Antiviral Agents, Topical Review

06/01/2009

Copyright © 2008 - 2009 by Provider Synergies, L.L.C. All rights reserved.
Printed in the United States of America.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage and retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
5181 Natorp Blvd., Suite 205
Mason, Ohio 45040

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Comments and suggestions may be sent to Editor@providersynergies.com.

PROVIDER SYNERGIES L.L.C.
Together, we can do more.

Antiviral Agents, Topical Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
acyclovir cream (Zovirax®)[1]	GSK	Treatment of recurrent herpes labialis (cold sores) in adults and children 12 years of age and older
acyclovir ointment (Zovirax®)[2]	Biovail	Management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients
docosanol (Abreva®)[3]	GSK	Treatment of cold sores/fever blisters on the face or lips in adults and children 12 years of age and older to shorten healing time and duration of symptoms
penciclovir (Denavir)[4]	Novartis	Treatment of recurrent herpes labialis (cold sores) in adults and children 12 years of age and older

Overview

Herpes labialis is an infection of the lips or "perioral" (around the mouth) area. The primary infection is usually asymptomatic; however, it can also present itself as herpes simplex virus (HSV) gingivostomatitis (of the mouth and gums). Herpes labialis (fever blisters, cold sores) can be caused by either herpes simplex virus-1 (HSV-1) or herpes simplex virus-2 (HSV-2). While the primary (first episode) infections with HSV-1 or HSV-2 do occur, recurrences are generally the result of HSV-1 infection. Oral recurrences with HSV-2 are very rare.

About 80 percent of the general adult population has serologic infection with HSV-1 with only about 30 percent of these individuals having clinically significant outbreaks. In the United States, approximately 130 million individuals over the age of 12 years are infected with HSV-1.[5,6] Approximately 20 percent of the adult population in the United States is seropositive for HSV-2.

Most people acquire HSV-1 asymptomatically. Most episodes of herpes labialis are preceded by a prodromic phase which may consist of tingling, itching, or redness. These can last for up to 24 hours before lesion development. Once a person begins to produce antibodies, the infection becomes latent in the sensory ganglia. HSV-1 infection remains latent in the trigeminal ganglia and HSV-2 in the sacral ganglia. The viruses become reactivated secondary to certain stimuli including fever, physical or emotional stress, ultraviolet light exposure, and axonal injury. Recurrent infections tend to be less severe because of existing cellular and humoral immunity from prior exposures. Infection by HSV requires a break in the skin's barrier; intact skin is resistant to the virus.

In most patients, fewer than two recurrences of herpes labialis manifest each year, but some individuals have monthly recurrences. The rate of recurrence of genital herpes depends on a

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

number of factors including viral type, prior immunity to autologous or heterologous virus, gender, and immune status of the host.[7]

Antiviral therapy includes both oral and topical preparations. Oral treatments have long been the standard of care for most patients, as supported by clinical trials.[8,9,10,11] Oral antivirals are commonly used as preventative care as well. Patients will take a low-dose oral antiviral daily to help prevent an outbreak or initiate treatment when they feel an episode coming on to help prevent a lesion. The topical preparations are reserved for treatment of an active lesion. Topical preparations should be started as early as possible in the prodrome phrase in order for treatment to be most beneficial.

Topical acyclovir was touted as effective in preventing herpes simplex labialis in 1983, but further trials cast doubt about whether it can significantly alter the course of disease and normal healing.[12,13] Suppression studies produced promising results, notably clinical trials that demonstrated significant differences favoring acyclovir in terms of healing time.[14,15] Topical penciclovir later demonstrated that it had similar antiviral properties as acyclovir. Although comparison trials have not been performed, studies showed penciclovir was as efficient in reducing healing time as other topical preparations on the market.[16]

In 2000, the FDA approved the first over-the-counter (OTC) medicine, docosanol (Abreva), to treat cold sores/fever blisters. Docosanol (Abreva) is the only FDA-approved OTC medication that will reduce healing time and duration of symptoms of herpes labialis.

Pharmacology[17,18,19,20]

Acyclovir is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). This inhibitory activity is highly selective due to its affinity for the enzyme thymidine kinase (TK). This enzyme converts acyclovir into acyclovir monophosphate, a nucleoside analogue. This is further converted into diphosphate and then into triphosphate. Acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: first, by competitive inhibition of viral DNA polymerase; second, incorporation into and termination of growing viral DNA chains; and third, inactivation of viral DNA polymerase. This phosphorylation is done more efficiently by HSV; therefore, a greater antiviral activity against HSV exists.

Penciclovir has a similar mechanism of action as acyclovir. It is highly selective for HSV-1 and HSV-2 infected cells which may be attributed to two factors. First, viral thymidine kinase phosphorylates penciclovir more rapidly than cellular thymidine kinase. Therefore, the active penciclovir triphosphate is present at a higher concentration in HSV-infected cells than in uninfected cells. Second, the activated drug binds to viral DNA polymerases with a higher affinity than to human DNA polymerases. As a result, penciclovir exhibits negligible cytotoxicity to healthy cells. Penciclovir appears at least as effective as acyclovir as an inhibitor of herpes virus DNA synthesis.

The exact mechanism of action of docosanol is not known, but it is thought to work by inhibiting viral replication. This inhibition is due to the ability of docosanol to block the fusion of lipid-enveloped viruses (e.g. HSV-1 and HSV-2) with cell membranes. This in turn leads to inhibiting cellular entry, nuclear localization, and subsequent viral replication.

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

Pharmacokinetics

Systemic absorption of all the topical antiviral agents is low.[21,22,23] However, the therapeutic effects of antiviral drugs in treating herpes labialis are evident when the cellular concentration of the drug approaches an optimum level. Oral acyclovir (even in high doses) does not produce the concentration necessary to generate that level of response consistently, despite positive results. Penetration of topical preparations of acyclovir through the stratum corneum has proven difficult.[24,25] The cream formulation has exhibited greater penetration in herpes labialis compared to the ointment formulation, however comparative studies have not been performed to compare their efficacy.[26,27] In contrast to acyclovir, penciclovir has a prolonged half-life (10 – 20 times longer) in HSV-infected cells.[28]

Contraindications/Warnings[29,30,31,32]

Hypersensitivity to these agents and any of their components is considered a contraindication. These agents are for topical use only. They should not be used for ophthalmic, intranasal, intraoral, intravaginal use, or in or near the eyes. Discontinued if sensitization or severe local irritation occurs. There are no data to support the use of acyclovir ointment 5% to prevent transmission of infection to other persons or prevent recurrent infection when applied in the absence of signs and symptoms. It should not be used to prevent recurrence of HSV infection.

Drug Interactions[33,34,35]

Clinical experience has identified no interactions resulting from systemic or topical administration of other drugs concomitantly with any of these agents.

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

Adverse Effects

Drug	Application Site Irritation	Pruritis	Rash	Pain	Allergic Reaction
acyclovir cream (Zovirax)[36]	5	<1	<1	<1	<1
acyclovir ointment (Zovirax)[37]	nr	4	nr	30	nr
docosanol (Abreva)[38]	2.9	0.4	0.5	nr	nr
penciclovir (Denavir)[39]	1.3	0	0.1	0	0

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Special Populations[40,41,42,43]

Pediatrics

An open-label, uncontrolled trial with acyclovir (Zovirax) 5% cream was conducted in 113 patients aged 12 to 17 years with herpes labialis. In the study, therapy was applied using the same dosing regimen as in adults, and subjects were followed for adverse events. The safety profile was similar to that observed in adults. Acyclovir (Zovirax) cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

Safety and effectiveness of acyclovir (Zovirax) 5% ointment in pediatrics have not been established.

Safety and efficacy of penciclovir (Denavir) 1% cream in children less than 12 years of age have not been established.

Docosanol (Abreva) cream is indicated in patients 12 years of age and older.

Pregnancy

All agents are Pregnancy Category B.

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

Dosages[44,45,46,47]

Drug	Patients age 12 years and older	Availability
acyclovir cream (Zovirax)	applied 5 times per day for 4 days	2 gm, 5 gm tube of 5% cream
acyclovir ointment (Zovirax)	applied every 3 hours or 6 times per day for 7 days	15 gm tube of 5% ointment
penciclovir (Denavir)	applied every 2 hours during waking hours for a period of 4 days	1.5 gm tube of 1% cream
docosanol (Abreva)	Applied 5 times per day until lesion is healed	2 gm tube of 10% cream

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials studying agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published head to head trials comparing docosanol and acyclovir or penciclovir in the treatment of herpes labialis. Due to the lack of studies, placebo-controlled trials have been included.

There are no current studies available for acyclovir (Zovirax) ointment. Previous placebo controlled studies have been performed and showed that acyclovir ointment was more effective at reducing healing time and, in some cases, duration of viral shedding and pain in immunocompromised patients with herpes labialis.[48]

acyclovir (Zovirax) cream versus penciclovir (Denavir)

A randomized, double-blind, active comparator study enrolling 248 patients with a diagnosis of herpes simplex facialis/labialis compared penciclovir 1% cream and acyclovir 3% cream.[49] Patients were evaluated before treatment and on days three, five, and seven of treatment. No severe adverse events were recorded in either treatment group. There were no significant differences in the efficacy endpoint or cure rate between groups, but a trend towards a shorter time to resolution of all symptoms, cessation of new blisters, and loss of crust ($p \leq 0.08$) was

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

seen with the penciclovir group. In addition, the clinical scores in penciclovir treated patients were significantly lower than those in the acyclovir group on days five and seven ($p \leq 0.05$). The study used acyclovir cream at a lower strength than the currently available US formulation.

penciclovir (Denavir) versus placebo

Two randomized, double-blind, parallel group studies were performed with 3,057 patients of which 83 percent developed clinical lesions. Patients were given either penciclovir 1% cream or placebo for the treatment of recurrent herpes simplex labialis defined as three or more episodes a year that typically manifested as classical lesions.[50] Patients self-initiated treatment within one hour of noticing the first signs and symptoms of a recurrence and were required to apply medication six times per day for the first day and every two hours while awake for four consecutive days. The penciclovir-treated group lost lesions 31 percent faster than the placebo-treated group ($p=0.0001$) and experienced 28 percent faster resolution of lesion pain ($p=0.0001$). Dosing frequency was vital to treatment outcomes.

docosanol (Abreva) versus placebo

Two identical multicenter, double-blind, placebo-controlled studies were performed with 737 patients who were given either docosanol 10% cream or placebo for the treatment of herpes simplex labialis in the prodrome or erythema stage.[51] Patients were treated five times daily until healing occurred (i.e., the crust fell off spontaneously or there was no longer evidence of an active lesion). The median time to healing in the docosanol-treated group ($n=370$) was 4.1 days, 18 hours shorter than that of the placebo-treated group ($n=367$) ($p=0.008$). The docosanol group also exhibited reduced times from treatment initiation to cessation of pain and all other symptoms ($p=0.002$), complete healing of lesion ($p=0.023$), and cessation of the ulcer or soft crust stage of the lesion ($p<0.001$). Aborted episodes were experienced by 40 percent of docosanol patients and 34 percent of placebo patients ($p=0.109$). Adverse events with docosanol were mild and similar to those with placebo. The study concluded that docosanol applied five times per day is safe and effective in the treatment of recurrent herpes simplex labialis.

Summary

While oral antiviral medication may be frequently used in preventing and treating oral herpes outbreaks, topical antiviral preparations have seen increasing usage especially since the addition of an OTC preparation, docosanol (Abreva). Untreated herpes labialis may take up to 10 days or more to heal. For treatment to be most beneficial, antiviral therapy must be initiated early.

Comparative literature for the cream and ointment formulations of acyclovir is lacking. Docosanol (Abreva) was shown to shorten healing time compared to placebo as well as the duration of symptoms such as tingling, pain, burning, and itching. Although docosanol (Abreva) has not been directly compared with penciclovir (Denavir), study results with the two agents are generally similar, and docosanol (Abreva) has the advantage of being available without a prescription.

Topical products for herpes labialis only provide modest benefit if used very early in the prodrome phase.

© 2008 - 2009 Provider Synergies, L.L.C.

A Coventry Health Care Company
All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.

References

[1] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[2] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[3] Abreva [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[4] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[5] Available at: http://www.herpesdiagnosis.com/labialis.html. Accessed June 1, 2009.
[6] Sharma R. Herpes Simplex. http://emedicine.medscape.com/article/783113-overview. Accessed June 1, 2009.
[7] Larry I Lutwick. Herpes Simplex. http://emedicine.medscape.com/article/218580-overview. Accessed June 1, 2009.
[8] Whitley RJ, Gnann JW. Acyclovir: a decade later. N Engl J Med. 1992; 327(11):782-789.
[9] Brady RC, Bernstein DI. Treatment of herpes simplex virus infections. Antiviral Res. 2004; 61(2):73-81.
[10] Spruance SL, Stewart JCB, Rowe NH, et al. Treatment of recurrent herpes simplex labialis with oral acyclovir. J Infect Dis. 1990; 161(2):185-190.
[11] Spruance SI, Bodsworth N, Resnick H, et al. Single-dose, patient-initiated famciclovir: a randomized double-blind, placebo-controlled trials for episodic treatment of herpes labialis. J Am Acad Dermatol. 2006; 55(1):47-53.
[12] Van Vloten WA, Swart RN, Pot F. Topical acyclovir therapy in patients with recurrent orofacial herpes simplex infections. J Antimicrob Chemother. 1983; 12(Suppl B):89–93.
[13] Shaw M, King M, Best JM, et al. Failure of acyclovir cream in treatment of recurrent herpes labialis. Br Med J (Clin Res Ed). 1985; 291(6487):7–9.
[14] 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(6):641–645.
[15] Gibson JR, Klaber MR, Harvey SG, et al. Prophylaxis against herpes labialis with acyclovir cream — a placebo controlled study. Dermatologica. 1986; 172(2):104–107.
[16] Spruance SL, Rea TL, Thoming C, et al. Peniciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Peniciclovir Collaborative Study Group. JAMA. 1997; 277(17):1374-1379.
[17] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[18] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[19] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[20] Pharmacology Review-Docosanol. Available at www.fda.gov/cder/foi/nda/2000/20-941_Abreva_pharmr_P1.pdf. Accessed on June 1, 2009.
[21] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[22] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[23] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[24] Whitley RJ, Gnann JW. Acyclovir: a decade later. N Engl J Med. 1992; 327(11):782-789.
[25] Freeman DJ, Sheth NV, Spruance SL. Failure of topical acyclovir in ointment to penetrate human skin. Antimicrob Agents Chemother. 1986; 29(5):730–732.
[26] Raborn GW, Grace MG. Recurrent Herpes Simplex Labialis: Selected Therapeutic Options. J Can Dent Assoc. 2003; 69(8):498-503.
[27] Kinghorn GR. Topical acyclovir in the treatment of recurrent herpes simplex virus infections. Scand J Infect Dis Suppl. 1985; 47:58-62.
[28] Raborn GW, Martel AY, Lassande M, et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. J AM Dent Assoc. 2002; 133(3):303-309.
[29] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[30] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[31] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[32] Abreva [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[33] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[34] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[35] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[36] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[37] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[38] Abreva [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[39] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[40] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[41] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[42] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[43] Abreva [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[44] Zovirax Cream [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[45] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[46] Denavir [package insert]. Parsippany, NJ; Novartis; October 2003.
[47] Abreva [package insert]. Research Triangle Park, NC; GlaxoSmithKline; May 2007.
[48] Zovirax Ointment [package insert]. Research Triangle Park, NC; GlaxoSmithKline; January 2004.
[49] 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(2):67-72.
[50] Raborn GW, Martel AY, Lassande M, et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. J AM Dent Assoc. 2002; 133(3):303-309.
[51] Sacks SL, Thisted RA, Jones TM, et al. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial. J Am Acad Derm. 2002; 47(3):457-458.

 All Rights Reserved.
Restricted Access – Proprietary and/or Confidential. Do not disseminate or copy without approval.