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Literature Scan: Antivirals for Herpes Simplex Virus

Date of Review: May 2016

Date of Last Review: January 2014
Literature Search: March 2016

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

Conclusions:

- A scan of the literature identified 3 new high quality systematic reviews and 2 new high quality clinical practice guidelines on antivirals for the treatment of herpes simplex virus (HSV).
- A Cochrane review investigating antiviral efficacy against herpes simplex labialis (HSL) in immunocompetent patients found short-term (5-7 days) oral acyclovir 400 mg twice daily effectively prevents HSL reoccurrence (RR 0.26; 95% CI 0.13 to 0.51); however, treatment with 800 mg twice daily and 200 mg five times daily found no preventative effects.[1] Long-term (> 1 month) oral acyclovir was more effective in preventing HSL compared to placebo (0.85 events/4 months vs. 1.80 events/ 4 months; P=0.009) based on one small trial.[1] Valacyclovir was associated with fewer HSL recurrent infections compared to placebo (0.12 vs. 0.21 episodes per month) in one trial (n=95) lasting 16 weeks.[1] Topical antivirals were not shown to be effective in preventing HSL.[1]
- One systematic review on the preventative effects of oral antivirals on genital herpes in immunocompetent and non-pregnant adults found at least one clinical reoccurrence in 54% of patients treated with valacyclovir compared to 46% of those treated with acyclovir (RR 1.16, 95% CI 1.01 to 1.34; P=0.04).[2] Famciclovir was associated with at least one clinical reoccurrence in 35% of patients compared to 29% in valaciclovir patients (P=0.30).[2] Antivirals (acyclovir, valacyclovir and famciclovir) were found to be superior to placebo for preventing genital herpes reoccurrence.[2]
- Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV recommend episodic or daily antiviral suppressive therapy for treating oral and genital HSV lesions.[3] Antivirals are also recommended for prevention in those with HIV and HSV.[3]
- Guideline recommendations for the treatment of sexually transmitted diseases recommend antivirals for the treatment and prevention of reoccurrence of genital herpes.[4]

Recommendations:

- No further research is needed at this time. Continue current prior authorization (Appendix 2). Costs should be evaluated in executive session.

Previous Conclusions:

- Evidence does not support a difference in effectiveness or harms outcomes between antiviral agents for HSV.

Previous Recommendations:

- No further review or research needed at this time.

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Date: May 2016

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
Cochrane - Interventions for prevention of herpes simplex labialis (cold sores on the lips)
A Cochrane review looked at the evidence to support treatment of HSL on the lips. Included trials looked at immunocompetent patients, age 12 years and older, in 32 trials of low to moderate quality.[1] For prevention, acyclovir 400 mg twice daily for 1 month or less was found to reduce the recurrence (RR 0.26, 95% CI 0.13 to 0.51) but no effect was found with acyclovir 800 mg twice daily and acyclovir 200 mg five times daily.[1] Evidence to support the use of valaciclovir was uncertain (RR 0.55, 95% CI 0.23 to 1.28).[1] The evidence to support famciclovir use was also uncertain, based on one RCT. HSL recurrence with long term (≥1 month) antiviral agent use was reduced with oral acyclovir (1.80 episodes/4-months vs. 0.85/4-months; P=0.003). Valacyclovir was also shown to decrease occurrence of HSV to 0.09 episodes/month. Short-term (≤ 1 month) use of topical agents was not shown to prevent recurrent HSL and long-term (> 1 month) use was inconclusive. Adverse events with antivirals were similar to placebo. Oral levamisole, lysine and LongoVital® (vitamin and herb supplement) found no significant effect on HSL reoccurrence. No statistical differences between foscarnet, 1, 5-pentanediol or sunscreen compared to placebo were found.[1]

Cochrane – Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients
The role of antivirals (acyclovir, valacyclovir, and famciclovir) in the prevention of genital herpes, HSV-1 and HSV-2, in immunocompetent individuals was the topic of a Cochrane review.[2] Almost 7,000 men and women with a mean age of 35 years and 11 yearly recurrences were treated for 2-12 months in studies of high or uncertain risk of bias.[2] Acyclovir 400-1000 mg (n=2049) daily was shown to decrease recurrence compared to placebo (52% vs. 96%; RR 0.48, 95% CI 0.39 to 0.58; I^2 = 81%). No dose-response was demonstrated. Valacyclovir was superior to placebo in reducing genital herpes in 4 trials of 1,788 patients (46% vs. 79%; RR 0.41, 95% CI 0.24 to 0.69; I^2 = 94%). Recurrences were decreased by 32% with famciclovir 125-750 mg daily compared to placebo (RR 0.57, 95% CI 0.50 to 0.64; I^2 = 0%).[2] In one trial (n= 1345), valacyclovir prevented less recurrences compared to acyclovir (RR 1.16, 95% CI 1.01 to 1.34) and famaciclovir was less effective based on reoccurrence compared to valaciclovir (RR 1.18, 95% CI 0.86 to 1.63).[2] The results were uncertain on which antiviral were most effective in decreasing one clinical recurrence.

Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis
A systematic review and meta-analysis for the treatment of HSV epithelial keratitis (EK) included the following antivirals: trifluridine, acyclovir, ganciclovir, and foscarnet (idoxuridine, vidarabine, brivudine and cidofovir were included but not available in the US).[6] Evidence was analyzed using the GRADE method. Four studies compared acyclovir and found no difference in healing after 14 days (90% vs. 89%; RR 0.99, 95% CI 0.90 to 1.09).[6] Ganciclovir was less effective in healing

at 14 days compared to acyclovir (55% vs. 76%; RR 1.38, 95% CI 1.22 to 1.57); however, there was a high degree of heterogeneity in the 28 included studies. Foscarnet was had similar healing rates to acyclovir, ganciclovir and trifluridine based on evidence involving one study for each comparison.[6] Oral acyclovir had healing rates similar to a topical antiviral (RR 0.92, 95% CI 0.79 to 1.07).[6] The combination of oral acyclovir and a topical antiviral compared to a topical antiviral produced more healing (RR 1.36, 95% CI 0.68 to 2.74); however, wide confidence intervals limits the certainty of the results.[6]

New Guidelines:

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America released an update to their 2010 recommendations for treating opportunistic infections in patients with HIV, including HSV.[3] Evidence was reviewed and assessed based on strength and quality of the evidence for the recommendation (Table 1.).

Table 1. System for Rating Recommendations

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

Suppressive antiviral therapy is not recommended for patients with HSV for prevention of HSV-2 if they are not being treated with ART based on AI evidence.[3] The use of antiviral prophylaxis to prevent primary HSV infection is not recommended (AIII).[3] Episodic or daily suppressive therapy is recommended for treatment of HSV. Acyclovir, valacyclovir and famciclovir treatment for 5 to 10 days is recommended for orolabial lesions (AIII) and the same treatment is recommended for genital lesions (AI).[3] Intravenous acyclovir is recommended for severe mucocutaneous lesions (AIII). For prevention of HSV, all oral antivirals are recommended to reduce recurrence (AI) and should be re-evaluated on a yearly basis but may need to continued indefinitely (BIII).[3] Antiviral therapy may be recommended for individuals with a CD4 cell count <250 cells/mm^3 starting antiretroviral therapy (BI). Acyclovir is most commonly recommended for pregnant patients with HSV and HIV; however, valacyclovir has also been used for adherence reasons.[3]

Centers for Disease Control and Prevention – Sexually Transmitted Diseases Treatment Guideline

In 2015 the CDC updated their guideline for sexually transmitted diseases, including HSV.[4] The GRADE methodology was used to analyze the evidence. They recommend that all individuals with a first clinical episode of HSV be treated with an antiviral due to possibility of extended illness and possible neurologic involvement. Acyclovir, famciclovir and valacyclovir are recommended for first clinical episode, suppressive therapy and recurrent genital herpes.[4]

New FDA Drug Approvals:

No new antivirals for HSV were approved.

New Formulations/Indications:

No formulations or indications were found.

Author: Kathy Sentena, PharmD Date: May 2016

New FDA Safety Alerts:
There were no new FDA safety alerts since the last review.

References:

1. Chi CC, Wang SH, Delamere FM, et al. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev*. 2015. Art. No.: CD010095.
2. Le Cleach L, Trinquart L, Do G, et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. *Cochrane Database of Systematic Reviews*. 2014. Issue 8. Art. No.: CD009036. DOI: 10.1002/14651858.CD009036.pub2.
3. Wilhemus K. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015. Art. No.: CD002898.
4. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morbidity and Mortality Weekly Report*. 2015; 64:1-137.
5. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed March 24, 2016.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	ACYCLOVIR	ACYCLOVIR	Y
ORAL	CAPSULE	ZOVIRAX	ACYCLOVIR	Y
ORAL	ORAL SUSP	ACYCLOVIR	ACYCLOVIR	Y
ORAL	ORAL SUSP	ZOVIRAX	ACYCLOVIR	Y
ORAL	TABLET	ACYCLOVIR	ACYCLOVIR	Y
ORAL	TABLET	ZOVIRAX	ACYCLOVIR	Y
BUCCAL	MA BUC TAB	SITAVIG	ACYCLOVIR	N
ORAL	TABLET	FAMCICLOVIR	FAMCICLOVIR	N
ORAL	TABLET	FAMVIR	FAMCICLOVIR	N
ORAL	TABLET	VALACYCLOVIR	VALACYCLOVIR HCL	N
ORAL	TABLET	VALTREX	VALACYCLOVIR HCL	N
TOPICAL	CREAM (G)	ABREVA	DOCOSANOL	N
TOPICAL	CREAM (G)	DENAVIR	PENCICLOVIR	N
TOPICAL	CREAM (G)	XERESE	ACYCLOVIR/HYDROCORTISONE	N
TOPICAL	CREAM (G)	ZOVIRAX	ACYCLOVIR	N
TOPICAL	OINT. (G)	ACYCLOVIR	ACYCLOVIR	N
TOPICAL	OINT. (G)	ZOVIRAX	ACYCLOVIR	N
TOPICAL	DROPS	ZIRGAN	GANCYCLOVIR	Y
TOPICAL	DROPS	VIROPTIC	TRIFLURIDINE	N

Appendix 2: New Clinical Trials

A total of 93 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to March Week 3 2016
Search Strategy:

#	Searches	Results
1	Acyclovir/	4567
2	famciclovir.mp.	684
3	ganciclovir.mp. or Ganciclovir/	5817
4	valacyclovir.mp.	1052
5	valganciclovir.mp.	813
6	penciclovir.mp.	314
7	docosanol.mp.	58
8	4 or 5 or 6 or 7	2134
9	limit 8 to (english language and humans and yr="2013 -Current")	317
10	limit 9 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review" or systematic reviews)	93

Antivirals, Oral and Topical - HSV

Goal(s):

- Cover oral and/or topical antivirals only for covered diagnoses.
- HSV infections are covered only when complicated by an immunocompromised host.

Length of Authorization:

- Up to 12 months (criteria specific)

Requires PA:

- Non-preferred drugs
- HIC3 = Q5V

Generic	Brand	Route
Famciclovir	Famvir	Oral
Valacyclovir	Valtrex	Oral
Acyclovir	Zovirax	Topical
Penciclovir	Denavir	Topical
Docosanol	Abreva	Topical

Covered Alternatives:

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

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the diagnosis uncomplicated herpes simplex virus infection (B002; B0089; B001; B009)?	**Yes:** Go to #4	**No:** Go to #7
4. Pass to RPh: Is the patient immunocompromised (document ICD10 code). Examples: • Current (not history of) diagnosis of cancer AND currently undergoing chemotherapy or radiation? Document therapy and length of treatment. • Diagnosis of HIV/AIDS?	**Yes:** Approve for the shorter of expected therapy duration or 12 months (applies to topical or oral antivirals for immunocompromised patients).	**No:** Go to #5

Approval Criteria		
5. Is the patient currently taking an immunosuppressive drug? Document name of drug. If drug not in list below, Pass to RPh for evaluation. Immunosuppressive drugs include, but are not limited to: **Immunosuppressants** Abatacept Adalimumab Anakinra Apremilast Azathioprine Basiliximab Certolizumab pegol Cyclosporine Cyclosporine Etanercept Golimumab Hydroxychloroquine Infliximab Leflunomide Methotrexate Natalizumab Rituximab Secukinumab Sirolimus Tacrolimus Tocilizumab Tofacitinib Ustekinumab Vedolizumab	**Yes:** Approve for the shorter of expected therapy duration or 90 days (applies to topical or oral antivirals for immunocompromised client).	**No:** If patient has diabetes mellitus or sickle cell disease, go to #6. All others go to #7.
6. Does the patient have diabetes mellitus or sickle-cell disease? Note: Diabetes mellitus and sickle-cell disease are not considered as immunocompromising for antivirals as for antifungals.	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Pass to RPh to evaluate for immunosuppression. • If not immunocompromised, deny; not funded by the OHP. • If immunocompromised, approve for up to 12 months.

Approval Criteria		
7. RPH only: All other indications need to be evaluated as to whether they are an OHP-funded condition. • If funded, viral diagnoses may be approved for treatment course with "PRN" renewals. If length of therapy is unknown, approve for 3 months intervals only (this is an exception to above guidelines and should be discussed with lead pharmacist). • If unfunded, deny (not funded by the OHP). • Deny non-viral diagnoses (medical appropriateness). • Deny viral ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).	If funded and clinic provides supporting literature, approve for length of treatment.	If unfunded, deny; not funded by the OHP.

P&T Review: *5/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *1/1/11*