Therapeutic Class Overview
Topical Antivirals

Therapeutic Class

- **Overview/Summary:** Both acyclovir (Zovirax®) and penciclovir (Denavir®) are synthetic nucleoside analogs derived from guanine that are approved for the management of initial herpes genitalis, recurrent herpes labialis and/or non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients. In addition, a combination of acyclovir and hydrocortisone (Xerese®) is approved to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in recurrent herpes labialis. These agents are active against various herpes simplex virus including types 1 and 2 (HSV-1 and HSV-2).[1-5] The two most common cutaneous manifestations of the herpes simplex virus infection are orolabial and genital herpes. Orolabial herpes presents most commonly as cold sores and is the most prevalent form of mucocutaneous herpes infection. Approximately 35 to 60% of Caucasians in the United States have serologic evidence of having been infected by HSV-1.[6] Genital herpes, is one of the most common viral sexually transmitted diseases in the world, but has demonstrated a decreased prevalence over the past few years. A majority of patients infected with HSV-2 have not been diagnosed, as symptoms may be mild in many cases and the presentation is highly variable between patients. Although infections may be mild or unrecognized, the virus continues to be shed 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.

  Prior to 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 antiviral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.[6] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted; however, the topical treatment is much less effective compared to oral or intravenous therapies. No antiviral agent currently available will eradicate HSV, and treatment is aimed at managing symptoms and reducing disease duration rather than curing the disease. Currently, acyclovir ointment is available generically.

Table 1. Current Medications Available in the Therapeutic Class[2-5]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Acyclovir (Zovirax®*)	Management of initial herpes genitalis†, treatment of recurrent herpes labialis‡, management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients†	Cream: 5% (2, 5 g tubes) Ointment: 5% (30 g tube)	✔
Penciclovir (Denavir®)	Treatment of recurrent herpes labialis	Cream: 1% (1.5 g tube)	-
Combination Products			
Acyclovir/ hydrocortisone (Xerese®)	Treatment of recurrent herpes labialis#	Cream: 5%/1% (5 g tube)	-

*Generic available in at least one dosage form or strength.
† Acyclovir 5% ointment only.
‡ Acyclovir 5% cream only.
#To reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time.

Evidence-based Medicine

- When the efficacy of acyclovir 5% cream was evaluated compared to placebo for the treatment of genital herpes, there was only a significant decrease in the duration of itching with acyclovir treatment compared to placebo.[7] When penciclovir 1% cream was compared to acyclovir 3% cream for the treatment of genital herpes, the only significant difference seen between the two treatment groups was time to crusting of lesions, which favored penciclovir treatment.[8]
- In the treatment of recurrent herpes labialis, acyclovir 5% cream significantly shortens the mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo. The lesion healing time and the number of episodes per month was not found to be significant between treatments.[9-13]
- The combination formulation of acyclovir/hydrocortisone 5%/1% cream was evaluated in a double-blind, active and placebo controlled study of more than 2,400 patients ≥18 years of age with a history of herpes simplex labialis who had experienced at least three recurrent episodes in the past year. The primary endpoint, prevention of ulcerative herpes simplex labialis lesions (frequency of patients with nonulcerative recurrences) was significantly greater in patients treated with acyclovir/hydrocortisone compared to patients treated with acyclovir or placebo (42 vs 35 and 26%, respectively; *P*<0.05 for both). [14]
- Compared to placebo, patients treated with penciclovir 1% cream experienced significant decreases in the overall lesion healing time, healing in early, late and vesicle stages, resolution of lesion pain and resolution of symptoms including itching, tingling, burning, numbness and tenderness.[15-17] Patients treated with penciclovir also were shown to have a significantly higher percent of cases healed at six and eight days. When penciclovir 1% cream was compared to acyclovir 5% cream, there was a significantly shorter time to crusting with penciclovir treatment compared to acyclovir. The percent of patients cured at seven days was not significantly different. [18,19]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - National and international guidelines including those published by the Centers for Disease Control and Prevention, state that the topical antiviral agents offer minimal clinical benefit and should not be recommended over other options in general use, such as the oral antivirals.[20,21]
- Other Key Facts
  - Acyclovir 5% ointment is the only topical antiviral agent available generically; however, several oral antiviral formulations are available generically in various formulations.

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Therapeutic Class Review
Topical Antivirals

Overview/Summary

Both acyclovir (Zovirax®) and penciclovir (Denavir®) are synthetic nucleoside analogs derived from guanine that are approved for the management of initial herpes genitalis, recurrent herpes labialis and/or non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients. In addition, a combination of acyclovir and hydrocortisone (Xerese®) is approved to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in recurrent herpes labialis. These agents are active against various herpes simplex virus including types 1 and 2 (HSV-1 and HSV-2).[1-5]

The two most common cutaneous manifestations of the herpes simplex virus infection are orolabial and genital herpes. Orolabial herpes presents most commonly as cold sores and is the most prevalent form of mucocutaneous herpes infection. Approximately 35 to 60% of Caucasians in the United States have serologic evidence of having been infected by HSV-1.[6] The incidence varies among regions and countries depending on hygiene and socioeconomic conditions, with the highest incidence of first infection occurring between six months and three years of age.[7]

Genital herpes, is one of the most common viral sexually transmitted diseases in the world, but has demonstrated a decreased prevalence over the past few years. Between the periods 1988 to 1994 and 1999 to 2000, the overall prevalence of HSV-2, the most common cause of genital herpes, declined 17.0%, from 21.3% of males and females infected with the virus to 17.6%. The prevalence in men declined by 35% from 17.3 to 11.2%.[8] A majority of patients infected with HSV-2 have not been diagnosed, as symptoms may be mild in many cases and the presentation is highly variable between patients. Although infections may be mild or unrecognized, the virus continues to be shed 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 antiviral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.[6] Topical antivirals reduce the duration of viral shedding and the length of time before all lesions become crusted; however, the topical treatment is much less effective compared to oral or intravenous therapies. No antiviral agent currently available will eradicate HSV, and treatment is aimed at managing symptoms and reducing disease duration rather than curing the disease. Currently, acyclovir ointment is available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Acyclovir (Zovirax®*)	Topical antiviral	✔
Penciclovir (Denavir®)	Topical antiviral	-
Combination Products		
Acyclovir/hydrocortisone (Xerese®)	Topical antiviral/glucocorticoid	-

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

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications[2-5]

Generic Name	Management of Initial Herpes Genitalis	Treatment of Recurrent Herpes Labialis	Management of Non-Life-Threatening Mucocutaneous Herpes Simplex Virus Infections in Immunocompromised Patients
Single-Entity Agents			
Acyclovir	✔ *	✔ †	✔ *
Penciclovir		✔	
Combination Products			
Acyclovir/ hydrocortisone		✔ ‡	

*Acyclovir 5% ointment only.
†Acyclovir 5% cream only.
‡To reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time.

Pharmacokinetics

Table 3. Pharmacokinetics[2-5]

Generic Name	Systemic Absorption	Distribution	Excretion (Renal)
Single-Entity Agents			
Acyclovir cream	Minimal	Not reported	0.04% of daily dose
Acyclovir ointment	Minimal	Not reported	<0.02% to 9.40% of daily dose
Penciclovir cream	Minimal	Not reported	Not detected
Combination Products			
Acyclovir/ hydrocortisone	Minimal	Not reported	Not reported

Clinical Trials

Clinical trials summarized in Table 4 support the Food and Drug Administration-approved indications for the topical antivirals.

Conflicting results have been reported in studies evaluating the efficacy of a five day treatment regimen of acyclovir ointment for the treatment of genital herpes.[9,10] Studies that evaluated the efficacy of a treatment regimen of more than five days demonstrated 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 compared to placebo.[11,12] These study results also demonstrated that treatment with acyclovir 5% ointment significantly decreased the mean 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 compared to placebo for the treatment of genital herpes, there was only a significant decrease in the duration of itching with acyclovir treatment compared to placebo.[13] When penciclovir 1% cream was compared to acyclovir 3% cream for the treatment of genital herpes, the only significant difference seen between the two treatment groups was time to crusting of lesions, which favored penciclovir treatment.[14]

In the treatment of recurrent herpes labialis, treatment with acyclovir 5% cream significantly shortens the mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo. The lesion healing time and the number of episodes per month was not found to be significant between treatments.[15-19] The combination formulation of acyclovir/hydrocortisone 5%/1% cream was evaluated in a double-blind, active and placebo controlled study of more than 2,400 patients ≥18 years of age with a history of herpes simplex labialis who had experienced at least three recurrent episodes in the past year. The primary endpoint, prevention of ulcerative herpes simplex labialis lesions (frequency of patients with nonulcerative recurrences) was significantly greater in patients treated

with acyclovir/hydrocortisone compared to patients treated with acyclovir or placebo (42 vs 35 and 26%, respectively; *P*<0.05 for both). In addition, the time for ulcerative lesion healing was reduced by 1.4 days with acyclovir/hydrocortisone compared to placebo (*P*=0.002); however, no significant difference was reported compared to acyclovir (0.3 days; *P*=0.297).[21]

Compared to placebo, patients treated with penciclovir 1% cream experienced significant decreases in the overall lesion healing time, healing in early, late and vesicle stages, resolution of lesion pain and resolution of symptoms including itching, tingling, burning, numbness and tenderness.[22-24] Patients treated with penciclovir also were shown to have a significantly higher percent of cases healed at six and eight days. When penciclovir 1% cream was compared to acyclovir 5% cream, there was a significantly shorter time to crusting with penciclovir treatment compared to acyclovir. The percent of patients cured at seven days was not significantly different. [25,26]

In one study involving immunocompromised patients with herpes simplex virus who received acyclovir 5% ointment or placebo, acyclovir treatment significantly accelerated the clearance of virus, as well as significantly shortened the time to resolution of pain and total healing compared to placebo.[27]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Herpes Genitalis				
Luby et al[9] Acyclovir 5% ointment, applied 6 times a day at 3 hour intervals vs placebo, applied 6 times a day at 3 hour intervals	MC, PC, RCT Patients with recurrent genital herpes who experienced a prodrome >75% of the time before occurrence of actual lesions	N=309 5 days	Primary: Duration of viral excretion Secondary: Duration of ulceration/crusting of genital lesions, healing time of lesions and duration of pain and itching	Primary: In female patients, the duration of viral excretion was significantly shorter in the acyclovir group compared to placebo (1.1 vs 2.0 days; *P*=0.04). In male patients, there was no difference between the acyclovir and placebo groups (1.8 days; *P* value not reported). Secondary: There was no difference between placebo and acyclovir in ulceration and/or crusting time for male patients who had genital lesions present at the initial clinic visit (2.2 days). The mean duration of pain and itching in males treated with acyclovir compared to placebo was 3.7 and 3.8 days, respectively. The mean duration of pain and itching in females treated with acyclovir compared to placebo was 5.4 and 4.4 days, respectively (*P* values not reported).
Reichman et al[10] Acyclovir 5% ointment applied 6 times a day at 3 hour intervals vs placebo applied 6 times a day at 3 hour intervals	DB, PC, RCT Patients with culture-proven recurrent herpes simplex genitalis who were within 48 hours of the onset of lesions	N=88 5 days	Primary: Duration of virus shedding, time to crusting of lesions, time required for lesions to heal and time to cessation of pain Secondary: Not reported	Primary: The duration of virus shedding from lesions present at time of study entry was significantly reduced for men who received acyclovir compared to placebo (2.0 vs 3.2 days; *P*<0.05). In women, the duration of virus shedding was 1.6 days for those in the acyclovir group compared to 1.2 days for the placebo group (*P* value not reported). There was no significant difference between acyclovir and placebo in time to crusting, time required for lesion healing, time to cessation of pain, or frequency with which new lesions developed during the course of therapy (*P* values not reported). Secondary: Not reported
Corey et al[11] Acyclovir 5% ointment	DB, PC, RCT Patients with initial or	N=180 21 days	Primary: Mean duration of viral shedding	Primary: Among patients with first episodes of genital herpes, the mean duration of viral shedding from genital lesions (2.0 vs 4.6 days), mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied 4 or 6 times a day vs placebo applied 4 or 6 times a day	recurrent episodes of genital herpes		from genital lesions, mean duration of local pain or itching and mean time to healing of lesions Secondary: Not reported	duration of local pain or itching (3.6 vs 6.7 days), and the mean time to healing of lesions (11.2 vs 15.8 days) were significantly shorter with acyclovir treatment compared to placebo (*P*<0.05 for all). Among patients with recurrent genital herpes, the mean time to crusting and healing of lesions was 3.5 and 7.5 days, respectively, in acyclovir recipients compared to 5.0 days (*P*=0.03) and 9.7 days (*P*=0.07), respectively, in patients treated with placebo. Secondary: Not reported
Kinghorn et al[12] Acyclovir 5% ointment applied topically 5 times a day vs placebo cream applied topically 5 times a day	DB, PC, RCT Patients with a clinically diagnosed first or recurrent episode of genital herpes	N=113 14 days	Primary: Duration of pain, time to healing, duration of viral shedding, duration of new lesion formation Secondary: Not reported	Primary: For first episodes treated with acyclovir, the duration of pain (4.0 vs 8.0 days; *P*<0.05), time to healing (8.0 vs 14.0 days; *P*<0.001), duration of viral shedding (4.0 vs 11.0 days; *P*=0.001) and duration of new lesion formation (0 vs. 2.5 days; *P*<0.001) were significantly reduced compared to placebo. Patients with recurrent episodes experienced reduced durations for all symptoms (three vs six days; *P*<0.001), for time to healing (four vs six days; *P*<0.01) and for the formation of new lesions (5 vs 29%; *P*<0.01) with acyclovir compared to placebo. Secondary: Not reported
Kinghorn et al[13] Acyclovir 5% cream applied topically 5 times a day for 7 days in combination with acyclovir 200 mg tablets taken 4 times a day vs	DB, PC, RCT Patients ≥16 years of age who presented within 6 days of onset of symptoms of first episode genital herpes	N=49 7 days	Primary: Duration of viral shedding, duration of symptoms and time to healing of lesions Secondary: Not reported	Primary: There was no statistically significant difference in the duration of viral shedding between the acyclovir cream group compared to placebo (external lesions, 2.6 vs 2.0 days; *P* value not reported; urethra or cervix, 2.1 vs 1.7 days; *P* value not reported). The mean duration of viral shedding for women in the acyclovir cream group compared to placebo was also not statistically significant (external lesions, 2.6 vs 2.8 days; *P* value not reported; cervix, 1.7 vs 1.8 days; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo applied topically 5 times a day for 7 days in combination with acyclovir 200 mg tablets taken 4 times a day				The duration of symptoms of pain, dysuria, and discharge was not significantly different between treatment groups (*P* value not reported). There was a decrease in the duration of itching with acyclovir cream compared to placebo (1.2 vs 2.2 days; *P*=0.08). The mean duration of time to healing of lesions was not significantly different (*P* value not reported). Secondary: Not reported
Chen et al[14] Penciclovir 1% cream applied topically 5 times a day vs acyclovir 3% cream applied topically 5 times a day	DB, MC, PG, RCT Patients 18 to 65 years of age with clinical diagnosis of genital herpes, treatment initiated within 24 hours of onset of the first sign of lesions	N=205 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: A significant decrease in crusting time was noted in patients with primary first episodes of genital herpes treated with penciclovir compared to acyclovir (two vs three days; *P*=0.03). Patients in the acyclovir had a longer time to healing, absence of blisters, cessation of new blisters and loss of crust group compared to the penciclovir group; however, none of these differences were statistically significant. A comparison of clinical efficacy in terms of cure rate at day seven indicated that there was no difference between penciclovir and acyclovir treatment (86/104 vs 80/101; *P*=0.53). Secondary: Not reported
Herpes Labialis				
Spruance et al[15] Acyclovir 5% cream initiated within 1 hour of first sign of symptoms and applied 5 times daily	2 DB, MC, PC, RCT Patients ≥18 years of age with a clinical history of recurrent herpes labialis (≥3	N=1,385 4 days	Primary: Clinician-assessed duration of herpes labialis episode	Primary: The mean clinician-assessed duration of herpes labialis episode was significantly shorter for patients treated with acyclovir cream compared to placebo in each of the two clinical trials (study one; *P*=0.007, study two; *P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo cream initiated within 1 hour of first sign of symptoms and applied 5 times a daily	episodes in the past year)		Secondary: Patient-assessed duration of pain, proportion of patients developing classical lesions (ulcers, vesicles and crust)	In study one, the mean duration of herpes labialis episodes for patients with a known duration was 4.3 days in the acyclovir group compared to 4.8 days for the placebo group (*P*=0.010). In study two, the duration of herpes labialis episodes for patients with a known duration was 4.6 days in the acyclovir group compared to 5.2 days for the placebo group (*P*=0.007). Secondary: The mean patient-assessed duration of pain was significantly shorter for patients in the acyclovir group compared to placebo in both studies (study one; *P*=0.017, study two; *P*=0.014). In study one, the mean duration of pain was 2.9 days for patients in the acyclovir group compared to 3.2 days in the placebo group (*P*=0.024). In study two, the mean duration of pain was 3.1 days for patients in the acyclovir group compared to 3.5 days for patients in the placebo group (*P*=0.027).
Gibson et al[16] Acyclovir 5% cream, applied 4 times a day vs placebo applied 4 times a day	DB, PC, RCT Patients ≥16 years of age with ≥6 recurrences of herpes labialis per year	N=23 32 weeks (16 weeks of acyclovir application and 16 weeks of placebo)	Primary: Number of recurrent sores, number of days with sores present and number of days with signs/ symptoms of disease present Secondary: Not reported	Primary: There was a significant difference in favor of the acyclovir group in mean number of doctor-confirmed recurrent sores (0.5 vs 1.1; *P*<0.05), mean number of sores present (9.5 vs 12.4; *P*<0.01) and mean number of days with no signs or symptoms of disease present (12.2 vs 17.4; *P*<0.001). There was no significant difference between the acyclovir and placebo groups in mean time to first patient recorded recurrence (40.7 vs 43.3; *P* value not reported), mean time to first doctor confirmed recurrence (64.2 vs 63.2; *P* value not reported), and mean number of patient recorded recurrent sores (1.6 vs 2.4; *P* value not reported). Secondary: Not reported
Raborn et al[17] Acyclovir 5% cream	DB, MC, PC, RCT Patients ≥18 years of	N=191 8 days	Primary: Number of lesions formed during	Primary: The difference in the number of patients who had lesions form during treatment was not statistically significant between patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied topically 4 times a day at 4 hour intervals vs placebo applied topically 4 times a day at 4 hour intervals	age with >3 episodes of sun-induced herpes labialis within the past year		treatment, number of lesions formed during follow-up Secondary: Not reported	acyclovir or placebo (15/91 vs 23/90, respectively; *P*=0.20). During the four day follow-up period, a smaller percentage of patients with lesion formation were found in the acyclovir group compared to the placebo group (21 vs 40%; *P*<0.01). The proportion of patients with no lesion formation in either the treatment period or the four day follow-up was significantly greater in the acyclovir group compared to placebo (*P*<0.01). Secondary: Not reported
Shaw et al[18] Acyclovir 5% cream, applied topically 5 times a day vs placebo, applied topically 5 times a day	DB, PC, RCT Patients ≥18 years of age with ≥3 recurrences of herpes labialis a year	N=45 5 days	Primary: Healing time of original lesions, and combined original and fresh lesion, time to first crust on original lesion and loss of crust from original lesion and duration of symptoms Secondary: Not reported	Primary: No significant differences were reported between acyclovir and placebo. The median healing times for acyclovir and placebo were nine and 10 days, respectively (*P*=0.82). The median duration of all symptoms was five days for the acyclovir group compared to six days for the placebo group (*P*=0.33). Secondary: Not reported
Spruance et al[19] Acyclovir 5% ointment, applied topically 4 times per day for 5 days vs	DB, PC Patients who had an episode of herpes simplex labialis	N=208 5 days	Primary: Decrease in median virus titers in lesions between the first and second clinic visit Secondary:	Primary: Acyclovir treatment was associated with a greater decrease in median virus titers in lesions compared to placebo (*P*=0.04). Antiviral effect occurred in the subgroup of patients who entered the study less than eight hours after the onset of lesions. No differences were found in patients who began treatment nine to 25 hours after lesion onset.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo, applied topically 4 times a day for 5 days			Not reported	The acyclovir group had a mean number of episodes per month of 0.38 compared to 0.45 in the placebo group (*P*=0.22). Secondary: Not reported
Strand et al[20] Acyclovir/hydrocortisone 5%/1% cream applied topically 5 times a day for 5 days	MC, OL Patients 12 to 17 years of age with a history of herpes simplex labialis and ≥2 recurrences during the past year	N=134 4 weeks	Primary: Adverse events, categorization of the recurrence as ulcerative or nonulcerative maximum lesion area Secondary: Not reported	Primary: Five adverse events occurred in five patients. Three were rated as mild in intensity and two of moderate intensity. Only one adverse event was considered to be related to the study medication (application site inflammation of moderate severity), leading to withdrawal from the study. Herpes simplex labials recurrence consisted of a single lesion in 126 (95.5%) and two lesions in six (4.5%). Overall, 78 patients (59.5%) had nonulcerative recurrences and 53 patients (40.5%) had ulcerative recurrences. The mean maximum lesion area in the 53 patients with ulcerative herpes lesions was 38.8±40.8 mm^2 (range six to 260 mm^2). Lesions healed completely in all evaluable patients, with normal skin and no signs or symptoms at the follow-up visit. Secondary: Not reported
Hull et al[21] Acyclovir/hydrocortisone 5%/1% cream applied topically 5 times a day for 5 days vs acyclovir 5% cream	AC, DB, MC, PC, RCT Patients ≥18 years of age with a history of herpes simplex labialis who had experienced ≥3 episodes in the past year (required to have experienced prodromal symptoms	N=2,437 3 weeks	Primary: Prevention of ulcerative herpes simplex labialis lesions (frequency of patients with nonulcerative recurrences) Secondary:	Primary: The proportion of patients with nonulcerative lesions was significantly greater in patients treated with acyclovir/hydrocortisone (42%) compared to patients treated with acyclovir (35%) or placebo (26%; *P*<0.05 for both compared to placebo). The proportion of patients with ulcerative lesions was lower with acyclovir/hydrocortisone treatment compared to both acyclovir and placebo from day one of treatment, and the difference between the groups was sustained following the end of treatment (day five) and throughout the observation period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied topically 5 times a day for 5 days vs placebo applied topically 5 times a day for 5 days	in ≥50% of episodes and developed ulcerative lesions that had progressed through vesicle, ulcer, and crust stages in ≥75% of the episodes)		Episode duration of ulcerative lesions; time to lesion healing of ulcerative lesions; maximum lesion area for ulcerative lesions; cumulative lesion area for ulcerative lesions; cumulative lesion area for all lesions and duration of lesion tenderness for ulcerative lesions	All treatments were significantly more effective (the proportion of ulcerative lesions was lower) when started earlier in the lesion development stage (P<0.05 for both compared to placebo). Secondary: The mean duration of ulcerative lesions until loss of hard crust was significantly shorter in patients treated with acyclovir/hydrocortisone compared to patients treated with placebo (5.7 vs 6.5 days; P=0.008). The reduction in duration in patients receiving acyclovir was not significantly different compared to the acyclovir/hydrocortisone group (5.9 days; P=0.365). The time for ulcerative lesion healing was reduced by 1.4 days with acyclovir/hydrocortisone compared to placebo (P=0.002); however, no significant difference was reported compared to acyclovir (0.3 days; P=0.297). The maximum lesion area for ulcerative lesions was not significantly different in patients treated with acyclovir/hydrocortisone compared to acyclovir (P=0.748) or placebo (P=0.219). The cumulative lesion area was significantly reduced with acyclovir/hydrocortisone treatment compared to placebo (P=0.005); however, the difference compared to acyclovir was not statistically significant (P=0.096). The cumulative lesion size for all lesions was significantly lower with acyclovir/hydrocortisone treatment compared to placebo (P=0.019) and acyclovir (P=0.014). Patients treated with acyclovir/hydrocortisone experienced a significant reduction in the duration of tenderness of ulcerative lesions compared to placebo (P=0.019); however, the difference compared to acyclovir was not statistically significant (P=0.838).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Raborn et al[22] Penciclovir 1% cream initiated within 1 hour of first sign of symptoms and applied 6 times on day 1 then every two hours while awake vs placebo initiated within 1 hour of first sign of symptoms and applied 6 times on day 1 then every two hours while awake	DB, MC, PC, PG, PRO, RCT Patients ≥18 years of age with a history of recurrent herpes simplex labialis, ≥3 episodes per year that typically manifested as classical lesions	N=4,573 4 days	Primary: Healing of classical lesions Secondary: Resolution of lesion pain and duration of viral shedding	Primary: Lesion healing occurred significantly faster in the penciclovir group compared to the placebo group (4.9 vs 5.5 days; *P*=0.0001). The percentage of cases healed by day six was significantly greater in the penciclovir group compared to the placebo group (70 vs 59%; *P*=0.001). The percentage of cases healed by day eight was significantly greater in the penciclovir group compared to the placebo group as determined by the investigator (85 vs 78%; *P*=0.012). A similar finding was reported by the patient at day eight with the penciclovir group compared to the placebo group at (84 vs 76%; *P*=0.002). Secondary: Resolution of lesion pain (days) was significantly different between the penciclovir group and the placebo group (3.5 vs 4.2 days; *P*=0.0001). There was a significant difference in healing in favor of penciclovir over placebo for early (*P*=0.001), late (*P*=0.0001) and vesicle (*P*=0.0115) stages. Loss of lesion pain also showed a significant difference in favor of the penciclovir group relative to the placebo group for early (*P*=0.0004), late (*P*=0.0001) and vesicle (*P*=0.0023) stages.
Boon et al[23] Penciclovir 1% cream initiated within 1 hour of first sign of symptoms and applied every 2 hours while awake vs	DB, PC, PG, RCT Patients 18 to 81 years of age with a history of sun-induced herpes labialis and ≥3 recurrences a year	N=541 4 days	Primary: Clinician-recorded time to lesion healing and severity Secondary: Patient-recorded time of healing and severity of	Primary: Penciclovir was significantly more effective than placebo in decreasing the time to lesion healing (*P*<0.001). Analysis of healing times for penciclovir patients who developed immediate lesions demonstrated a reduction of two days in median healing time compared to the placebo group (*P*<0.001). Secondary: The lesion-associated symptoms of itching, tingling, burning, tenderness, and numbness resolved significantly faster with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo initiated within 1 hour of first sign of symptoms and applied every 2 hours while awake			pain as well as other lesion symptoms	penciclovir treatment than with placebo (*P*=0.026). The median loss of symptoms was seven days for penciclovir patients compared to eight days for patients using placebo. Fewer penciclovir-treated patients rated their pain, itching, burning, and tenderness as moderate or severe due to lesions compared to the placebo group (*P*<0.027).
Spruance et al[24] Penciclovir 1% cream applied every 2 hours while awake vs placebo applied every 2 hours while awake	DB, MC, PC, PG, PRO, RCT Healthy patients with a history of frequent episodes of herpes labialis, treatment was self-initiated by the patient within 1 hour of the first sign or symptoms of recurrence	N=1,573 4 days	Primary: Lesion healing, proportion of patients who lost their lesions by days six to eight Secondary: Time to loss of lesion pain	Primary: Healing of classical lesions based on the investigator-assessed data was found to be one day faster in the patients who received penciclovir compared to the patients who received placebo (five vs six days; *P*<0.001). Patient-assessed healing time was found to be 0.7 days faster for penciclovir-treated patients compared to those who received placebo (4.8 vs 5.5 days; *P*<0.001). Investigator-assessed proportion of patients who lost classical lesions by days six, seven or eight in the penciclovir group compared to the placebo group increased by 11, nine and seven percent, respectively (*P*<0.001, *P*<0.001 and *P*=0.001). In the patient-assessed data, the proportion of patients who lost classical lesions by days six, seven or eight in the penciclovir group compared to the placebo group increased by 11, 10 and six percent, respectively (*P*<0.001, *P*<0.001 and *P*=0.001). Secondary: Time to loss of pain (3.5 vs 4.1 days; *P*<0.001) resolved more quickly for penciclovir-treated patients compared to patients who applied the placebo control.
Femiano et al[25] Penciclovir 1% cream applied every 2 hours	RCT Individuals ranging from 12 to 47 years	N=40 4 days	Primary: Clinicians' judgment of the appearance of	Primary: In the prodromal acyclovir group, labial lesions reached a crusting stage by six days, with pain ceasing at day five. In the prodromal penciclovir group, phases were reached earlier; the crusting phase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
while awake at onset of prodrome phase or at appearance of vesicles vs acyclovir 5% cream applied every 2 hours while awake at onset of prodrome phase or at appearance of vesicles	who had a history of frequent episodes of recurrent herpes labialis (≥5 each year)		vesiculation to crusting and patients' experience of pain Secondary: Not reported	was reached and pain ceased by day four, a difference that was significant (*P*=0.002041). In the disease therapy (appearance of vesicles) group, the acyclovir patients' clinical evolution and symptomatology were similar to those seen in the absence of any therapy. The penciclovir patients benefited from a reduction of 30% in the time to lesional crusting and a 20% reduction of the duration of pain compared to baseline and acyclovir (*P*<0.05). Secondary: Not reported
Lin et al[26] Penciclovir 1% cream applied up to 5 times a day vs acyclovir 3% cream applied up to 5 times a day	DB, MC, PG, RCT Patients 18 to 65 years of age with clinical diagnosis of herpes simplex facialis/labialis	N=248 7 days	Primary: Time to healing, resolution of all symptoms, absence of blisters, cessation of new blisters, crusting and loss of crust Secondary: Not reported	Primary: There was a trend towards shorter times in the penciclovir-treated primary cases, but the differences were not found to be statistically significant (*P*<0.08). In all groups treated with study medication, there was a significant reduction in scores relative to baseline (*P*<0.01). On days five and seven of treatment, the clinical scores in penciclovir-treated patients were significantly lower than those in the acyclovir-treated patients (*P*<0.01 and *P*<0.05, respectively). On day seven evaluations, treatment was recorded as a clinical cure in 75.4% of the penciclovir-treated patients and 64.9% of the acyclovir-treated patients. The difference was not statistically significant. Secondary: Not reported
Herpes Simplex Virus in Immunocompromised Patients				
Whitley et al[27] Acyclovir 5% ointment applied topically 6 times a day	DB, PC, RCT Immunocompromised patients with diagnosed herpes	N=63 28 days	Primary: Viral clearance, resolution of pain, total lesion healing	Primary: Individuals in the acyclovir group experienced acceleration in the clearance of virus (*P*=0.0006), resolution of pain (*P*=0.004), and total healing (*P*=0.038) compared to placebo. Median differences between groups averaged six days for each of these parameters.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo applied topically 6 times a day	simplex virus regardless of type		Secondary: Not reported	Secondary: Not reported

Study abbreviations: AC=active control, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial

Special Populations

Table 5. Special Populations[2-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Acyclovir	Safety and efficacy in the elderly have not been established. Safety and efficacy have not been established in children less than 12 years of age.	No dose adjustment is necessary.	No dose adjustment is necessary.	B	Unknown for topical administration.
Penciclovir	No dosage adjustment is required in the elderly. Safety and efficacy have not been established in children less than 12 years of age.	No dose adjustment is necessary.	No dose adjustment is necessary.	B	Unknown for topical administration.
Combination Products					
Acyclovir/ hydrocortisone	Safety and efficacy in the elderly have not been established. Safety and efficacy have not been established in children less than 12 years of age.	No dose adjustment is necessary.	No dose adjustment is necessary.	B	Unknown for topical administration.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[2-5]

Adverse Event(s)	Single Entity Agents			Combination Products
	Acyclovir Cream	Acyclovir Ointment	Penciclovir	Acyclovir/ Hydrocortisone
Central Nervous System				
Headache	-	-	5.3	-
Paresthesia	-	-	✔	-
Dermatological				
Aggravated condition	-	-	✔	-
Burning skin	<1	-	-	<1
Cracked lips	<1	-	-	-

Adverse Event(s)	Single Entity Agents			Combination Products
	Acyclovir Cream	Acyclovir Ointment	Penciclovir	Acyclovir/ Hydrocortisone
Desquamation	<1	-	-	-
Dryness of the lips	<1	-	-	-
Edema	-	✔	✔	-
Erythema	-	-	✔	<1
Flakiness of the skin	<1	-	-	<1
Inflammation	✔	-	-	<1
Local anesthesia	-	-	<1	-
Pain at application site	-	✔	✔	-
Pruritus	<1	✔	✔	-
Rash	-	✔	<1	-
Skin discoloration	-	-	✔	<1
Stinging of the skin	<1	-	-	<1
Urticaria	-	-	✔	-
Other				
Decreased therapeutic response	-	-	✔	-
Oral/pharyngeal edema	✔	-	✔	-
Pain	-	-	✔	-
Parosmia	-	-	✔	-
Taste perversion	-	-	<1	-
Anaphylaxis	✔	-	-	-

✔ Percent not specified.
- Event not reported.

Contraindications/Precautions

Topical antivirals are contraindicated in patients with a known hypersensitivity to any of the topical antiviral agents or to any component of the individual products.[2-5]

Drug Interactions

Due to limited systemic absorption when acyclovir and penciclovir are administered topically, no drug interactions are likely to occur and none are documented with these topical antivirals.[2-5]

Dosage and Administration

Table 7. Dosing and Administration[2-5]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-Entity Agents			
Acyclovir	Recurrent herpes simplex labialis: Cream: Apply topically five times per day for four days Genital herpes simplex initial therapy: Ointment: Apply topically every three hours (six times per day) for seven days in sufficient quantities to adequately cover lesions	Safety and efficacy have not been established in children less than 12 years of age.	Cream: 5% (2, 5 g tubes) Ointment: 5% (30 g tube)

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Herpes simplex, non-life-threatening mucocutaneous immunocompromised - patient: Ointment: Apply topically every three hours (six times per day) for seven days in sufficient quantities to adequately cover lesions; the dose size per application will vary depending upon the total lesion area but should be approximately a one-half inch ribbon of ointment per four square inches of surface area		
Penciclovir	Recurrent herpes simplex labialis: Apply topically every two hours while awake for four days	Safety and efficacy have not been established in children less than 12 years of age.	Cream: 1% (1.5 g tube)
Combination Products			
Acyclovir/ hydrocortisone	Recurrent herpes labialis: Cream: Apply topically five times per day for five days	Safety and efficacy have not been established in children less than 12 years of age.	Cream: 5%/1% (5 g tube)

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2010)**[28]	Management of genital herpes • Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. • Systemic antiviral drugs can partially control the signs and symptoms of herpes episodes when used to treat first clinical and recurrent episodes, or when used as daily suppressive therapy. • Systemic antiviral drugs do not eradicate latent virus or affect the risk, frequency or severity of recurrences after the drug is discontinued. • Randomized clinical trials indicate that acyclovir, famciclovir and valacyclovir provide clinical benefit for genital herpes. • Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. • Topical therapy with antiviral drugs provides minimal clinical benefit, and use is discouraged. • 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. • Recommended regimens for first episodes of genital herpes include acyclovir 400 mg orally three times daily for seven to 10 days, acyclovir

Clinical Guideline	Recommendation(s)
	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. • 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. • 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. • 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. • Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment. • Periodically during suppressive therapy (e.g., once a year), health care professionals should discuss the need to continue therapy. • 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. • 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. • 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. • 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. • Intravenous acyclovir should be provided to patients with severe HSV disease or complications that necessitate hospitalization or central nervous system complications. • The sex partners of patients who have genital herpes can benefit from evaluation and counseling. • 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.

Clinical Guideline	Recommendation(s)
	• 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. • The safety of systemic acyclovir, famciclovir and valacyclovir therapy in pregnant women has not been definitively established. • 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)**[29]	• Acyclovir, famciclovir and valacyclovir are antiviral drugs approved for treatment of genital herpes. • Comparative trials of these medications suggest they have similar clinical efficacy and result in comparable decrease in viral shedding. • Treatment should be offered for first episode, even if they appear to be mild initially. • Treatment decreases lesions, viral shedding and symptoms, but does not affect the long term natural history of infection. • Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral intake or has prominent neurologic involvement. • Intravenous acyclovir should be used for severe cases. • Topical antiviral medications are not an effective therapy and do not add to the benefit of oral medication; their use is discouraged.

Conclusions

Acyclovir, penciclovir and acyclovir/hydrocortisone are approved for the treatment of oral and/or genital herpes simplex infections and have been shown to be efficacious when compared to placebo.[9-13,15-19,21] These agents have been shown to be safe with no significant drug interactions and limited adverse events.[2-5] Most national and international guidelines including those published by the Centers for Disease Control and Prevention, state that the topical antiviral agents offer minimal clinical benefit and should not be recommended over other options in general use, such as the oral antivirals.[28,29] Acyclovir 5% ointment is the only topical antiviral agent available generically; however, several oral antiviral formulations are available generically in various formulations.

Studies comparing the efficacy of these agents for the treatment of oral and/or genital herpes simplex have been conducted and have not consistently demonstrated one topical antiviral agent to be significantly more effective for all outcomes. Chen et al. demonstrated that there was no significant difference between the penciclovir and acyclovir treatment groups in genital herpes cure rate.[14] 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.[25] 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.[26]

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