PUBLIC SUMMARY DOCUMENT

Product: Famciclovir, Tablet, 500 mg, Famvir®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission requested an extension to the PBS listing of famciclovir 500 mg tablets to include the treatment of moderate to severe recurrent orolabial herpes in patients with human immunodeficiency virus (HIV) infection and CD4 cell counts of less than 500 per microlitre.

2. Background

Famciclovir 125 mg and 250 mg tablets have been listed on the PBS since 1995 for the treatment of herpes zoster and 1996 for genital herpes. Famciclovir 500 mg tablets were recommended for listing as a secretariat listing at the March 2006 meeting and listed on the PBS on 1st April 2006 for immunocompromised patients with genital herpes or herpes zoster.

3. Registration Status

Famciclovir is registered for:

- Treatment of herpes zoster infection in adult patients who commence therapy within 72 hours of the onset of the rash.
- The treatment of recurrent episodes of genital herpes in adults and adolescents aged 12 years and older;
- Suppression of recurrent genital herpes
- In immunocompromised patients for
    - Treatment of uncomplicated herpes zoster;
    - Treatment of recurrent herpes simplex;
    - Suppression of recurrent herpes simplex.

4. Listing Requested and PBAC's View

Authority Required

Episodic treatment of moderate to severe recurrent orolabial herpes in patients with HIV infection and CD4 cell counts of less than 500 per micro litre;

Suppressive therapy of moderate to severe recurrent orolabial herpes in patients with HIV infection and:

a) CD4 cell counts of less than 200 per microliter; or
b) other opportunistic infections or AIDS defining tumours.

Microbiological confirmation of diagnosis (viral culture, antigen detection, or nucleic acid amplification by PCR) is required but need not delay treatment.

NOTE

Famciclovir 500 mg is not PBS subsidised for herpes zoster, chicken pox, genital herpes or other herpes simplex infections in immunocompromised patients.

The PBAC considered it appropriate to use the CD4 cell limit of less than 150 per microliter, as used in the current aciclovir listing, in the famciclovir suppressive therapy listing.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Famciclovir 500 mg provides a treatment option for immunocompromised patients with HIV infection who have moderate to severe orolabial herpes. As opposed to other available antivirals subsidised on the PBS, the twice daily dosage regimen is of assistance to this patient group who have an already high pill burden.

6. Comparator

The submission nominated aciclovir for patients with advanced HIV disease (CD4 cell count < 200 million per litre); and no treatment (placebo) for patients with less advanced HIV disease (CD4 cell count ≥ 200 million per litre, but < 500 million per litre).

The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented a randomised trial comparing famciclovir 500mg twice daily with aciclovir 400mg five-times daily in HIV positive patients with a recurrent herpes simplex infection (as evidence for episodic treatment in patients with less advanced disease); and a randomised placebo-controlled trial of famciclovir in the suppression of recurrent herpes simplex in persons infected with HIV (as evidence for suppressive therapy in patients with advanced disease or other opportunistic infections or AIDS defining tumours).

For episodic treatment in patients with less advanced HIV disease (where placebo is the appropriate comparator), the submission relied on the PBAC's acceptance (at its June 1996 meeting) of famciclovir for episodic treatment of genital herpes in immunocompetent patients, which presented two trials demonstrating that famciclovir is superior to placebo. The submission claimed it is reasonable to assume that the superiority of famciclovir over placebo would also hold true for the treatment of orolabial herpes in patients with HIV. Limited data were presented to support this claim.

For suppressive treatment in patients with advanced HIV disease (where aciclovir is the appropriate comparator), the submission relied on the PBAC's acceptance that famciclovir and aciclovir are equivalent for the suppression of genital herpes in immunocompetent patients (September 1997 PBAC meeting) and claimed it is reasonable to assume that equivalence of famciclovir and aciclovir would also hold true for the suppression of orolabial herpes in patients with HIV. No data were presented to support this claim.

The trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Lavender E Trial 083	A randomised double blind double dummy multicentre acyclovir controlled study to assess the safety and efficacy of oral famciclovir in HIV positive patients with recurrent herpes simplex infection. SmithKline Beecham 03 1997	Romanowski B et al. Efficacy and safety of famciclovir for treating mucocutaneous herpes simplex infection in HIV-infected individuals. AIDS 2000: 14:1211-1217
Jurewicz R. Trial 102	A randomised double blind placebo controlled single centre cross over	Schacker T et al. Famciclovir for the suppression of symtomatic and

Trial/First author	Protocol title	Publication citation
	study to assess the safety and efficacy of oral famciclovir in the suppression of symptomatic and asymptomatic recurrent herpes simplex in persons infected with HIV. SmithKline Beecham 03 1997	asymptomatic herps simplex virus reaction in HIV-infected persons. Annals of Internal Medicine 1998:128:21-28

8. Results of Trials

Episodic treatment

Trial 083 was a pre-specified non-inferiority trial. For the primary outcome, proportion of patients with new lesion formation, famciclovir was considered equivalent to aciclovir if the upper limit of the two-sided 95% confidence interval of the difference in proportions was less than 15%.

The results of the primary outcome from Trial 083, the proportion of patients with new lesion formation while on the study drug, showed that the pre-specified non-inferiority criterion was met. The 95% CI suggested that there could be up to 23.6% of patients on famciclovir with new lesion formation (compared with 20.0% of aciclovir patients).

From the results of the pre-defined subgroup analyses similar proportions of patients with anogenital and orolabial herpes experienced new lesions and the differences between treatments were also similar. For the analyses by CD4 count and CDC classification, however, higher proportions of famciclovir patients with less-advanced disease experienced new lesions.

For the secondary outcomes, time to complete healing of all lesions, time to loss of lesion-associated symptoms and time to cessation of viral shedding, the non-inferiority criterion was met if the 95% confidence interval of the hazard ratio included one. Each of the above time-to-event analyses met the non-inferiority criterion.

Suppressive therapy

During the first period of the crossover study, Trial 102, famciclovir-treated patients had statistically significantly fewer days of viral shedding than patients treated with placebo, and this conclusion held, regardless of site.

Significantly fewer famciclovir-treated patients experienced HSV shedding from the anogenital site and from any site compared with placebo during period 1 of Trial 102.

The rates of adverse events in Trial 083 were similar in famciclovir- and aciclovir-treated patients. The most common adverse events were headache, nausea and diarrhoea. In Trial 102, similar rates of adverse events were observed in patients treated with famciclovir and placebo. The most common adverse events were nausea, granulocytopenia, dizziness and maculo-papular rash.

9. Clinical Claim

The submission claimed that famciclovir is no worse than aciclovir in terms of effectiveness and toxicity for the episodic treatment of orolabial herpes in patients with HIV infection. The

PBAC considered that this description may be reasonable, however, there was uncertainty about the appropriateness of the pre-defined non-inferiority criteria.

The submission further claimed that famciclovir has significant advantages in effectiveness over placebo and has similar toxicity for the suppressive treatment of orolabial herpes in patients with HIV infection. Based on the supporting data, the PBAC considered this description to be reasonable.

10. Economic Analysis

Two preliminary (trial-based) economic evaluation analyses were presented for each of episodic treatment and suppressive therapy: one comparing famciclovir versus aciclovir (in patients with advanced HIV disease); the other comparing famciclovir versus placebo (in patients with less advanced HIV disease).

Episodic treatment

Patients with advanced HIV disease:
The submission presented a cost minimisation analysis. Famciclovir was less expensive than aciclovir.

Patients with less advanced HIV disease:
A cost effectiveness analysis was conducted, comparing the results from the famciclovir arm of Trial 083 in patients with HIV and orolabial herpes with the results from the placebo arm of Trial 035, in immunocompetent patients with genital herpes, presented in the June 1996 submission.

The trial-based incremental cost/additional patient avoiding new HSV lesions was estimated to be < $1,000.

Suppressive therapy

Patients with advanced HIV disease:
The submission presented a cost minimisation analysis. Famciclovir was less expensive than aciclovir.

Patients with less advanced HIV disease:
The submission presented cost effectiveness analyses. The trial-based incremental cost/additional patient avoiding HSV shedding was estimated to be < $15,000; and the trial-based incremental cost/additional patient avoiding lesions or symptoms was estimated to be < $15,000.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be < 5,000 in Year 4.

The financial cost/year to the PBS was estimated to be < $5 million in Year 4.

12. Recommendation and Reasons

The PBAC recommended the listing of famciclovir for suppressive therapy of moderate to severe recurrent oral or labial herpes in patients with HIV infection with CD4 cell counts of less than 150 per microliter or other opportunistic infections or AIDS defining tumours, on a cost-minimisation basis against aciclovir at the price proposed in the submission. The equi-effective doses are the Australian approved doses for both agents, that is, famciclovir 500 mg twice daily and aciclovir 800 mg four times daily.

The PBAC further recommended the listing of famciclovir for the episodic treatment of moderate to severe recurrent oral or labial herpes in patients with HIV infection and CD4 cell counts of less than 500 per micro litre on a cost-effectiveness basis against placebo at the price proposed in the submission.

The PBAC considered that the evidentiary basis of the submission is poor. However, the Committee agreed that the totality of evidence for episodic treatment suggests that famciclovir would be equivalent to aciclovir in terms of efficacy in suppressing oral or labial herpes in the patients targeted by the restriction. The Committee accepted that famciclovir is associated with similar toxicity to aciclovir but with a reduced pill burden. The PBAC considered it appropriate to use the CD4 cell limit of less than 150 per microliter, as used in the current aciclovir listing, in the famciclovir suppressive therapy listing.

In the episodic treatment of oral or labial herpes the Committee considered that the trial based incremental cost per additional patient avoiding new HSV lesions of <$1,000 represented acceptable cost effectiveness in a high risk group with a demonstrated clinical need.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation

FAMCICLOVIR, tablet, 500 mg

Restriction: Authority Required

Episodic treatment of moderate to severe recurrent oral or labial herpes in a patient with HIV infection and a CD4 cell count of less than 500 million per litre;

Suppressive therapy of moderate to severe recurrent oral or labial herpes in a patient with HIV infection and:

a) a CD4 cell count of less than 150 million per litre; or

b) other opportunistic infections or AIDS defining tumours.

Microbiological confirmation of diagnosis (viral culture, antigen detection, or nucleic acid amplification by PCR) is required but need not delay treatment.

NOTE:

Famciclovir 500 mg is not PBS subsidised for herpes zoster, chicken pox, genital herpes or other herpes simplex infections in immunocompetent patients.

Maximum quantity: 56

Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis welcomes the recommendation of the PBAC and thanks the Committee for their decision.