Published in final edited form as:
J Clin Virol. 2012 January ; 53(1): 6–11. doi:10.1016/j.jcv.2011.08.003.

Current management and recommendations for access to antiviral therapy of herpes labialis

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Abstract

Herpes labialis is a common skin infective condition, worldwide, which is primarily caused by HSV-1. Recurrent episodes of herpes labialis, also known as cold sores, can be frequent, painful, long-lasting and disfiguring for infected patients. At present, there are two types of antivirals for the treatment of herpes labialis, topical and oral, which are available over the counter or as prescription-only. The aim of antiviral therapy is to block viral replication to enable shortening the duration of symptoms and to accelerate healing of the lesions associated with herpes labialis. This review examines the evidence for the effectiveness of current topical and oral antivirals in the management of recurrent episodes of herpes labialis. In most countries, oral antivirals for herpes labialis are available as prescription-only. However, in early 2010, the oral antiviral famciclovir was reclassified from prescription-only medicine to pharmacist-controlled status in New Zealand. The benefits and risks associated with moving an antiviral therapy for herpes labialis from prescription-only to pharmacist-controlled status are reviewed here, and the implications for patients, general physicians and pharmacists are considered.

Keywords

Herpes labialis; Coldsores; Famciclovir; Aciclovir; Valaciclovir; HSV-1

Herpes labialis is a common condition worldwide. The primary cause is HSV-1, but the epidemiology has changed dramatically in recent decades. HSV-1 infection was traditionally acquired in childhood and adolescence through non-sexual contact but is now becoming the

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most common cause of primary genital HSV infections.[1] At least 50% of new cases of herpes genitalis in developed countries are now caused by HSV-1.[2] Although HSV-2 more commonly causes recurrent herpes genitalis,[3,4] it has been identified as a cause of oropharyngeal infection and herpes labialis[5]. The prevalences of HSV-1 and HSV-2 are generally higher in developing than in developed regions of the world,[6,7] but seroprevalence rates are declining for both HSV-1 and HSV-2 in the USA.[7] In eastern European countries (most notably Bulgaria), the seroprevalences of HSV-1 and HSV-2 are higher than in more northern European countries (England and Wales, Germany, Netherlands, Belgium and Finland).[8] In Australia, a nationwide population-based survey reported HSV-1 and HSV-2 seroprevalences of 76% and 12%, respectively, in 1999–2000, being higher in women (80.4% and 16.3%, respectively) than in men (71.3% and 8.9%, respectively) and rising to 77.3% and 16.4%, respectively, in the 35–44-year age group.[9] Higher socioeconomic status is associated with a lower prevalence of HSV-1[5] and cross-sectional evaluations have identified risk factors for herpes labialis including female gender, older age (65–74 years), white race/ethnicity, frequent upper respiratory infections and low lymphocyte counts.[9,10] Smokers report fewer herpes labialis outbreaks than nonsmokers.[10]

Primary HSV-1 infection can be either asymptomatic or cause self-limiting gingivostomatitis in the immunocompetent host.[11] The virus establishes latency in the sensory ganglia and, when reactivated, causes herpes labialis. Reactivation stimuli include exposure to ultraviolet light,[12,13] fever,[12] psychological stress[14] and menstruation.[15] Recurrent episodes of herpes labialis can be frequent, painful, long-lasting and disfiguring.[5,16] In immunocompromised patients, episodes are usually longer and more severe, potentially involving the oral cavity or extending across the face.[5,17] The prodrome (symptoms of reactivation) is associated with itching, burning and/or paraesthesia prior to the appearance of erythema and papule formation.[17] Clinical progression evolves through the development of a vesicle, pustulation, ulceration and, ultimately, scabbing. Peak viral titres occur in the first 24 h after lesion onset, when most lesions are in the vesicular stage, with a subsequent progressive decline as most lesions are converted to ulcers/crust.[17,18]

The aim of antiviral therapy is to block viral replication in order to enable shortening the duration of symptoms and accelerate the resolution of lesions. Since the natural healing process starts within the first 24 h of onset of an episode, if treatment is either warranted or requested, it is imperative that therapy is initiated as soon as possible to ensure an optimal therapeutic beneficial effect.[19] Two categories of antivirals are available for treatment of herpes labialis: topical and oral therapies. In this review, we examine these therapies for herpes labialis available OTC and as prescription-only, and analyse the benefits and risks associated with moving an antiviral therapy from prescription-only to pharmacist-controlled status.

1. Current diagnosis and management of herpes labialis

Diagnosis of herpes labialis by GPs is usually based on the patient history of this condition, the clinical signs and symptoms. Laboratory confirmation, however, may be required in immunocompromised patients if the clinical presentation is atypical.

Many patients neither require nor use any treatment because the disease is self-limiting.[20] For individuals with frequent recurrences, application of a sunscreen or zinc oxide to decrease the probability of recurrent outbreaks may help.[21,22] Some resort to alternative therapies available OTC for prophylaxis and/or treatment, such as herbal-based products and dietary supplements, despite unproven efficacy,[23,24] or use OTC topical anaesthetics, analgesics, antipyretics, antiseptics and emollients. For many, however, the pain, unaesthetic

and embarrassing appearance, and the social stigma warrant using approved antiviral therapy (Table 1).

A recent metaanalysis found that the therapeutic effectiveness of OTC topical anaesthetic agents and zinc-based creams in treating herpes labialis is inconclusive due to limited evidence.[21] OTC topical antiviral therapies applied numerous times a day for up to 5 days are widely used. Clinical studies have shown that these products provide a small clinical benefit by reducing the duration of symptoms.[21] Patients with particularly severe, frequent or complicated disease require early treatment and may also benefit from a chronic prophylaxis with a licensed systemic drug that is approved for the indication. Topical antivirals are not effective prophylactically,[25] because topical application will not get the drug to the site of reactivation.

Topical antiviral medication does not impact the host immune response and consequent inflammatory cascade, but the co-administration of a topical corticosteroid may limit the inflammation.[26–28] An experimental topical combination of aciclovir and hydrocortisone has proved to confer clinical benefit, but the need for frequent application (five or six times daily) would make it less convenient than high-dose, short-course oral antiviral therapy.[29] A controlled trial showed that aciclovir/hydrocortisone cream significantly reduced the frequency of both ulcerative and nonulcerative recurrences in immunocompetent adults and adolescents.[28]

For therapy of the initial outbreak of herpetic gingivostomatitis, oral aciclovir is of some benefit,[21] by reducing the time to healing.[30] The FDA, however, has not approved any antiviral agent for initial primary gingivostomatitis. For treatment of recurrent herpes labialis, a metaanalysis of five placebo-controlled and two dose-comparison studies evaluating aciclovir, famciclovir or valaciclovir indicates that oral antiviral therapy decreases outbreak duration and the associated pain by 1 day.[31] However, none of the studies were head-to-head comparisons. Short-course, high-dose antiviral therapy offers greater patient and physician convenience,[25] are cost beneficial,[25,32] and may improve patient adherence.[32]

2. Risks versus benefits of reclassification of antiviral therapy

Despite the recent publication of an evidence-based review suggesting that oral antiviral agents are more beneficial than topical agents for treating recurrent episodes,[21] antiviral tablets are currently only available by prescription (POM or Rx only) in most countries. Availability would be facilitated by a product being reclassified as a pharmacy-only (pharmacist-controlled) medicine. This is defined as a product that can be obtained without a prescription provided that a pharmacist is present at the time of sale and that the drug is controlled by the pharmacist following a patient's request. The pharmacist can query the patient to ensure that the medication is both warranted and correctly used for herpes labialis. This approach should save the patient's time and offers greater convenience, as well as affording greater personal responsibility in the therapeutic choice and early administration of the drug as first symptoms occur during the brief window of therapeutic opportunity.[33,34] Furthermore, a physician's time spent in consultations and writing prescriptions may be reduced.[33]

However, there are four main factors that should be considered when reclassifying a therapy from a prescription-only status to a pharmacy-only or OTC medicine: evidence of efficacy; documented safety; probability of the development of resistance; and on-going monitoring.

2.1. Efficacy

The US FDA has approved short-course regimens of valaciclovir and famciclovir as prescribed oral treatments for recurrent herpes labialis[30] based on efficacy results summarized in Table 2 and Fig. 1. The approval of short-course oral therapy regimen for herpes labialis is a reflection of the trend towards greater convenience and resource management in medicine, with healthcare providers, patients and payers all potentially benefiting. Such treatments are now recommended for recurrent herpes labialis having shown that they can accelerate healing and decrease pain.[32,34] In addition, suppressive oral aciclovir,[21,22] famciclovir[35] and valaciclovir[22] have all been shown to be effective for the management of severe, frequent or complicated disease.

If there is a greater ease of access to oral antiviral therapy as a result of a change to pharmacy-only status, patients may initiate therapy earlier in the course of the illness and, as a result, the treatment should be more effective.[34] In addition, patient-initiated episodic therapy of recurrent herpes labialis may even prevent lesion development.[34] However, it should be noted that there are no data on the effectiveness of early versus delayed antiviral therapy on herpes labialis lesions because no randomised controlled trials comparing these strategies in herpes labialis have been performed to date.

2.2. Safety

Clinical studies evaluating the safety of oral aciclovir, famciclovir and valaciclovir for treatment of herpes labialis have indicated that these agents are generally well tolerated and associated with minimal adverse events in patients.

The number of adverse events and drug-related adverse events was similar in a head-to-head trial of valaciclovir (1-day and 2-day therapy) vs placebo for herpes labialis.[36] Headache was more common with valaciclovir than with placebo, but other adverse events, such as nausea and diarrhoea, in addition to a small number of cases of dyspepsia, dry mouth and flatulence, were recorded in all three treatment arms.[36] No serious adverse events were reported.[36] Data pooled from two identical trials of valacyclovir 500 mg ($n = 49$) versus placebo ($n = 49$) once daily for 16 weeks revealed a slightly higher incidence of adverse events in the placebo (29 events, 39% of patients) than in the valacyclovir arm (22 events, 33% of patients).[37] In a more recent study comparing the combination of oral valacyclovir 2 g twice daily for 1 day and topical clobetasol gel 0.05% twice daily for 3 days with placebo, the adverse events reported were mild and infrequent.[27]

A randomized, placebo-controlled trial of episodic famciclovir treatment in adults found that the adverse events were similar in the placebo and two famciclovir arms (1500 mg once a day for 1 day or 750 mg twice a day for 1 day). The adverse events, headache and nausea, were mild-to-moderate in intensity,[38] occurring in <10% and <4% of patients, respectively, in each treatment group. These safety data for famciclovir support the findings from an earlier dose-ranging study in which patients received 125 mg, 250 mg, or 500 mg of famciclovir or placebo 3 times per day for 5 days initiated 48 h after UVR exposure.[39] There were no statistically significant differences in incidence of headaches and nausea reported by patients across the four treatment groups and no serious adverse events.[39] In adolescents with herpes labialis treated with famciclovir in an open-label study, adverse events were generally mild and transient.[40]

The importance of prompt use and/or the need for rapid relief of symptoms has been recognized by the reclassification of certain medicines. Some examples are provided in Table 3. These products have been deemed sufficiently safe based on post-marketing studies not to require a doctor consultation. However, patients still need to be advised by a pharmacist; a key requirement of the regulatory authorities is that the manufacturers of drugs

reclassified to OTC status must show that they are providing adequate training and education for both patients and pharmacists. A post-marketing surveillance program for oral antiviral agents will help in collating data on adverse events related to the use of these therapies.

2.3. Resistance

Despite the increasing use of HSV-specific antiviral agents for recurrent herpes labialis in the past 20 years, as well as a variety of other herpesvirus infections, the incidence of resistant HSV-1 strains remains low (<0.5% in the immunocompetent host for the commonly used anti-HSV-1 agents).[41–44] In immunocompromised patients, although higher than in immunocompetent patients, rates of resistance are still low: aciclovir 7% vs <0.5%[45] and penciclovir 2.1% vs 0.22%, respectively.[43] Furthermore, analysis of herpes simplex isolates from immunocompetent patients with frequently recurring herpes genitalis who stopped successful suppressive aciclovir therapy after 6 years showed that there was no selection for resistance.[46] Thus, while a concern, it is unlikely that development of resistance to oral antiviral agents when used episodically in immunocompetent patients will occur.

2.4. On-going monitoring

Although not much is known about how often people obtain prescription drugs from online pharmacies, a substantial number of patients appear willing to accept considerable risk from off-label use to gain greater access to medication.[47] The potential for accidental, or deliberate, misuse of the agent across a wider range of clinical conditions needs to be addressed and monitored.

The oral antiviral agents used for herpes labialis (aciclovir, famciclovir and valaciclovir) all have POM approval for herpes genitalis,[48–50] albeit usually at different dosage regimens. Despite the introduction of pharmacist controls, some might deliberately use OTC oral antiviral agents intended for treatment of herpes labialis to treat herpes genitalis, because of the stigma associated with the latter.[51] A key concern is that the patient with genital herpes would miss the opportunity to receive correct and valuable medical advice, thus perhaps increasing risks of transmission and complications. Short-course therapy with some agents, using similar regimens to those for herpes labialis, has been investigated for the treatment of recurrent herpes genitalis and has been shown to be as safe as the traditional longer courses of therapy.[52–54] These therapies, however, have yet to receive approval in most countries with only a few countries, such as Australia (single 500 mg dose, followed by three doses of 250 mg famciclovir for genital herpes) and the US (250 mg of famciclovir twice daily for suppression of recurrent episodes of genital herpes), where a short course of famciclovir has been approved. Thus, patients buying an OTC herpes labialis treatment to use for herpes genitalis treatment would be unlikely to suffer an adverse event. The small amounts of medication that are permitted when obtained OTC reduce the potential for overdosing, and most patients always or often following the directions on the OTC package insert.[55]

Incorrect patient's self-diagnosis, concurrent disease and non-disclosed co-medications are important concerns that should be addressed when a pharmacist advises patients seeking OTC medication. Other concerns, such as dosing adherence issues, are not specific to the OTC medication. The experience with OTC antibacterial agents have shown that education and product labelling are essential to the success of reclassification.[56] Ensuring the correct diagnosis and establishing patient history is necessary for the correct treatment to be sold. Pharmacist education through training, continuing professional development and suitable approved protocols will improve pharmacy resources.[56] All information provided should be consistent and relevant, and linked to additional resources so that pharmacists can refer

patients to if they need further information.[56] Patient education using targeted campaigns are specifically recommended for HSV, stressing the importance of initiating treatment during the prodrome phase.[57]

Lessons can also be learnt from the New Zealand experience. Reclassification of famciclovir from a POM to a restricted medicine was recommended at the 42nd meeting of the New Zealand Medicines Classification Committee.[58] Pharmacist-controlled purchase of oral famciclovir for the treatment of herpes labialis was approved in early 2010. The transTasman therapeutic products agency agreement between New Zealand and Australia is likely to result in the rescheduling of famciclovir to a pharmacist-only medicine in Australia too. Based on the acceptability of reclassification of oral famciclovir in New Zealand, it is likely that the same will be sought in the rest of the world for famciclovir and the other oral antivirals. It should be noted that these moves towards OTC are being made for therapies marketed exclusively for herpes labialis, and not herpes genitalis. Indeed, a submission to switch aciclovir for herpes genitalis to OTC status was not supported in the USA.[59]

3. Pharmaco-economic benefits of OTC therapies

Generally, OTC therapies are more accessible and convenient than prescription medications and are usually cheaper because they are often generic.[60] In some countries, patients may have to pay the full cost of a POM but, in others, patients may only have to pay a fixed prescription charge that could be the same or less than the OTC price. The change from POM to OTC status of medications has been the direction followed by more than 700 treatments over the past 30 years and has led to annual healthcare cost savings of over $20 billion for US consumers.[61] For example, the switch from POM to OTC status for topical hydrocortisone saved US consumers $200 million in the first year and $400 million in the second, taking into account both the direct and indirect costs.[60,62] In Europe, switching appropriate medicines for the treatment of minor illnesses to OTC could realise an annual saving of € 16 billion.[63] In allergic rhinitis,[64] migraine,[65] emergency contraception[66] and weight control,[67] marked cost savings are achievable.

4. Conclusions

Initial diagnosis of herpes labialis should be made by GPs. With patient education, thereafter, a significant reduction in a GP's work burden, as well as cost-savings for both the patient and the GP, could result from the availability of pharmacy-controlled antiviral medication for herpes labialis. Another important consideration is reducing the delay in the start of treatment, with patients being able to self-medicate as soon as they feel the prodrome of a herpes labialis outbreak. Suitable safeguards need to be in place, such as the monitoring for safety and appropriate package labelling of the medication. In addition, if there is a change from prescription-only to pharmacy-only status for antiviral agents in the treatment of herpes labialis, surveillance systems should be in place to assess the impact on treatment of genital herpes.

Pharmacist and patient education on the efficacies of systemic and topical antiviral agents, and the importance of treatment adherence to prevent the emergence of resistance are essential. Although systemic agents have proved to be highly efficacious in the treatment of herpes labialis based on data from placebo-controlled trials, randomized-controlled trials directly comparing systemic versus topical therapies are required. The benefits also need to be communicated at the governmental and/or payer levels, using the experience with other OTC medications as examples, as well as the recent reclassification of famciclovir for herpes labialis in New Zealand.

Acknowledgments

Competing interests AC has participated in roundtable discussions on antivirals for herpesviruses sponsored by Novartis, GlaxoSmithKline and 3M, and in clinical trials of antivirals sponsored by Novartis and GlaxoSmithKline. LS is a consultant in vaccine development for GlaxoSmithKline and Sanofi-Pasteur; and has also received funding from the National Institutes of Health. RP has participated in advisory board meetings and speaker panels for Astellas, Becton Dickenson, GlaxoSmithKline and Novartis; and also received financial support for conference attendance from Janssen, ViiV and Gilead. PL has received funding from and participated in speaker bureaus for Novartis, GlaxoSmithKline and Abbott Diagnostics.

Funding `The availability of OTC oral antivirals for cold sores' Advisory Board Meeting, held 16–17 April 2009, in Annecy, France, was sponsored by an educational grant from Novartis.

Abbreviations

FDA	Food and Drug Administration
GP	general practitioner
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
OTC	over-the-counter
POM	prescription-only medicine
vs	versus

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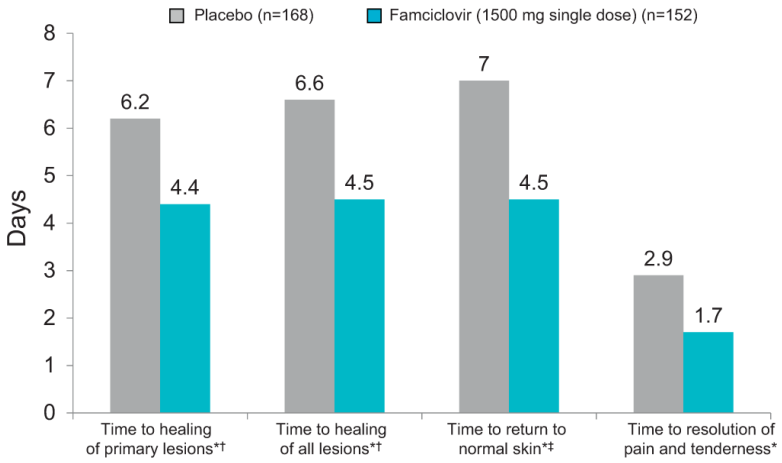

Fig. 1.

Efficacy of short-course famciclovir and valaciclovir in the treatment of herpes labialis. Famciclovir 1500 mg single dose for 1 day significantly reduced time to healing of primary vesicular herpes labialis lesions.[38] *$p < 0.001$ vs placebo; †vesicular lesions; ‡Normal skin defined as loss of crust, swelling, and dry flaking for all lesions (vesicular and aborted).

Table 1

Antiviral agents approved for treatment of herpes labialis in the UK and USA.

Antiviral agent [trade name]	Dosing schedule	Manufacturer	Country (legal status)
Penciclovir cream (1%) [Fenistil® Cold Sore Cream[68]; Denavir®,[69]]	Approximately 8 times daily (2- hourly intervals) during waking hours for 4 days	Novartis Consumer Health New American Therapeutics	UK (pharmacist-controlled) USA (Rx only)
Aciclovir cream (5%) [Zovirax®;[48,70] Clearsore Aciclovir; Action Coldsore; Aviral; Soothelip; Virasorb]	Approximately 5 times daily (3–4 hourly intervals) during waking hours for 4 days	GlaxoSmithKline Consumer Healthcare BTA Pharmaceuticals Inc	UK (pharmacist-controlled) USA (Rx only)
Famciclovir [Famvir®,[49]]	1500 mg as a single dose	Novartis Pharmaceuticals Corporation	USA (Rx only)
Valaciclovir (Valtrex®,[50])	2 g every 12 h for 1 day	GlaxoSmithKline	USA (Rx only)

Table 2

Summary of studies examining effectiveness of oral antiviral agents for management of recurrent herpes labialis outbreaks.

Study design	N	Outcome
Aciclovir		
400 mg twice daily, 12 h before ultraviolet exposure vs placebo[21,71]	147	Aciclovir reduced frequency of attacks and duration of symptoms overall (p <0.05)
		Fewer lesions with aciclovir (7%) vs placebo (26%)
400 mg 5 times daily for 5 days vs placebo taken during tingling stage[21,72]	174	Shorter duration of symptoms with aciclovir (8.1 days) vs placebo (12.5 days) (p =0.02)
		Mean duration of pain shorter with aciclovir (2.5 days) vs placebo (3.9 days) (p = 0.02)
800 mg twice daily for 3–7 days vs placebo[73]	237	No significant difference in lesion occurrence with aciclovir vs placebo
200 mg 5 times daily for 5 days vs placebo taken within 12 h of the onset of the first episode[21,74]	149	No significant difference in healing time or pain duration with aciclovir vs placebo
400 mg twice daily for 4 months vs placebo[75]	20	Longer median time to recurrence with aciclovir (118 days) vs placebo (46 days) (p = 0.05)
		53% fewer clinical recurrences with aciclovir vs placebo (p = 0.009)
Valaciclovir		
500 mg once daily for 4 months vs placebo[21,37]	98	Significantly longer mean time to recurrence with valaciclovir (13.1 weeks) vs placebo (9.6 weeks) (p = 0.016)
		More patients were recurrence-free with valaciclovir (60%) vs placebo (38%) (p = 0.041)
2 g twice daily for 1 day vs 2 g twice daily on Day 1, then 1 g twice daily on Day 2 vs placebo[21,36]	954	Shorter median duration of episode with 1-day valaciclovir (5.0 days; p < 0.001) and 2-day valaciclovir (4.5 days; p = 0.009 vs placebo) vs placebo (5.0 days)
2 g twice daily for 1 day vs 2 g twice daily on Day 1, then 1 g twice daily on Day 2 vs placebo[21,36]	902	Shorter median duration of episode with 1-day valaciclovir (4.0 days; p < 0.001 vs placebo) and 2-day valaciclovir (4.5 days; p = 0.009 vs placebo) vs placebo (5.0 days)
Famciclovir		
125, 250 or 500 mg, 3 times daily for 5 days vs placebo[39]	248	No significant difference in number of lesions between four groups.
		Famciclovir 500 mg reduced median time to healing (4 days) vs placebo (6 days; p = 0.010).
		Reduced mean lesion size in all famciclovir groups in a dose-proportional manner vs placebo
1500 mg single dose for 1 day vs 750 mg twice daily for 1 day vs placebo[38]	701[a]	Reduced median healing times of primary lesions with single-dose famciclovir (4.4 days; p < 0.001 vs placebo) twice-daily famciclovir (4.0 days; p < 0.001 vs placebo) vs placebo (6.2 days)

[a]Analysis only included the 477/701 (68%) of participants who subsequently developed vesicular herpes labialis lesions during the course of treatment.

Table 3

Examples of drugs that have switched prescribing status in the UK.

Drug	Indication	Legal status
Chloramphenicol (1%) eyedrops	Treatment of acute bacterial conjunctivitis	Pharmacist-controlled
Levonorgestrel	Emergency contraception in women aged 16 years and over[76]	Pharmacist-controlled
Azithromycin	Treatment of known or suspected asymptomatic *Chlamydia trachomatis* genital infection in adults 16 years and over[77]	Pharmacist-controlled
Diclofenac potassium (oral)	For short-term relief of headache, backache, dental pain, period pain, rheumatic and muscular pain, cold and flu symptoms	OTC