorn et al 1983*). These studies also showed a significant decrease with acyclovir ointment in the average time to crusting and healing of lesions and duration for all symptoms in patients with recurrent episodes.
- When the efficacy of acyclovir 5% cream was evaluated against placebo for the treatment of genital herpes, only a significant decrease in the duration of itching was seen in the acyclovir group (*Kinghorn et al 1986*).
- A Cochrane review evaluating the effectiveness and safety of the different existing treatments for first-episode genital herpes on duration of symptoms and time to recurrence found low-quality evidence which did not show that topical antivirals reduced symptom duration for patients undergoing their first episode of genital herpes (mean difference [MD] -0.61 days, 95% confidence interval, -2.16 to 0.95; 3 randomized controlled trials [RCTs], 195 participants, I^2 statistic = 56%) (*Heslop et al 2016*).
- Studies involving acyclovir 5% cream for the treatment of recurrent herpes labialis have demonstrated a significantly shorter mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo (*Gibson et al 1986, Raborn et al 1997, Shaw et al 1985, Spruance et al 1984, Spruance et al 2002*). However, changes in healing time of lesions and the number of episodes per month were not found to be significantly different.
- When compared to placebo, patients with herpes labialis treated with penciclovir 1% cream were shown to have significant decreases in overall healing time, resolution of lesion pain, and resolution of symptoms including itching, tingling, burning, numbness, and tenderness (*Boon et al 2000, Raborn et al 2002, Spruance et al 1997*). Patients treated with penciclovir were also shown to have a significantly higher proportion of cases healed at 6 and 8 days. In RCTs by

Femiano et al and Lin et al, penciclovir 1% cream was compared to acyclovir cream (5% and 3%, respectively). Penciclovir showed significantly shorter time to crusting. However, the percent of patients cured at 7 days was not significantly different (*Femiano et al 2001, Lin et al 2002*).

- The combination cream Xerese (acyclovir 5%/hydrocortisone 1%) was shown to reduce the occurrence of ulcerative lesions in patients with a history of herpes labialis compared to placebo in a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. Acyclovir/hydrocortisone reduced the progression of cold sores to ulcerative lesions and significantly reduced the lesion area compared with acyclovir and placebo (*Hull et al 2011*). The safety of acyclovir/hydrocortisone was also demonstrated in adolescents with herpes labialis (*Strand et al 2012*). Adverse events were similar to other clinical trials of the combination cream in adults.
- The topical antivirals have not been well studied in the immunocompromised patient population. A study involving 63 hospitalized immunocompromised patients with herpes simplex virus (regardless of virus type or infection site) who received acyclovir 5% ointment or placebo demonstrated that acyclovir significantly accelerated the clearance of virus ($p = 0.0006$), as well as significantly shortened the time to resolution of pain ($p = 0.004$) and total healing ($p = 0.038$) (*Whitley et al 1984*).
- No studies have been conducted which directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

CLINICAL GUIDELINES

- National guidelines published by the CDC report that the topical antiviral agents offer minimal clinical benefit for genital herpes infections and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, and valacyclovir) (*CDC 2015).*
- The Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend oral antivirals for treatment of orolabial or genital herpes infections. Prophylaxis with antiviral drugs to prevent primary HSV infection is not recommended. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous acyclovir. Suppressive therapy with oral antivirals is effective in preventing recurrences and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences *(Panel on Opportunistic Infections in Adults and Adolescents with HIV 2020*).

SAFETY SUMMARY

- Topical antivirals should not be applied to the eye.
- Safety and efficacy of the topical antivirals have not been established in patients with immunosuppression, except for acyclovir ointment, which can be used in limited non-life-threatening mucocutaneous HSV infections in immunocompromised patients.
- Adverse effects are mostly local in nature. Common adverse events include application site reaction, dryness, burning or stinging with application, and pruritus.
- Due to the topical application of these products, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration†

Drug	Available Formulations	Route	Usual Recommended Frequency
Denavir (penciclovir)	1% cream	Topical	Every 2 hours while awake
Xerese (acyclovir/hydrocortisone)	5%/1% cream	Topical	5 times daily
Zovirax (acyclovir cream)	5% cream	Topical	5 times daily
Zovirax (acyclovir ointment)	5% ointment	Topical	6 times daily

See the current prescribing information for full details

† Dosing for Abreva (docosanol 10% cream): Apply topically to affected area 5 times daily

CONCLUSION

- Denavir (penciclovir), acyclovir cream, and Xerese (acyclovir/hydrocortisone) are indicated for the treatment of recurrent herpes labialis. Acyclovir ointment is indicated for the initial treatment of genital herpes and in limited non-life-threatening mucocutaneous HSV infections in immunocompromised patients.
- The topical antiviral agents have demonstrated efficacy compared to placebo for their FDA-approved indications. They are generally safe with no significant drug interactions and limited adverse events.
- Head-to-head trials for the treatment of oral and/or genital herpes simplex have not consistently demonstrated superiority of one product over another. In a comparison trial in the treatment of herpes labialis, penciclovir cream resulted in a quicker time to crusting and cessation of pain compared to acyclovir; however, there was no significant difference in time to healing (*Femiano et al 2001*). Lin et al also compared penciclovir and acyclovir in the treatment of herpes labialis and found that there was no significant difference in clinical cure rates and time to healing (*Lin et al 2002*).
- National guidelines published by the CDC report that the topical antiviral agents offer minimal clinical benefit for genital herpes infections and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, and valacyclovir) (*CDC 2015).* The Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend oral antivirals for the treatment of orolabial or genital herpes infections *(Panel on Opportunistic Infections in Adults and Adolescents with HIV 2020*). However, no studies have been conducted which directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

REFERENCES

- Abreva prescribing information. Glaxo SmithKline Consumer Healthcare Holdings, LLC. Moon Township, PA. December 2018.
- Boon R, Goodman JJ, Martinez J, et al. Penciclovir cream for the treatment of sunlight-induced herpes simplex labialis: a randomized, double-blind, placebo-controlled trial. *Clin Ther*. 2000;22(1):76-90.
- Bradley H, Markowitz LE, Gibson T, et al. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. *J Infect Dis*. 2014;209(3):325-33.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR*. 2015 June 5;64(3):1-140. http://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed May 18, 2020.
- Centers for Disease Control and Prevention. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14-49: United States, 2015-2016. https://www.cdc.gov/nchs/products/databriefs/db304.htm. Accessed May 18, 2020.
- Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidenced-based review. *Arch Intern Med*. 2008;168(11):1137-1144. doi:10.1001/archinte.168.11.1137.
- Chemaitelly H, Nagelkerke N, Omori R, Abu-Raddad LJ. Characterizing herpes simplex virus type 1 and type 2 seroprevalence declines and epidemiological association in the United States. *PLoS One*. 2019;14(6):e0214151. doi: 10.1371/journal.pone.0214151.
- Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. *Am J Med*. 1982;73(1A):326-34.
- Corey L. Herpes simplex virus Infections. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill; 2018. http://accesspharmacy.mhmedical.com/content.aspx?bookid=2129&sectionid=192024643. Accessed May 18, 2020.
- Denavir prescribing information. Mylan Pharmaceuticals, Inc. Morgantown, WV. November 2018.
- Drugs@FDA [database on the Internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 18, 2020.
- Femiano F, Gombos F, Scully C, et al. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir (aciclovir). *Oral Dis*. 2001;7:31-3.
- Gibson JR, Klaber MR, Harvey SG, et al. Prophylaxis against herpes labialis with acyclovir cream—a placebo-controlled study. *Dermatologica*. 1986;172:104-7.
- Heslop R, Roberts H, Flower D, Jordan V. Interventions for men and women with their first episode of genital herpes. *Cochrane Database Syst Rev*. 2016 Aug 30;(8):CD010684.
- Hull CM, Harmenberg J, Arlander E, et al. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. *J Am Acad Dermatol*. 2011 Apr;64(4):696.e1-11. doi: 10.1016/j.jaad.2010.08.012.
- Kinghorn GR, Abeywickreme I, Jeavons M, et al. Efficacy of combined treatment with oral and topical acyclovir in first episode genital herpes. *Genitourin Med*. 1986;186-8.
- Kinghorn GR, Turner EB, Barton IG, et al. Efficacy of topical acyclovir cream in first and recurrent episodes of genital herpes. *Antiviral Res*. 1983;3:291-301.
- Lin L, Chen XS, Cui PG, et al. Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double blind, multicenter, acyclovir-controlled trial. *J Dermatolog Treat*. 2002;13:67-72.
- Luby JP, Gnann JW Jr, Alexander WJ, et al. A collaborative study of patient-initiated treatment of recurrent genital herpes with topical acyclovir or placebo. *J Infect Dis*. 1984;150:1-6.

- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2020. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed May 18, 2020.
- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institute of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Last updated February 11, 2020. https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed May 18, 2020.
- Raborn GW, Martel AY, Grace MG, et al. Herpes labialis in skiers: randomized clinical trial of acyclovir cream versus placebo. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;84:641-5.
- Raborn GW, Martel AY, Lassonde M, et al, for the Worldwide Topical Penciclovir Collaborative Study Group. Effective treatment of herpes simplex labialis with penciclovir combined results of two trials. *J Am Dent Assoc*. 2002;133:303-9.
- Reichman RC, Badger GJ, Guinan ME, et al. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. *J Infect Dis*. 1983;147(2):336-40.
- Shaw M, King M, Best JM, et al. Failure of acyclovir cream in treatment of recurrent herpes labialis. *Br Med J*. 1985;291:7-9.
- Spruance SL, Crumpacker CS, Schnipper LE, et al. Early, patient-initiated treatment of herpes labialis with topical 10% acyclovir. *Antimicrob Agents Chemother*. 1984;25:553-5.
- Spruance SL, Nett R, Marbury T, et al. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002;46(7):2238-43.
- Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. *JAMA*. 1997;277(17):1374-9.
- Strand A, Böttiger D, Gever LN, et al. Safety and tolerability of combination acyclovir 5% and hydrocortisone 1% cream in adolescents with recurrent herpes simplex labialis. *Pediatr Dermatol*. 2012 Jan-Feb;29(1):105-10.
- Whitley RJ, Levin M, Barton N, et al. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. *J Infect Dis*. 1984;150(3):323-9.
- Xerese prescribing information. Bausch Health US, LLC. Bridgewater, NJ. December 2019.
- Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296:964-73.
- Zovirax cream prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. April 2018.
- Zovirax ointment prescribing information. Valeant Pharmaceuticals North America, LLC. Bridgewater, NJ. January 2017.

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