Summary

Aciclovir, valaciclovir and famciclovir are all nucleoside analogues active against herpes simplex virus types 1 and 2, and varicella zoster virus. Valaciclovir is a pro-drug of aciclovir which is absorbed more quickly and therefore has a higher absolute bioavailability; it is therefore dosed less frequently. Famciclovir is a pro-drug of penciclovir, the active form of which is more stable than that of aciclovir, allowing less frequent dosing.

Valaciclovir is the only antiviral currently licensed for the reduction of transmission of genital herpes (GH); all three are licensed for the treatment and suppression of GH and the treatment of herpes zoster.

Treatment of first episode of GH: Aciclovir, valaciclovir and famciclovir all reduce the severity and duration of episodes when initiated within 72 hours of the onset of lesions; they are probably equally effective but there is more evidence for aciclovir.

Treatment of recurrent GH infection: Aciclovir, valaciclovir and famciclovir all reduce the severity and duration of acute recurrent episodes; there is no evidence for a superior agent out of the three in terms of clinical outcomes.

Suppression of recurrent GH infection: There is no evidence to suggest that either famciclovir or valaciclovir is superior to aciclovir when used as suppressive therapy to reduce the frequency of GH recurrences (no comparative data available for famciclovir vs. aciclovir). Limited data suggest that valaciclovir may have a small advantage over famciclovir in terms of virologically-confirmed recurrence; however this was a secondary endpoint and no difference was demonstrated between the two in clinically-confirmed recurrence. A small study found that valaciclovir may be superior to famciclovir in terms of viral shedding, but this did not assess clinical consequences and requires confirmation in a larger study.

Treatment of herpes zoster: There is some evidence from one RCT to suggest that valaciclovir may reduce the time to complete cessation of pain and the duration of post-herpetic neuralgia (by a median of 13 days; secondary endpoint) when compared to aciclovir; although both are similar in terms of resolution of cutaneous manifestations. There is some evidence that famciclovir is also superior to aciclovir in terms of pain resolution, but this was only significant for the UK licensed dose in a subgroup of patients who were treated within 48 hours of rash onset and who were compliant with treatment – therefore this may not reflect the ‘real world’ scenario.

Aciclovir has been monitored for two decades and has not been associated with significant adverse effects in this time, even with long-term use. There are less data available for valaciclovir and famciclovir, but these also have low toxicity profiles. No evidence for improved compliance (and/or improved outcomes associated with such) for famciclovir or valaciclovir versus aciclovir were located.

Summary: There is currently no good evidence to suggest superiority of either valaciclovir or famciclovir over aciclovir within their licensed indications; due to the cost considerations, aciclovir should be considered as first-line for treatment/suppression of GH and treatment of herpes zoster unless compliance or other issues favour the use of an alternative.
Comparison of aciclovir, famciclovir and valaciclovir for management of herpes simplex and herpes zoster infections

As aciclovir is the only one currently available as a generic, the prices of each differ substantially (see table).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Aciclovir</th>
<th>Valaciclovir</th>
<th>Famciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of initial GH episode</td>
<td>£4.01</td>
<td>£21.86 – £43.72</td>
<td>£102.07</td>
</tr>
<tr>
<td>Treatment of recurrent GH episode</td>
<td>£4.01</td>
<td>£21.86</td>
<td>£34.02</td>
</tr>
<tr>
<td>Treatment of recurrent GH episode (immunocompromised)</td>
<td>£3.26</td>
<td>£21.86</td>
<td>£190.54</td>
</tr>
<tr>
<td>Suppression of recurrent GH (per month)</td>
<td>£7.31 (400mg BD)</td>
<td>£65.58 (500mg OD)</td>
<td>£381.03</td>
</tr>
<tr>
<td>Treatment of herpes zoster (cost per course)</td>
<td>£9.22</td>
<td>£91.61</td>
<td>£136.39 (750mg OD)</td>
</tr>
<tr>
<td>Treatment of herpes zoster (immunocompromised)</td>
<td>£9.22</td>
<td>£91.61</td>
<td>£408.17</td>
</tr>
</tbody>
</table>

**Background**

The nucleoside analogues aciclovir (ACV), valaciclovir (VAL) and famciclovir (FAM) all exhibit antiviral activity against herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2), and varicella zoster virus (VZV). FAM is an oral pro-drug of penciclovir; this differs structurally from ACV only by the presence of an additional hydroxyl group, and it has a similar mechanism of action to ACV. The phosphorylated (active) form of penciclovir is more stable than that of ACV, resulting in prolonged intracellular half-lives; FAM therefore does not need to be dosed as frequently as ACV. VAL is the L-valine ester prodrug of ACV, which is almost completely absorbed from the gastrointestinal tract and rapidly converted to ACV and valine by first-pass intestinal or hepatic metabolism (1). As VAL is absorbed through the intestines more quickly than ACV, the absolute bioavailability of VAL (54%) is higher (by 10-20%) and a less frequent dosing frequency is therefore possible (2).

The licensed doses of each antiviral for herpes zoster and herpes simplex (genital) are summarised in table 1. This review summarises the comparative evidence currently available for ACV, VAL and FAM, focusing on the treatment/prevention of genital herpes (GH) and the treatment of herpes zoster (HZ).

Table 1: Licensed indications and doses for aciclovir, valaciclovir and famciclovir in the UK

<table>
<thead>
<tr>
<th>Indication</th>
<th>Aciclovir</th>
<th>Valaciclovir</th>
<th>Famciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of initial GH episode</td>
<td>200mg five times a day [5 days +]; 400mg if severely immunocompromised</td>
<td>500mg BD [5-10 days]</td>
<td>250mg TDS [5 days]</td>
</tr>
<tr>
<td>Treatment of recurrent GH episode</td>
<td>200mg QDS or 400mg BD</td>
<td>500mg BD [5 days]</td>
<td>125mg BD [5 days]</td>
</tr>
<tr>
<td>Treatment of recurrent GH episode (immunocompromised)</td>
<td>200-400mg 4/day</td>
<td>500mg BD</td>
<td>500mg BD</td>
</tr>
<tr>
<td>Suppression of recurrent GH (immunocompetent)</td>
<td>200mg QDS or 400mg BD</td>
<td>250mg BD or 500mg OD (if &lt;10 recurrences/yr)</td>
<td>250mg BD</td>
</tr>
<tr>
<td>Suppression of recurrent GH (immunocompromised)</td>
<td>200-400mg 4/day</td>
<td>500mg BD</td>
<td>500mg BD</td>
</tr>
<tr>
<td>Reduction of transmission of GH</td>
<td>-</td>
<td>500mg OD</td>
<td>-</td>
</tr>
<tr>
<td>Treatment of herpes zoster</td>
<td>800mg 5/day [7 days]</td>
<td>1000mg TDS [7 days]</td>
<td>750mg OD or 250mg TDS [7 days]</td>
</tr>
<tr>
<td>Treatment of herpes zoster (immunocompromised)</td>
<td></td>
<td></td>
<td>500mg TDS [10 days]</td>
</tr>
</tbody>
</table>
Comparison of aciclovir, famciclovir and valaciclovir for management of herpes simplex and herpes zoster infections

Genital Herpes

The Clinical Effectiveness Group of the Association for Genitourinary Medicine and the Medical Society of Veneral Diseases published a national guideline on the management of genital herpes in 2001 (3).

1) Treatment of first episode

Oral antivirals are indicated within five days of the start of the first episode of GH. Although there is no evidence for continuing treatment beyond five days, this may be prudent if new lesions are still forming; some clinicians also advocate longer treatment courses (10 days) in HIV-positive individuals. ACV, VAL and FAM all reduce the severity and duration of episodes, and are probably equally effective (although there is more evidence for ACV) (3, 4).

a) Famciclovir

The effectiveness of FAM in the treatment of a first episode of GH (initiation within 72 hours of appearance of lesions) was assessed in three double-blind, randomised studies (reported in one paper) (5). Each trial compared the efficacy of a range of FAM doses for either 5 days (250, 500 or 750mg TDS) or 10 days (125, 250 or 500mg TDS) duration, to that of an equal duration of ACV 200mg five times a day. Primary endpoints included time to complete healing of all lesions, and time to cessation of viral shedding from all genital lesions. No difference in efficacy was seen between ACV and FAM in any of the endpoints studied; the efficacy of the 10-day regimen of FAM was similar to that of the 5-day regimen (3, 6).

b) Valaciclovir

VAL was compared to ACV in the treatment of a first episode of GH in a multicentre, double-blind RCT (7). A total of 643 immunocompetent adults were randomised within 72 hours of symptom onset to treatment with ten days of VAL (1g BD) or ACV (200mg five times a day). The primary efficacy endpoints (intention-to-treat) were time to healing of all lesions and the duration of viral shedding; secondary endpoints included the proportion of patients still forming lesions at 48 hours, the maximum number of lesions, duration and severity of pain, and duration and severity of systemic symptoms. No statistically significant differences were observed between the two groups for any endpoint studied (7). Of note, the trial was not designed to demonstrate equivalence, but it had 80% power to detect a 10% improvement in healing at 10 days with one of the regimens. The authors state that a difference of even 10% if it existed is unlikely to be clinically meaningful, and therefore they conclude that the two treatments are ‘functionally equivalent’. The dose of VAL used in this trial is that licensed for the treatment of first episode genital herpes in the US (i.e. 1g BD for ten days); in the UK however, the licensed dose is 500mg BD for 5-10 days. The UK dose has been found to have a similarly efficacy to ACV 200mg five times a day for the treatment of recurrent episodes (discussed later); the Summary of Product Characteristics (SPC) does not distinguish between the treatment of first and recurrent episodes but states a general dose for treatment (longer duration may be necessary for initial episodes) (8). No randomised, prospective studies directly comparing the UK licensed dose of VAL with ACV and/or FAM for the treatment of a first episode of GH were located.

2) Treatment of acute recurrent infection

Following primary infection, HSV becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic, but infectious, viral shedding (3). Recurrent episodes of GH are often mild and supportive measures alone may be sufficient. If recurrences are frequent or severe, treatment with an antiviral drug may be considered – either intermittently to treat symptoms, or constantly to prevent or minimize recurrent episodes (4).

Episodic oral ACV, VAL and FAM have all been found to reduce the duration and severity of recurrent episodes of GH. Patient-initiated treatment should be started as early in the episode as possible; this may require the person to keep a prescription for future use or to have a supply of the antiviral drug at home. There is no evidence of the superiority of a particular antiviral in terms of clinical outcomes; guidance produced for clinicians in the Clinical Knowledge Summary recommends ACV be used first-line due to the cost implications, and suggests VAL or FAM if there is likely to be an issue with compliance (4).

a) Famciclovir

FAM (125mg BD; n=107) has been compared to ACV (200mg five times a day; n=97) in a Phase III double-blind trial involving immunocompetent adults who had experienced three or more recurrences of GH within the 12 months prior to study entry (9). Treatment was self-initiated within 12 hours of the onset of their next recurrence (i.e. prodromal symptoms or presence of genital lesions) and continued for five days. The primary endpoint was time to lesion healing (intention-to-treat); FAM was found to be equivalent to ACV according to the pre-specified definition (difference of 0.25 days; 95% CI -0.32 to 0.82). The two treatments were also found to be similar in terms of secondary endpoints studied, including the proportion of patients having complete lesion healing at the different days of evaluation and the time to resolution of all symptoms. The groups were comparable at baseline apart from age (median 45 years for FAM versus 40 years for ACV; p=0.01) but age-adjusted values for the endpoints studied also demonstrated equivalence.

In the US, the licensed regimen of FAM for the treat-
ment of an acute recurrence of GH is 1g BD for one
day; there is only evidence of this being effective
when treatment is initiated within six hours of
the onset of symptoms/appearance of lesions. In a
multicentre trial, 329 immunocompetent adults with an
acute recurrence of GH (and a history of at least four recurrences in the year prior to study entry) were randomised to double-blind treatment with
FAM 1g BD (n=163) or placebo (n=166) for one day
(10). Treatment was initiated by the patient within
six hours of the onset of prodromal symptoms and/or
the appearance of lesions. The primary endpoint
was time to healing (re-epithelialisation) of all non-aborted lesions (modified intention-to-treat popula-
tion); this was a median of 4.3 days in the FAM arm
and 6.1 days in the placebo arm (difference of 1.2
days; 95% CI 0.5 – 2.0 days; p<0.001). Time to
healing of all lesions was 3.5 days versus 5.0 days,
respectively (HR 1.79; p<0.001). The median time
to resolution of all symptoms (e.g., burning, itching,
pain, tenderness, tingling), was 3.3 (2.8–4.1) days in
FAM-treated patients vs. 5.4 (4.5–6.5) days in pla-
lopeo-treated patients (HR 1.66; 95% CI 1.23–2.24,
p<0.001). Of note, lesions were aborted in 23.3% of
famciclovir recipients compared to 12.7% of placebo
recipients (p=0.003). This emphasises the clinical
benefits that can be achieved if patients are edu-
cated about the natural history of recurrent GH and
use patient initiated therapy at the first signs of pro-
dromal symptoms (tingling) rather than waiting for
lesions to appear on the mucosa. This regimen is
not licensed in the UK, and no active comparator
studies were located.

b) Valaciclovir

VAL has demonstrated efficacy in the episodic treat-
ment of recurrent GH in several placebo-controlled
and ACV-controlled studies. In a double-blind, pa-
tient-initiated dose-ranging trial (n=987), a five day
course of VAL 500mg BD was found to be as
equally effective as 1000mg BD for the acute treat-
ment of one episode of recurrent GH (11). The
measures of efficacy used in the trial included me-
dian length of recurrence, median lesion healing
time, and median time to termination of viral shed-
ing.

Trials comparing VAL to ACV have employed both
the 1000mg BD and the 500mg BD doses (12, 13).
In one multicentre, double-blind trial of patient-
initiated therapy, a total of 999 patients with a his-
tory of recurrent GH infection (at least four recur-
rences in the year prior to enrolment, or one recur-
rence within three months after stopping suppres-
sive ACV) were randomised to VAL 500mg BD or
ACV 200mg five times a day for five days (12). Pa-
ients were instructed to initiate treatment at the first
signs or symptoms of their next recurrence. The
primary endpoints were the length of the episode
(number of days from treatment initiation to com-
plete resolution of all signs and symptoms) and le-
sion healing time (number of days between treat-
ment initiation and complete re-epithelialisation of all
mucocutaneous lesions). Of those randomised, 739
returned to the clinic for assessment and formed the
intention-to-treat population. The main results are
summarised in table 2; the authors concluded that
VAL 500mg BD was equivalent to ACV 200mg five
times a day in the episodic treatment of recurrent
genital HSV infection. Although they found that the
VAL regimen increased the systemic exposure to
ACV by twofold over the standard ACV regimen,
there was no evidence presented to suggest that
this resulted in superior outcomes. The main results
of the study comparing the VAL 1000mg BD regi-
men to placebo are summarised in the table but are
not discussed further here, as this exceeds the UK
licensed dose (13). The results of the dose ranging
study above do however suggest that 500mg BD
and 1000mg BD are equivalent (11).

The licensed dose of VAL for the treatment of an
acute recurrent episode of GH in the US is 500mg
BD for three days; this is based on the results of a
study that found this shorter course to be as effec-
tive as the 5-day regimen (14). A total of 800 adults
with a history of at least four episodes of genital or
perianal HSV recurrences in the previous year (or
two in the previous six months) were randomised to
double-blind treatment with VAL 500mg BD for three
(n=402) or five (n=398) days. The primary endpoint
of median time to lesion healing was 4.7 for the 5-
day regimen and 4.4 days for the 3-day regimen
(HR 0.95; 95% CI 0.81–1.13, p=NS); respective val-
ues for secondary endpoints were as follows: 2.5
versus 2.9 days for pain duration, and 4.4 days ver-
sus 4.3 days for episode length (no significant differ-
ences between the two groups). No published stud-
ies directly comparing this three-day regimen of VAL
to ACV and/or VAL were located, and this shorter
regimen is not currently approved in the UK.

3) Suppression of recurrent GH infection

Suppressive antiviral treatment is indicated if recur-
rences are frequent and severe. There are no set
guidelines around what frequency of recurrence
would warrant suppressive therapy – trials have in-
cluded patients with at least six recurrences in one
year, but the decision to start such treatment is a
subjective one, and patients should be given full
information on the associated advantages and dis-
advantages. In certain patient groups, suppressive
treatment may be warranted when recurrences are
less frequent (e.g. immunocompromised patients;
those with severe episodes, or severe related psy-
chosocial morbidity). Suppressive therapy should
be interrupted periodically at intervals of six to
twelve months in order to reassess the frequency of
recurrence; those who continue to have unaccepta-
bly high rates of recurrence may restart treatment
(3, 4).

Study results suggest that VAL may have a small
advantage over FAM in terms of viral shedding (but
Comparison of aciclovir, famciclovir and valaciclovir for management of herpes simplex and herpes zoster infections

small patient numbers) and virologically-confirmed recurrence (secondary endpoint); there is no published evidence that either is superior to ACV. The BASHH guidelines recommend that the choice of treatment is based on consideration of patient compliance (i.e. frequency of administration) and cost; the Clinical Knowledge Summary on GH states that all three are probably equally effective, and therefore recommends ACV based on cost (3, 4).

a) Famciclovir

The efficacy of FAM in preventing recurrence of GH has been assessed in three placebo-controlled RCTs, which included individuals who had suffered from at least six recurrences during 12 months in the absence of any ACV suppressive therapy (15). FAM (all regimens except once-daily) was found to reduce the number of recurrences and increased the median length of time until first recurrence (as much as six times longer than seen with placebo); also a higher proportion of patients were recurrence free (at 120 days or six months) and this difference was maintained at 12 months (15).

FAM was compared to VAL for the suppression of recurrent GH in two studies; one (Study 1) assessed clinical recurrences and the other (Study 2) measured viral shedding on the genital mucosa. The results of both were reported together (16). In study 1, adults with a history of at least six recurrences in the previous year were randomised in a double-blind fashion to suppressive therapy with FAM 250mg BD (n=159) or VAL 500mg OD (n=161). The primary endpoint was the proportion of patients who had clinically confirmed recurrence during the study (16 weeks); this was reached by 34% of the FAM group and 28% of the VAL group (HR 1.10; 95% CI 0.94-1.28; p=NS). A small but statistically significant benefit was found for VAL in terms of virologically confirmed recurrence (6% versus 13% with FAM; p=0.035), however this was a secondary endpoint. The results of study 2 are summarised in the next section.

No published comparison of FAM in the suppression of GH was located. The safety and efficacy of continued treatment for over 12 months has not been established.

b) Valaciclovir

The licensed dose of VAL for the suppression of genital herpes is 500mg daily; this can be taken as 250mg BD or 500mg OD and is the only antiviral licensed for this indication as a once-daily dosing regimen (8). In a 52-week multi-centre, double-blind, placebo-controlled dose-finding study, a range of once-daily VAL doses (250, 500 or 1000mg) were assessed for efficacy in the suppression of recurrent GH; twice daily regimens of VAL (250mg BD) and ACV (400mg BD) were also evaluated (17). Adults with a history of at least six genital HSV recurrences per year were enrolled; those who had been receiving suppressive therapy with ACV must have stopped therapy and must have had a recurrence within three months of stopping; this recurrence had to be within three months of study enrolment. The primary endpoint was the time to first recurrence (number of days from randomisation to first onset of lesions); subgroup analyses were planned to estimate the treatment differences within subgroups of patients with <10 and ≥10 HSV recurrences per year (prior HSV recurrence frequency is known to be a prognostic factor affecting time to first recurrence). Absolute data for the primary endpoint are not discussed in the publication, but hazard ratios are reported and according to these VAL 250mg BD was found to be equivalent to ACV 400mg BD (HR 1.01; 95% CI 0.74-1.30) and VAL 1g daily (0.95; 0.74-1.22). All active regimens used were superior to placebo for the primary endpoint (p<0.0001). Although VAL 1g OD appeared to be superior (borderline significance) to 500mg OD (0.78; 0.61-0.99), there was no evidence of a difference between the two regimens within the pre-specified subgroup of patients with <10 recurrences a year. Patients with more frequent recurrences (≥10 per year) were more effectively managed with 1g OD or 250mg BD VAL, or with 400mg BD ACV. VAL also demonstrated efficacy in the suppression of recurrent genital HSV infection as a once daily dose (500mg) in a 16-week double-blind, placebo-controlled trial (Patel et al, 1997).

For details of two studies comparing VAL with FAM, please see the FAM section above (16).

4) Reduction of asymptomatic shedding and transmission

Studies have assessed ACV, FAM and VAL for the suppression of clinical GH recurrences; however asymptomatic reactivations may also result in sexual transmission (18). A few studies have therefore looked at the effect of antivirals on the asymptomatic shedding of HSV, and one published trial has evaluated the effect of VAL suppressive therapy on the sexual transmission on HSV-2.

The effect of FAM 250mg BD (n=34) versus VAL 500mg OD (n=336) on shedding of HSV from the genital area in adults with at least six GH recurrences in the previous year was assessed in Study 2 (16). The mean number of days with swabs of genital secretions collected for analysis was 66.4 days (65.5 days for FAM and 63.8 days for the VAL group). The primary endpoint of proportion of days with HSV (detected by PCR) in genital swabs was low for both groups, with a significant benefit seen for VAL (1.3% versus 3.2% for FAM; RR for FAM of 2.33; 95% CI 1.18-4.89, p=0.014). At least one day of genital HSV shedding was detected in 18 FAM recipients (53%) and 18 VAL recipients (50%; P=NS). Other studies evaluating the effect of ACV and FAM on HSV shedding have found them to be
superior to placebo.

VAL is the only antiviral to be licensed in the UK for the reduction of transmission of genital herpes. This was assessed in a randomised, double-blind trial, involving 1,484 monogamous, heterosexual couples; one out of each couple had clinically symptomatic genital HSV-2 infection (no more than ten recurrences per year) and they were randomised to treatment with VAL 500mg OD (n=743) or placebo (n=741) for eight months (18). The predefined primary endpoint was laboratory-confirmed, clinically symptomatic first episode of genital HSV-2 infection in the susceptible partner. The rate of HSV-1 seropositivity in the susceptible partners was 78.5% of the women and 64.4% of the men. Around half of the HSV-2 infected (source) partners were also seropositive for HSV-1 at baseline. A total of 41 HSV-2 infections were detected during the study period; of these, 20 were associated with symptomatic new GH (primary endpoint) – 16 (2.2%) cases in partners of placebo recipients and 4 (0.5%) in partners of VAL recipients (RR 0.25; 95% CI 0.08-0.74, p=0.01). When all 41 cases were considered (i.e. total acquisition of HSV-2), VAL was still found to be superior to placebo (1.9% of the partners of VAL recipients versus 3.6% of the partners of placebo recipients; HR 0.52; 95% CI 0.27-0.99, p=0.04). VAL also prolonged the time to development of a symptomatic first episode in the susceptible partner (HR 0.25; 95% CI 0.08-0.75; p=0.008).

In a substudy, HSV was detected in genital secretions during HSV-2 reactivation (19). Breaks in the genital mucosa and skin caused by HSV-2 infection facilitates entry of the HIV virus and this increases the risk of HIV infection through sexual transmission. In addition, those who are co-infected with HSV-2 and HIV are more likely to transmit HIV, possibly due to high titres of HIV in genital secretions during HSV-2 reactivation (19). Treatment may be complicated by refractory lesions and the emergence of resistant strains of HSV (4).

Management of GH in HIV-positive patients

In patients with HIV or those who are otherwise immunocompromised, episodes of genital HSV infection may be prolonged, more severe, and require a longer duration or higher doses of antiviral treatment. In HIV-negative individuals, the ulcers and breaks in the genital mucosa and skin caused by HSV-2 infection facilitates entry of the HIV virus and this increases the risk of HIV infection through sexual transmission. In addition, those who are co-infected with HSV-2 and HIV are more likely to transmit HIV, possibly due to high titres of HIV in genital secretions during HSV-2 reactivation (19). Treatment may be complicated by refractory lesions and the emergence of resistant strains of HSV (4).

The clinical effectiveness group of the BASHH published guidance on the treatment of genital herpes in HIV-positive individuals as part of its national guideline on the sexual health of people with HIV (20).

a) Famiciclovir

i) Prevention of recurrence

In a small double-blind crossover trial, researchers compared FAM 500mg BD to placebo in the prevention of herpes simplex recurrence (genital and orolabial) in 48 HIV-positive individuals (21). Those who had received suppression with ACV during the six months prior to study entry were excluded, as were those who had current/previous infection with ACV-resistant HSV. Following an initial eight week treatment period (FAM or placebo), patients crossed over to treatment with the alternative, separated by a seven day washout period. During the initial treatment period, 5 patients (21%) assigned to FAM and 17 (71%) assigned to placebo shed HSV at least once. FAM was found to be superior to placebo in terms of median days with symptoms (13.8% less with FAM), median days on which HSV was isolated from the affected area (5.4% less with FAM), and the proportion of days with shedding of HSV (1.3% versus 9.7% with placebo); all p<0.001.

No trials comparing FAM to ACV or VAL in the prevention of herpes simplex recurrence in HIV-positive individuals were identified.

ii) Treatment

The efficacy of FAM and ACV in the treatment of herpes simplex infection in HIV-positive adults was compared in a double-blind, randomised, parallel-group equivalence study (22). A total of 293 adult patients with recurrent mucocutaneous herpes simplex (around half of cases were anogenital) were randomised to receive treatment within 48 hours of the onset of lesions with FAM 500mg BD (n=150) or ACV 400mg five times a day (n=143) for seven days in total. The primary endpoint of the study was the proportion of patients developing new lesions during treatment – this was 16.7% for FAM and 13.3% for ACV (95% CI of the difference -4.8 to 11.5), thus satisfying the non-inferiority criteria (i.e. upper 95% CI limit of the inter-group difference was <15%). FAM was also found to be non-inferior to ACV in terms of several secondary endpoints studied, including median time to healing of all lesions (7 days for both; HR 1.01, 95% CI 0.79-1.29, p=NS) and median time to cessation of viral shedding (2 days for both; HR 0.93, 95% CI 0.68-1.27, p=NS). In summary, FAM 500mg BD was found to be of comparable efficacy to ACV 400mg five times a day in the treatment of HSV infection in HIV-positive individuals.

b) Valaciclovir

Two randomised, controlled studies, reported together, compared VAL to ACV in the episodic treatment and the suppression of recurrent anogenital herpes in HIV-infected individuals (23). Of note, both were conducted between 1991 and 1996, be-
fore highly active anti-retroviral treatment (HAART) was widely used.

i) Prevention of recurrence

Study 1 was a 3-arm double-blind, parallel study comparing VAL 500mg BD, 1000mg OD and ACV 400mg BD for the prevention of recurrent anogenital HSV infection in HIV-positive adults (CD4 count of 100 cells/mm³ or above) with one or more recurrences in the year prior to study entry. The primary endpoint was time from randomisation to first recurrence; time to second recurrence was also recorded. There were no statistically significant differences between either VAL regimen and ACV in terms of the primary endpoint; hazard ratios for VAL 500mg and 1000mg versus ACV were 0.73 (0.50-1.06; p=NS) and 1.31 (0.94-1.82; p=NS), respectively. The hazard ratio for the comparison of 1000mg OD and 500mg BD VAL was 1.80 (1.26-2.57; p=0.001), suggesting that the twice daily regimen is superior. A similar trend was seen in terms of time to second recurrence, and the estimated proportion of patients remaining recurrence free at 48 weeks (end of study) were 82%, 71% and 78% for VAL twice daily, once daily and ACV, respectively. A placebo-controlled trial also found that 500mg VAL BD was effective at reducing recurrence of genital HSV infection in HIV-positive individuals receiving antiretroviral therapy (24). The authors found that VAL reduced the risk of recurrence (RR 2.5; 95% CI 1.8-3.5) and increased the median time to first recurrence (>180 days versus 59 days with placebo; HR 16.7; 95% CI 7.3-33.3).

ii) Treatment

Study 2 was a 2-arm comparison of patient-initiated VAL 1000mg BD and ACV 200mg five times a day for the episodic treatment of a single episode of recurrent anogenital HSV. This is above the UK licensed dose and therefore is not discussed further (although as discussed previously, one study has shown 500mg BD and 1000mg BD show similar efficacy in the treatment of acute recurrent HSV infection in immunocompetent individuals – 11). The licensed dose for treatment of acute recurrent episodes in the UK does not differ depending on immune status.

Viral resistance

Resistance to ACV is rare among immunocompetent patients, with an estimated prevalence of below 1% (25). Most cases of resistance reported in this group have occurred in the setting of recurrent GH. Prevalence of ACV resistance is higher among immunocompromised patients and has been estimated to be around 5% overall; this varies according to type of immunosuppression, with higher values reported for allogeneic bone marrow transplant recipients (up to 30%), and lower values for HIV-positive individuals and solid organ transplant recipients (25).

Activation of ACV, FAM and VAL depends on phosphorylation by viral thymidine kinase (TK), which allows them to be highly selective for cells infected with herpes virus. The majority (around 95%) of ACV-resistant HSV isolates are due to mutations in the TK gene, which lead to premature chain termination and production of an inactive TK protein. In a minority of cases, specific mutations can occur in the active site of the viral TK gene such that it can still recognise the natural substrate thymidine but has poor affinity for ACV. In a small percentage of cases, mutations occur in the DNA polymerase such that ACV triphosphate (or the equivalent in the other compound) is poorly recognised by this enzyme (25). TK-deficient strains are of reduced pathogenicity in immunocompetent individuals but may cause local or systemic disease in immunocompromised individuals (3).

Most ACV-resistant clinical isolates of HSV are TK deficient and cross-resistant to penciclovir - therefore it is very unlikely that a patient failing to respond to therapy with ACV or VAL will respond to FAM (26). However, strains with altered TK or DNA polymerase mutations may be selectively resistant to one or another nucleoside (27). In one small uncontrolled study, the authors report that 10 of 12 immunocompetent and 2 of 5 immunocompromised patients with recurrent GH symptoms that had not responded to ACV or VAL had healing of baseline lesions following open-label FAM 500mg TDS for 7-10 days (15). Partially resistant strains may sometimes be successfully treated with high dose intravenous (IV) ACV and other nucleoside analogues (20). Antivirals with a different mechanism of action may be used to manage ACV-resistant infections; options include foscarnet and cidofovir, which act directly on viral DNA polymerase without prior activation by viral TK and so are active on viruses resistant to ACV due to a mutation in the TK gene (25).

TK-deficient strains of HSV appear less likely to be associated with the development of latency; hence, subsequent clinical reactivations of GH are often caused by ACV-sensitive isolates. For this reason, antiviral prophylaxis of severely immunocompromised patients with acyclovir, VAL, or FAM should be considered after resolution of an acute lesion which was clinically resistant (20, 26).
Table 2) Valaciclovir and famciclovir comparative studies in the acute treatment of GH

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>Median number of days to:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>lesion healing</td>
<td>symptom resolution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of first episode of genital herpes</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Loveless et al* Study A (5)</td>
<td>FAM 250mg, 500mg or 750mg TDS [5 days]</td>
<td>383</td>
<td>7-8</td>
<td>6-8</td>
</tr>
<tr>
<td></td>
<td>ACV 200mg 5/day [5 days]</td>
<td></td>
<td>6-7</td>
<td>7-13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loveless et al Study B and C (5)</td>
<td>FAM 125mg, 250mg or 500mg TDS [10 days]</td>
<td>212 and 356</td>
<td>7-8</td>
<td>8-12</td>
</tr>
<tr>
<td></td>
<td>ACV 200mg 5/day [10 days]</td>
<td></td>
<td>6-7</td>
<td>7-13</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fife et al, 1997 (7)</td>
<td>ACV 200mg 5/day [10 days]</td>
<td>320</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>VAL 1g BD [10 days]</td>
<td>323</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>note – VAL dose used is higher than UK license for this indication</em></td>
<td></td>
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<tr>
<td><strong>Treatment of acute recurrent genital herpes</strong></td>
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<td></td>
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<tr>
<td>Choisdow et al, 2001 (9)</td>
<td>FAM 125mg BD [5 days]</td>
<td>107</td>
<td>5</td>
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<tr>
<td></td>
<td>ACV 200mg 5/day [5 days]</td>
<td>97</td>
<td>5</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Bodsworth et al, 1997 (12)</td>
<td>VAL 500mg BD [5 days]</td>
<td>378</td>
<td>4.4</td>
<td><strong>4.7</strong></td>
</tr>
<tr>
<td></td>
<td>ACV 200mg 5/day [5 days]</td>
<td>361</td>
<td>4.5</td>
<td><strong>4.6</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Rowmanowski B et al, 2000 (22)</td>
<td>FAM 500mg BD [7 days]</td>
<td>150</td>
<td>7</td>
<td>2</td>
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<tr>
<td>(HIV-POSITIVE PATIENTS)</td>
<td>ACV 400mg 5/day [7 days]</td>
<td>143</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

*results of studies A, B and C presented in the same paper

NR – not reported

Bold text – primary endpoints
Table 3) Valaciclovir and famciclovir comparative studies in the suppression of recurrent GH

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>Treatment duration</th>
<th>Time to first recurrence (days)</th>
<th>Pts free of recurrence (%)</th>
<th>Days of viral shedding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wald et al, 2006 (16)</td>
<td>FAM 250mg BD 159</td>
<td>16 weeks</td>
<td>(study duration)</td>
<td>66</td>
<td>RR 1.10 (95% CI 0.94-1.28; p=NS)</td>
<td></td>
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<tr>
<td></td>
<td>VAL 500mg OD 261</td>
<td></td>
<td></td>
<td>72</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>FAM 250mg BD 34</td>
<td>10 weeks</td>
<td></td>
<td>3.2</td>
<td>(RR for FAM of 2.33; 95% CI 1.18-4.89, p=0.014)</td>
<td></td>
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<tr>
<td></td>
<td>VAL 500mg OD 36</td>
<td></td>
<td></td>
<td>1.3</td>
<td></td>
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</tr>
<tr>
<td>Reitano et al, 1998 (17)</td>
<td>VAL 250mg BD 274</td>
<td>52 weeks</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>VAL 1g OD 269</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VAL 500mg OD 266</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>VAL 250mg OD 269</td>
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<td></td>
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<tr>
<td></td>
<td>ACV 400mg BD 267</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Placebo 134</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Conant et al, 2002 (23)</td>
<td>VAL 500mg BD 355</td>
<td>Up to 48 weeks</td>
<td>Primary endpoint = time from randomisation to first recurrence (no absolute data reported)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VAL 1g OD 358</td>
<td></td>
<td>HR for VAL 500mg and 1000mg versus ACV were 0.73 (0.50-1.06; p=NS) and 1.31 (0.94-1.82; p=NS), respectively.</td>
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<tr>
<td></td>
<td>ACV 400mg BD 349</td>
<td></td>
<td>HR for 1000mg OD versus 500mg BD VAL was 1.80 (1.26-2.57; p=0.001), suggesting that the twice daily regimen is superior.</td>
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</tbody>
</table>

Herpes zoster (shingles)

Antivirals for HZ are recommended for adults aged 50 years and over, and adults of any age who:

- Present with severe acute pain or extensive rash
- Have ophthalmic involvement
- Are immunocompromised
- Have Ramsay Hunt Syndrome
- Have atopic eczema
- Have contact with very young infants, immunocompromised individuals, or pregnant women.

Expert opinion is divided as to whether antivirals should routinely be offered to people under the age of 50 years who are not in the categories above - the incidence of post herpetic neuralgia (PHN) is low in people in this age group (therefore will have minimum impact in terms of this) but antivirals may provide benefit for those people who would otherwise have gone on to develop a severe or extensive rash (28). Antivirals should only be started in those who present within 72 hours of rash onset (7 days for ophthalmic infection); however treatment after this time should be considered if they are in one of the above high-risk groups.

1) Valaciclovir versus aciclovir

There has been one main RCT comparing VAL to ACV in the treatment of HZ, in which immunocompetent adults aged at least 50 years who presented within 72 hours of the onset of rash were randomised in a double-blind fashion to treatment with VAL 1g TDS for seven (n=384) or 14 (n=381) days or ACV 800mg five times daily (n=376) for seven days (29). The primary endpoints were time to the complete cessation of pain (pain-free for at least 28 days with no recurrence during the study period), time to cessation of new lesion formation and/or increase in lesion area, and time to ≥50% crusting or healed rash. The main findings were:

- VAL was associated with a shorter time to complete cessation of HZ-associated pain – median of 38 days for the 7-day VAL regimen (HR 1.34; 1.12-1.60; p=0.001) and 44 days for the 14-day regimen (HR 1.22; 1.03-1.46; p=0.03), versus 51 days for the ACV group.

- There were no differences between the...
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groups in terms of the other primary endpoints (cutaneous manifestations), including time to cessation of new lesion formation (3 days) or time to ≥50% crusting or healed rash (5 days).

• VAL was associated with a reduced median duration of pain after rash healing (PHN) – 30 days (7-day regimen) and 35 days (14-day regimen) versus 39 days for ACV (secondary endpoint), and fewer patients randomised to VAL had pain persisting for 6 months (19.3% versus 25.7%; P = 0.02; NNT = 16).

A smaller study (n=57) in Taiwanese patients also found that VAL was associated with faster resolution of pain, with 71.9% of the group pain-free at day 29 versus 48% of the ACV group (p=0.006) (30).

In summary, there is some evidence in immunocompetent patients to suggest VAL may reduce the time to complete cessation of pain, and reduce the duration of PHN when compared to ACV (although there is no evidence of any difference between the two in pain intensity).

2) Famciclovir versus aciclovir

There have been two main published RCTS comparing FAM (three regimens) to ACV in the treatment of acute uncomplicated HZ in immunocompetent adults. In the first, 545 patients presenting within 72 hours of rash onset were randomised to 7 days of treatment with FAM 250mg (n=134), 500mg (n=134) or 750mg (n=138) three times a day, or ACV 800mg five times a day (n=139) (31 – sponsored by SmithKline Beecham). The primary endpoint is not stated; assessments included time to full crusting of lesions, time to cessation of new lesion formation, time to loss of vesicles, time to loss of crusts, time to loss of acute pain (prior to lesion healing) and time to resolution of all zoster-related pain.

• All groups were of comparable efficacy in terms of cutaneous endpoints (as stated above) and acute pain, with a median of 6 days to full crusting, 3 days to cessation of new lesions, 5 days to loss of vesicles, and 20-21 days to loss of crusts.

• According to intention-to-treat analysis, only the FAM 500mg group was associated with a statistically significantly faster resolution of zoster-associated pain than the ACV group (absolute data not reported).

• When only efficacy-evaluable patients treated within 48 hours of rash onset were included in the analysis (n=158), all three doses of FAM were found to be superior to ACV in terms of time to pain resolution. When age was fitted as a covariate in the model, only the 250mg FAM group remained statistically significantly superior to ACV (HR 1.616, 95% CI 1.062-2.458, p=0.025).

The second RCT was of a similar design but compared three different dosing frequencies of FAM – 750mg OD (n=140), 500mg BD (n=142) and 250mg TDS (n=139) to ACV 800mg five times daily (n=138) (32). The primary endpoint was time to full crusting in the intention-to-treat population; secondary endpoints included time to loss of acute pain, loss of vesicles, ulcers and crusts, cessation of new lesion formation in the primary dermatome, and complete healing. (This study did not evaluate the effects of the treatments on duration of post-herpetic neuralgia).

The study had an 80% power to detect a 50% difference in the median time to full crusting between FAM and ACV. The main findings were:

• Median time to crusting was similar between treatment arms – 7 days for FAM 250mg TDS, FAM 500mg BD and ACV, and 8 days for FAM 750mg OD. There were no statistically significant differences between any of the groups for either the intention-to-treat or efficacy evaluable analysis.

• There were no statistically significant differences reported between any of the groups for any of the secondary endpoints studied or in terms of adverse events.

In summary, FAM appears to have a similar efficacy to ACV in terms of resolution of cutaneous symptoms in immunocompetent patients with HZ. Furthermore, once daily administration of FAM appears to result in comparable efficacy to a thrice daily regimen (both 250mg TDS and 750mg OD licensed in the UK). Although an advantage was shown for FAM over ACV in terms of pain resolution in one study, this was apparent for the 250mg group (i.e. licensed UK dose) only in a subgroup analysis involving efficacy evaluable patients treated within 48 hours of rash onset. The definition of ‘efficacy evaluable’ excluded those with crusts at enrolment and those who were non-compliant with treatment, so does not reflect the ‘real world’ scenario. In addition, no absolute data are reported, so the clinical significance of any differences cannot be evaluated.

3) Famciclovir versus valaciclovir

The efficacy of VAL compared to FAM in the treatment of acute HZ in immunocompetent individuals has been assessed in a multicentre RCT involving individuals aged 50 years or above (this inclusion criterion was chosen as guidelines generally recommend antiviral treatment for all patients in this age group) (33). Patients with localised HZ presenting within 72 hours of the onset of rash were randomised to double-blind treatment with VAL 1g TDS
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(n=297) or FAM 500mg TDS (n=300) for 7 days (the FAM dose used is the US licensed dose for this indication; this exceeds the dose recommended in the UK SPC). All participants were otherwise healthy, with no use of topical or systemic antiviral medications within the previous four weeks. The primary endpoint was time to complete resolution of zoster-associated pain; secondary endpoints included time to cessation of zoster-associated abnormal sensations, pain intensity, rash healing, and lesion dissemination. The main findings were:

- There was no difference between the two groups in the primary endpoint (intention-to-treat) - the median duration until resolution of zoster-associated pain was 42 days with VAL versus 49 days with FAM (HR 1.02; 95% CI 0.84-1.23, p=NS).

- No differences were evident between FAM and VAL in rash healing rates – after seven days the rash was considered 100% crusted or healed in 32% of the VAL group and 25% of the FAM group; by 14 days the respective figures were 89% and 82%.

- There were no differences between the groups in terms of resolution of PHN (various analyses carried out but no statistically significant differences noted).

- The incidence of side effects was similar for both treatments, with 34% of the VAL group and 38% of the FAM group reporting at least one adverse event within the first ten days of treatment. The most common included headache, nausea, constipation, diarrhoea and fatigue; such limited treatment in eleven cases (5 with VAL and 6 with FAM).

4) Immunocompromised patients with herpes zoster

There are no data on the efficacy or safety of VAL in the treatment of HZ in immunocompromised individuals.

FAM has been compared to ACV in the treatment of HZ in immunocompromised patients in a multicentre RCT (34). A total of 149 patients aged 12 years and above (mean 43 years) who were immunocompromised following bone marrow (n=100) or solid organ (n=3) transplantation, or oncology treatment (chemotherapy and/or radiotherapy; n=45), were randomised within 72 hours of rash onset to treatment with FAM 500mg TDS (n=72) or ACV 800mg five times a day (n=77) for ten days. The study was designed to demonstrate the equivalence of ACV to FAM with respect to the proportion of patients who developed new lesions whilst on study medication (primary endpoint); other endpoints (superiority testing used for these rather than equivalence) included time to complete healing of all lesions, time to full crusting of all lesions, and time to loss of acute phase pain.

The majority (81%) of patients experienced prodromal symptoms prior to rash appearance and over half (58%) had severe rash (>50 lesions) at enrolment. The main findings were:

- A total of 55 FAM patients (77%) and 56 ACV patients (73%) developed new lesions whilst on study medication – the 95% CI of the intergroup difference was -9.2% to 18.6% which met the predefined criteria for equivalence (i.e. upper limit of the difference was less than 20%).

- There were no significant differences between treatment groups in terms of median time to cessation of new lesion formation (3 days FAM vs. 4 days ACV), time to full crusting (8 days FAM vs. 9 days ACV), time to complete healing of all lesions (20 days FAM vs. 21 days ACV) or median time to loss of acute phase pain (14 days FAM vs. 17 days ACV).

- A total of 2 patients (3%) in the FAM group and 6 patients (8%) in the ACV group developed disseminated zoster during the study.

Pain data were only recorded until complete healing had occurred, therefore there was no comparison of treatments in terms of PHN.

The authors note that immunocompromised patients with HZ are often hospitalised for IV ACV therapy – a comparison of oral FAM with IV ACV would therefore be warranted so that it is compared to clinical practice in such patients.

Individuals with HIV were excluded from this trial, therefore the safety and efficacy of FAM in this patient group has yet to be examined.

The Herpes Management Forum recommends that people with severe immunosuppression (e.g. those with cancers, bone marrow transplants, organ transplants) be admitted for treatment with intravenous ACV because they are at the highest risk of complications and disseminated herpes zoster (35). Therefore RCTs comparing oral FAM and VAL to IV ACV are warranted, in order to establish their efficacy in this patient group compared to the current standard of care.
Table 4 – Valaciclovir and famciclovir comparative studies for the treatment of herpes zoster

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (N)</th>
<th>Median number of days to:</th>
<th>Full crusting</th>
<th>Complete healing/ loss of crusts</th>
<th>Cessation of new lesions</th>
<th>Resolution of pain (acute)</th>
<th>Resolution of PHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degroof et al, 1994 (31)</td>
<td>FAM 250mg TDS 7 dy (134)</td>
<td></td>
<td>6</td>
<td>21</td>
<td>3</td>
<td>No absolute data presented</td>
<td></td>
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<tr>
<td></td>
<td>FAM 500mg TDS 7 dy (134)</td>
<td></td>
<td>6</td>
<td>20</td>
<td>3</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>FAM 750mg TDS 7 dy (138)</td>
<td></td>
<td>6</td>
<td>21</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACV 800mg 5/day 7 dy (139)</td>
<td></td>
<td>6</td>
<td>21</td>
<td>3</td>
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<td></td>
</tr>
<tr>
<td>Shafran et al, 2004 (32)</td>
<td>FAM 250mg TDS 7 dy (139)</td>
<td></td>
<td>7</td>
<td>20</td>
<td>3</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FAM 500mg BD 7 dy (142)</td>
<td></td>
<td>7</td>
<td>19</td>
<td>3</td>
<td>19</td>
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</tr>
<tr>
<td></td>
<td>FAM 750mg OD 7 dy (140)</td>
<td></td>
<td>8</td>
<td>20</td>
<td>3</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACV 800mg 5/day 7 dy (138)</td>
<td></td>
<td>7</td>
<td>20</td>
<td>3</td>
<td>14</td>
<td></td>
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<tr>
<td>Tyring et al, 2000 (33)</td>
<td>VAL 1g TDS 7 dy (297)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
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<tr>
<td></td>
<td>FAM 500mg TDS 7 dy (300)</td>
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<td></td>
<td></td>
<td>49</td>
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<tr>
<td>Beutner et al, 1995 (29)</td>
<td>VAL 1g TDS 7 dy (384)</td>
<td></td>
<td></td>
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<td>3</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>VAL 1g TDS 14 dy (381)</td>
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<td></td>
<td></td>
<td>3</td>
<td>44&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>ACV 800mg 5/day 7 dy (376)</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>51</td>
<td></td>
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<tr>
<td>Tyring et al, 2001 (34)</td>
<td>FAM 500mg TDS 10 dy (71)</td>
<td></td>
<td>8</td>
<td>20</td>
<td>4</td>
<td>14</td>
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<tr>
<td>(Immunocompromised)</td>
<td>ACV 800mg TDS 10 dy (77)</td>
<td></td>
<td>9</td>
<td>21</td>
<td>3</td>
<td>17</td>
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</tbody>
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