ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien Austria	Famvir 125 mg – Filmtabletten	125 mg	Film-coated tablets	Oral use
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien Austria	Famvir 250 mg – Filmtabletten	250 mg	Film-coated tablets	Oral use
Austria	Novartis Pharma GmbH Brunner Strasse 59 1235 Wien Austria	Famvir 500 mg – Filmtabletten	500 mg	Film-coated tablets	Oral use
Cyprus	Demetriades & Papaellinas Ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Famvir	125 mg	Film-coated tablets	Oral use
Cyprus	Demetriades & Papaellinas Ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Famvir	250 mg	Film-coated tablets	Oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	125 mg	Film-coated tablets	Oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	500 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Famvir	125 mg	Film-coated tablets	Oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Famvir	250 mg	Film-coated tablets	Oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Famvir	500 mg	Film-coated tablets	Oral use
France	Novartis Pharma S.A.S. 2 - 4, rue Lionel Terray 92500 Rueil-Malmaison France	Oravir	125 mg	Film-coated tablets	Oral use
France	Novartis Pharma S.A.S. 2 - 4, rue Lionel Terray 92500 Rueil-Malmaison France	Oravir	500 mg	Film-coated tablets	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg Germany	Famvir 125 mg Filmtabletten	125 mg	Film-coated tablets	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg Germany	Famvir 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg Germany	Famvir Zoster 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz Germany	Famciclovir-Sandoz 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz Germany	Famciclovir-Sandoz 500 mg Filmtabletten	500 mg	Film-coated tablets	Oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz Germany	Famciclovir-SB 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Germany	Grünwalder Gesundheitsprodukte GmbH Ruhlandstr. 5 83646 Bad Tölz Germany	Famciclovir-SB Zoster 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis Greece	Famvir	125 mg	Film-coated tablets	Oral use
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis Greece	Famvir	250 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Greece	Novartis (Hellas) S.A.C.I. 12th Km National Road No. 1 GR-144 51 Metamorphosis Greece	Famvir	500 mg	Film-coated tablets	Oral use
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest Hungary	Famvir	125 mg	Film-coated tablets	Oral use
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest Hungary	Famvir	250 mg	Film-coated tablets	Oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	125 mg	Film-coated tablets	Oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø Denmark	Famvir	500 mg	Film-coated tablets	Oral use
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	125 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	250 mg	Film-coated tablets	Oral use
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	750 mg	Film-coated tablets	Oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famvir	125 mg	Film-coated tablets	Oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famvir	250 mg	Film-coated tablets	Oral use
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famvir	500 mg	Film-coated tablets	Oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famciclovir Sandoz	125 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famciclovir Sandoz	250 mg	Film-coated tablets	Oral use
Italy	Sandoz S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio Italy	Famciclovir Sandoz	500 mg	Film-coated tablets	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg Germany	Famvir 125 mg Filmtabletten	125 mg	Film-coated tablets	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg Germany	Famvir 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg Germany	Famvir Zoster 250 mg Filmtabletten	250 mg	Film-coated tablets	Oral use
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	125 mg	Film-coated tablets	Oral use
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	250 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Netherlands	Novartis Pharma B.V. P.O. Box 241 6800 LZ Arnhem The Netherlands	Famvir	125 mg	Film-coated tablets	Oral use
Netherlands	Novartis Pharma B.V. P.O. Box 241 6800 LZ Arnhem The Netherlands	Famvir	250 mg	Film-coated tablets	Oral use
Netherlands	Novartis Pharma B.V. P.O. Box 241 6800 LZ Arnhem The Netherlands	Famvir	500 mg	Film-coated tablets	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes 764.E-08013 Barcelona Spain	Famvir	125 mg	Film-coated tablets	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes 764.E-08013 Barcelona Spain	Famvir	250 mg	Film-coated tablets	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes 764.E-08013 Barcelona Spain	Famvir	500 mg	Film-coated tablets	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes 764.E-08013 Barcelona Spain	Famvir	750 mg	Film-coated tablets	Oral use
Sweden	Novartis Sverige AB Box 1150 183 11 Täby Sweden	Famvir	125 mg	Film-coated tablets	Oral use

Member State EU / EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	Novartis Sverige AB Box 1150 183 11 Täby Sweden	Famvir	250 mg	Film-coated tablets	Oral use
Sweden	Novartis Sverige AB Box 1150 183 11 Täby Sweden	Famvir	500 mg	Film-coated tablets	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	125 mg	Film-coated tablets	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	250 mg	Film-coated tablets	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	500 mg	Film-coated tablets	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Famvir	750 mg	Film-coated tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF FAMVIR AND ASSOCIATED NAMES (SEE ANNEX I)

Famvir (famciclovir) was included in the list of products for SPC harmonisation and a referral was triggered in order to resolve divergences and harmonise the nationally authorised SPCs across Europe. The scope of the referral included all strengths (125mg, 250mg, 500mg and 750mg) and licenses.

Famciclovir is the oral prodrug of the antiviral nucleoside analogue penciclovir, which has activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). Following oral administration, famciclovir undergoes extensive first-pass metabolism to be transformed into penciclovir. The absolute bioavailability of penciclovir after administration of famciclovir is 77%.

In infected cells, penciclovir is rapidly converted via viral thymidine kinase to penciclovir monophosphate which, in turn, is converted to penciclovir triphosphate by cellular kinases. Penciclovir triphosphate resembles deoxyguanosine triphosphate (dGTP), a component of DNA. The viral DNA polymerase mistakenly incorporates the nucleoside analogue, penciclovir triphosphate, into the growing viral DNA strand instead of dGTP, which results in termination of the viral DNA chain and halting of viral replication. Thus, penciclovir is virustatic. Penciclovir reaches its maximum plasma concentration within 1 hour of administration.

Section 4.1 Therapeutic indication

Several indications were identified for Famvir in the SPCs of different MSs.

Having considered available data and current scientific knowledge, the CHMP considered the following as the harmonised indications:

Varicella zoster virus (VZV) infections – **herpes zoster**

Famvir is indicated for

- the treatment of herpes **zoster** and **ophthalmic** zoster in **immunocompetent** adults (see section 4.4)
- the treatment of herpes zoster in **immunocompromised** adults (see section 4.4)

Herpes simplex virus (HSV) infections – **genital herpes**

Famvir is indicated for

- the treatment of **first and recurrent** episodes of genital herpes in **immunocompetent** adults
- the treatment of **recurrent** episodes of genital herpes in **immunocompromised** adults
- the suppression of **recurrent** genital herpes in **immunocompetent** and **immunocompromised** adults

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV[1]-infection (see section 5.1).

A break down of the discussions held per indication is shown below.

a) HERPES ZOSTER IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED ADULTS

The pivotal studies 007 and 008 formed the basis of initial registration dossiers. Study 007 was a randomised, double-blind, double-dummy, active-controlled study. Study 008 was a randomised, double-blind, placebo-controlled study. Immunocompetent patients with uncomplicated herpes zoster were enrolled in both studies. The primary efficacy endpoint in both studies was time to full crusting of lesions in the primary affected dermatomal region in the intent-to-treat (ITT) population. Secondary endpoints included time to loss of each vesicles, ulcers and crusts; duration of viral shedding; time to loss of acute pain; and duration of post-herpetic neuralgia (PHN).

[1] HIV: human immunodeficiency virus

Study 008 demonstrated statistically significant differences of famciclovir 750mg tid (*ter in die,* three times a day) as compared to placebo with respect to the primary as well as several secondary endpoints. The choice of placebo as a comparator was however considered disputable given the available active treatment option aciclovir. The CHMP agreed that famciclovir resulted in a significant reduction in time to resolution of cutaneous signs of herpes zoster. In the acute treatment of herpes zoster famciclovir 750mg tid resulted in a shorter time to full crusting than placebo, and both 750mg and 500mg tid resulted in shortened time to loss of vesicles and time to loss of ulcers. The design of Study 007 was considered to have some deficiencies. Superiority was not shown for the main outcome measures and concluding from statistically not different results on non-inferiority was not possible. However, the data were considered supportive.
Study 086 was a randomised, double-blind, double-dummy, active-controlled multicentre study. Patients were enrolled if they were immunocompromised following bone marrow or solid organ transplantation, or oncology treatment and had uncomplicated herpes zoster.
The primary efficacy parameter was the proportion of patients with new lesions while on study medication. Secondary efficacy parameters included time to full crusting of lesions, time to complete healing, and evaluations of pain and dissemination. Famciclovir was effective in the treatment of herpes zoster in immunocompromised patients. It was equivalent to aciclovir in the prevention of new lesion formation and there were no significant differences between the 2 treatment groups in any of the efficacy parameters. Additionally, the reduced dosing frequency of famciclovir gave a greater patient acceptability. It was however noted that although the secondary endpoints results did not indicate a difference, the study was not powered for proving non-inferiority.
Based on the available data, the CHMP agreed that the indication treatment of herpes zoster in immunocompetent and immunocompromised patients was recommended.

b) OPHTALMIC ZOSTER IN IMMUNOCOMPETENT ADULTS

Study 098 was a multicentre randomised, double-blind, double-dummy study, comparing famciclovir 500mg tid with aciclovir 800mg 5 times daily. Patients with localized herpes zoster involving the ophthalmic branch of the trigeminal nerve were enrolled. The primary efficacy endpoint was the proportion of patients who had an ocular manifestation during the study (7-day treatment phase and 6-month follow-up period).
The proportion of patients who experienced an ocular manifestation during the study was similar between famciclovir and aciclovir recipients. The proportion of patients with severe ocular manifestations was also similar in both treatment groups. The percentage of patients who experienced a loss in visual acuity during the study was twice as high for the aciclovir recipients as compared to those who received famciclovir. For either the primary or secondary efficacy endpoints, there were no significant differences.
The CHMP agreed that the active treatments lead to a reduction in the rate of complications of ophthalmic zoster; the extent of which however remains disputable. At that time the clinical benefits of aciclovir treatment had been well established and aciclovir was the standard of care for minimizing the ocular complications associated with ophthalmic zoster. Therefore, a placebo arm was not included, which makes comments on the absolute effectiveness of antiviral agents in preventing ocular complications in this study tenuous. Nevertheless, in comparison with literature reports for untreated or placebo-treated patients, famciclovir appeared to reduce important ocular manifestations.
The CHMP agreed that the indication treatment of ophthalmic zoster in immunocompetent patients was supported by the available data.

c) GENITAL HERPES, FIRST AND RECURRENT EPISODES IN IMMUNOCOMPETENT ADULTS AND RECURRENT EPISODES IN IMMUNOCOMPROMISED ADULTS

Studies 004, 011, and 040 were randomised, multicentre studies. Aciclovir was used as a comparator and the primary endpoint was time to cessation of viral shedding. Studies 035 and 036 were randomised, double-blind, placebo-controlled multicentre trials designed to compare the efficacy and safety of 3 doses of famciclovir (125mg, 250mg, 500mg) with that of placebo for acute treatment of a recurrent episode of genital herpes. Patients had to have lesions in the genital area. These studies demonstrated that famciclovir was significantly better than placebo in the treatment of recurrent

genital herpes. However, the selection of placebo controls for both studies was questionable. The pivotal studies were conducted with different famciclovir dosing arms.
Study 083 was presented to show efficacy in immunocompromised patients with herpes simplex virus infections. The study was a randomised, aciclovir-controlled, double-blind, double-dummy multicentre study of famciclovir vs. aciclovir in clinic-initiated episodic treatment of recurrent muco-cutaneous herpes simplex virus infections in HIV-infected patients. For the primary efficacy parameter, confidence intervals for the difference in proportions (famciclovir minus aciclovir) were used to assess treatment effects. Famciclovir was considered equivalent to aciclovir if the upper limit of the 2-sided 95% confidence interval was less than 15%. Secondary variables included proportion of patients who developed new lesions during the study period (including time off study medication), time to complete healing, time to cessation of viral shedding and time to loss of lesion pain. Study 083 showed that famciclovir was as effective against herpes simplex in HIV positive patients as aciclovir.

The CHMP agreed that the indication treatment of first and recurrent episodes of genital herpes in immunocompetent patients and treatment of recurrent episodes of genital herpes in immunocompromised patients was supported by the available data.

d) SUPPRESSION OF RECURRENT GENITAL HERPES IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED ADULTS

To support the therapeutic benefit of famciclovir for the suppressive treatment of genital herpes, one dose-finding study (study 024) and two pivotal studies (studies 033 and 049) in immunocompetent patients, and one dose finding study (study 102) in immunocompromised patients were presented.
All genital herpes suppression trials were placebo controlled. Pivotal studies 033 and 049 in immunocompetent patients were randomised, double-blind, placebo controlled trials. Patients who met eligibility criteria were randomly assigned to receive either famciclovir (125mg tid, 250mg bid, or 250mg tid.) or placebo for 52 weeks. The patient population was comprised of patients who were candidates for suppressive treatment. Results from studies 033 and 049 showed a significant effect of famciclovir with regard to suppression of recurrent genital herpes.
Study 024 was a randomised, double-blind, placebo-controlled trial which looked at time to first recurrence. The results showed that both bid (*bis in die*, twice a day) regimens (125 and 250 bid) were significantly better than placebo. Most of the analyses performed showed that only famciclovir 250mg bid gave significantly better results than placebo.
Study 102 was a randomised, double-blind, placebo-controlled, crossover study to assess the safety and efficacy of oral famciclovir in the suppression of symptomatic and asymptomatic recurrent genital herpes in HIV-infected patients. Participants were randomly assigned to receive either famciclovir 500mg or placebo bid for 8 weeks, followed by a 7-days wash-out period and then by a second 8-week period during which the patients had the regimen not experienced during the first period. The primary efficacy parameter was the number (%) of days of viral shedding from anogenital sites. Key secondary efficacy parameters were the number (%) of days of viral shedding from any site and the number (%) of days of site-specific viral shedding during each treatment period.
All patients who initiated study medication during Period 1 were included in the ITT analysis for that period. There were 48 patients enrolled and treated. Of these, only 27 completed the study. A total of 14 patients were withdrawn in Period 1 and 7 patients were withdrawn in Period 2. No differences were noted between treatment groups for time of withdrawal. The duration of the study was considered too short to allow for a reliable assessment of the prophylactic efficacy of famciclovir. However, it was noted that the proportion of placebo recipients with shedding from anogenital sites in Period 1 was approximately 4 times greater than that of famciclovir-treated patients with anogenital shedding, and differences between treatment groups in proportions of patients with shedding were statistically significant in both Period 1 and cross-over analyses.

The CHMP acknowledged that no comparative study with aciclovir was conducted. However, it agreed that the indication suppression of recurrent genital herpes in immunocompetent and immunocompromised adults was supported by the available data.

Section 4.2: Posology and Method of Administration

HERPES ZOSTER

HERPES ZOSTER IN IMMUNOCOMPETENT ADULTS

Several doses and regimens (bid, tid) were studied in different clinical trials. Based on available data, the CHMP considered that the 500mg tid regimen appeared to be more efficacious than the 250mg tid regimen, with respect to the investigated endpoints. The 750mg tid regimen did not demonstrate any advantage compared to the 500mg tid regimen.
The CHMP endorsed the 500mg tid dose during a period of 7 days for this indication.

HERPES ZOSTER IN IMMUNOCOMPROMISED ADULTS

In study 086, immunocompromised patients with herpes zoster were treated for 10 days with famciclovir 500mg tid or aciclovir 800mg tid for 10 days. The famciclovir 500mg tid dose regimen was chosen as representing the highest approved dose for herpes zoster in immunocompetent patients. The 10-day treatment duration was chosen to maximize the efficacy in this 'at risk' population.
The CHMP considered that the study submitted in support of this indication (086) had several deficiencies (e.g. primary endpoint "new lesion formation while on medication"of questionable relevance, study not powered for comparison of secondary endpoints), but the data indicated a similar efficacy for famciclivir as aciclovir 5 x 800mg/day. The proposed regimen (500mg bid) is also in line with current recommendations and with the SPCs in the vast majority of the MSs.

OPHTHALMIC ZOSTER IN IMMUNOCOMPETENT ADULTS

In study 098 the famciclovir 500mg tid dose proved to be non-inferior to aciclovir 5 x 800 mg/day. It was noted that this dose is also in line with current literature recommendations (*Dworkin RH et al*, Clin. Inf. Dis. 2007; 44 (Suppl. 1): S1-26, Volpi A. Herpes 2007; 14 (Suppl. 2): 35A-39A). No disharmony on the dosage regimen for this indication was noted across MS. The CHMP noted that the Study 098 appeared acceptable with respect to design as well as results. The suggested dose of 500 mg tid famciclovir for 7 days could be endorsed.

GENITAL HERPES

IMMUNOCOMPETENT ADULTS

INITIAL (FIRST) EPISODE

Several doses were investigated in pivotal studies (004, 011, 040). No statistically significant differences were observed between all famciclovir dose groups and aciclovir for all primary efficacy parameters in all three clinical trials. In study 004 the 750mg tid famciclovir dose was not superior to either the 250mg tid or 500mg tid dose on the primary efficacy endpoints and was not included in subsequent studies.
For the 125mg famciclovir dose group there appeared to be a decrease in efficacy for some endpoints when compared with the higher dose groups that was consistent across the two trials. The famciclovir 125mg dose also appeared inferior to the higher doses in primary patients experiencing new lesions after start of antiviral treatment. As primary patients typically experience a more severe first episode than patients experiencing a recurrent episode (*Sacks* 1995), it was deemed that a starting dose of 125mg famciclovir would be less efficacious than a higher dose. No differences in efficacy outcomes were noted between the 250mg and 500mg doses of famciclovir. All doses of famciclovir were well tolerated with no differences in either the nature or frequency of adverse events among the different doses of famciclovir. Therefore, the 250mg dose of famciclovir was selected as the lowest effective dose to treat first episode genital herpes.

EPISODIC TREATMENT OF RECURRENT HERPES AND SUPPRESSION OF RECURRENT HERPESNo inconsistencies were observed with regards to episodic treatment across MSs therefore 125mg twice bid for five days was considered as the acceptable posology for this indication.

Regarding suppression, the posology of 250mg bid is in accordance with existing guidelines. In the two pivotal studies three regimen were investigated: 125mg tid, 250mg bid, 250mg tid. All regimens were superior to placebo in terms of the two primary endpoints, and these were considered relevant. In studies 033, and 049 it was noted that a dose-response relationship was not observed.
The CHMP noted that the daily dose recommended for episodic treatment of recurrent genital herpes (125mg bid) in immunocompetent patients is lower than the recommended dose for suppression (250mg bid). The doses selected for episodic treatment and suppression of recurrent genital herpes in the immunocompetent patient were determined in replicate, multiple-dose, placebo-controlled trials. Two studies (035 and 036) were presented to examine three doses (125mg, 250mg and 500mg bid for five days) for the episodic treatment of recurrent genital herpes in immunocompetent patients. All three doses were significantly superior to placebo in the time to healing of lesions, loss of symptoms and the time to cessation of viral shedding. There were no differences in efficacy noted among the three active dose groups. Overall, there were no differences in the nature, frequency or severity of adverse events among the three active dose groups or placebo. Therefore, 125mg bid dose was identified as the lowest effective dose.
The dose regimen for suppression of recurrent genital herpes in immunocompetent patients was addressed in three studies too. A dose ranging study (024) found that both 125mg and 250mg bid regimens were significantly better than placebo. However, the 250mg bid dose had the greatest effect on suppression in analysis of time to the first clinically confirmed recurrence of genital herpes. While it appears paradoxical that the dose recommended to suppress recurrence of genital herpes is larger than that used to treat the active flare of a recurrence, the key endpoint was the time to clinically confirmed recurrence. On this endpoint the 250mg bid dose was superior to the 125mg bid dose.
In the pivotal studies 033 and 049, the 250mg bid dose was assessed along with 125mg tid and 250mg tid doses. All dose regimens were effective compared to placebo and similar to each other based on time to first clinically confirmed recurrence and proportion of patients free from virologically confirmed lesion episodes at 6 months.
Based on results of these three studies, the 250mg bid dose was selected for suppression of genital herpes since it was superior to the once daily and 125mg bid regimens in study 024, its effectiveness was demonstrated in all three studies, and there was no clear advantage of the tid regimens over it in studies 033 and 049.
The CHMP concluded that the available data supported the efficacy and safety of the selected doses, both, the 125mg bid for treatment of recurrent episodes and the 250bid for suppressive therapy of genital herpes.

IMMUNOCOMPROMISED ADULTS

EPISODIC TREATMENT OF RECURRENT HERPES

Famvir is indicated for episodic treatment of recurrent herpes simplex infections in the HIV-infected patient where the recommended dose regimen is 500 mg twice daily for seven days. Thus the CHMP endorsed the restriction to recurrent genital herpes in HIV infected patients which reflects the outcome of the respective clinical study (083).
A summary of the combined studies 102 and 195 show the benefits of famciclovir in suppressing HSV recurrence in the immunocompetent patient to the HIV-infected patient. In Study 102, 83% of HIV-infected patients receiving famciclovir remained recurrence-free as compared to 42% of patients receiving placebo. Over the 4 months of Study 195, 90% of HIV-infected patients remained free from clinically diagnosed recurrences. The results of both studies are similar to what was reported by (Mertz, et al 1997) for immunocompetent patients in a 4-month study where 90% of patients receiving famciclovir remained free from virologically confirmed genital herpes as compared with 48% of placebo-treated patients. While both Studies 102 and 195 were small in size and breadth of patients

included, the results for suppression of viral recurrence were consistent and extended to both patients with CD4+ cell counts below and above 200 cells/mm3. The duration of the active treatment period was only 8 weeks. Although uncontrolled, study -195 provided some supportive evidence for the suppressive efficacy also in terms of other endpoints (virological/clinical recurrence).
Although the pivotal study for this indication/group (083) presented with some deficiencies, which taken together preclude a reliable conclusion on non-inferiority of the 500mg famciclovir bid regimen versus 5x 400mg aciclovir, it was acknowledged that this regimen is approved for the majority of the EU MSs. An article by (*Strick, et al* 2006) discussed the merits of suppressive versus episodic treatment of HSV in the HIV-infected patient. In summary, famciclovir 500mg bid. is effective and safe in suppressing recurrent HSV outbreaks in HIV-infected patients. The CHMP thus endorsed the 500mg bid for seven days as the approved posology in this indication.

SUPPRESSION OF RECURRENT HERPES

The 500mg bid regimen is recommended by some of the guidelines and no other regimen was studied. Study 102 compared the famciclovir 500mg bid dose with placebo. The approved daily dose regimen for either episodic or suppressive therapy of recurrent genital herpes in HIV-infected patients is 500mg bid. The recommended dose for treating HIV-infected patients is larger than that recommended for immunocompetent patients as clinical experience and prescribing practice suggested that higher doses of antivirals are required to provide adequate suppression in HIV-infected patients. Moreover, famciclovir 500 mg bid was found in clinical trials to be effective, safe and well tolerated in this group of patients.
The posology was thus endorsed by the CHMP.

Special population
The dose recommendations proposed for patients with renal impairment, renal impairment on haemodialysis, hepatic impairment and elderly were endorsed by the CHMP.
Famvir is not recommended for use in children and adolescents below 18 years of age as no safety and efficacy data have been generated in this patient population.

Considerations on the 750mg dose
The CHMP noted the recommended doses for the different posologies as indicated above. The highest dose to be administered based on the assessment of the data submitted is 500mg famciclovir. Thus, the 750mg tablet strength is considered obsolete. The CHMP thus recommends the revocation of this strength in the concerned MSs. Within the EEA, the 750mg tablet strength is currently approved only in Ireland, UK and Spain.

Section 4.3: Contraindications

This section was updated to remove patient populations not studied as this should be mentioned in section 4.4. Famvir should not be used in case of hypersensitivity to the active substance, any of the excipients and penciclovir.

Section 4.4: Special warnings and precautions for use

This section was updated to reflect the use in special populations which had previously been included in section 4.3. Additionally, a warning was revised to state that even though the frequency of viral shedding was reduced with the use of an antiviral, the risk of transmission is still theoretically possible so patients should be advised to avoid intercourse. A recent publication, by *Money B et al*, supported the inclusion of this warning, which was endorsed by the CHMP.

Section 4.5: Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified. However, famciclovir is rapidly converted in vivo to penciclovir, which is eliminated from plasma predominantly by renal excretion. Probenecid, a known inhibitor of the organic acid transport system, or drugs significantly eliminated by active renal tubular secretion may affect the renal elimination of penciclovir by inhibition or competition at

the tubular secretion site. There is evidence in the literature that probenecid affects the elimination of compounds structurally related to penciclovir. Therefore, an interaction of famciclovir/penciclovir with probenecid cannot be ruled out. In analogy with the above reports, it was hypothesized that probenecid may increase penciclovir AUC by approximately 50%. The CHMP agreed that patients treated with 500mg tid co-administered with probenecid should be monitored for toxicity. Also was agreed that dose reduction to 250mg tid is the best option when significant toxicity occurs. The wording of the SPC was updated to reflect this.
The section was also updated to reflect drug interactions due to aldehyde oxidase involvement. The *in vivo* conversion of famciclovir to penciclovir involves two steps: the deacetylation of famciclovir to 6-deoxy penciclovir and the oxidation of 6-deoxy penciclovir to penciclovir. The deacetylation is catalyzed by the enzyme aldehyde oxidase. Recently two papers on human liver aldehyde oxidase inhibition in *in vitro* investigations were published (*Obach* 2004; *Obach, et al* 2004). The most potent inhibitor identified in these in vitro studies was raloxifene.

Section 4.6: Pregnancy and lactation

In line with the information in section 5.3, this section was updated, in particular regarding male fertility. The results from trials show the lack of any effect on sperm count or concentration in particular, which provides strong evidence that the type of testicular toxicity seen in animals was not evident in patients. In contrast with toxicological findings, where famciclovir produced testicular toxicity in rats, mice and dogs at doses of at least 150mg/kg, these clinical studies clearly demonstrate that at therapeutic doses of 250mg bid (about 6mg/kg), famciclovir does not affect human spermatogenesis or semen quality. Furthermore, long-term famciclovir treatment, at a dose of 250mg bid for 52 weeks, was well tolerated in men with recurrent genital herpes and demonstrated a safety profile comparable to placebo.
No consistent changes were observed in several sperm parameters following long-term treatment with 250mg famciclovir bid. However, it cannot be excluded that short-term treatment with high dosages (e.g., 500mg tid) may affect male fertility in humans. Section 4.6 was updated accordingly.

Section 4.7: Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience certain adverse events should refrain from driving or operating machinery.

Section 4.8: Undesirable effects

The frequencies and listing of adverse events in this section were updated based on an integrated safety evaluation of adverse events observed in clinical trials and post marketing experience.

Section 5.1: Pharmacodynamic properties

An analysis of current data on viral resistance to famciclovir was reviewed and reflected in this section. There is no evidence of any increase in resistance despite the progressive increase in antiviral use The ability of HSV to establish a lifelong latent infection, together with the finding that the vast majority of resistant HSV isolates studied to date have reduced pathogenicity relative to wild-type virus, help to explain this observation. This section of the SPC was thus revised to reflect current knowledge on viral resistance.
Section 5.2: Pharmacokinetic properties

The section was reviewed, in particular the regarding special populations, as the elderly. Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired.
Section 5.3: Preclinical safety data

The statement regarding the reversibility of the degenerative testicular epithelium was updated. The statement that the testicular findings were largely reversible is supported by observations made in the chronic dose toxicity studies in which the testicular findings were largely reversible after a 12-week duration of recovery and partially reversed after shorter recovery periods.

The CHMP regarded the MAH's response not fully satisfactory. However, the CHMP endorsed the MAH's proposal to commit to specifically monitor and report malignancies within future PSURs.

Package leaflet
The package leaflet was updated to reflect the SPC harmonisation.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted harmonised Product Information documents for the various presentations of Famvir and associated names, taking into account the pharmaceutical forms. In particular, the indications and their associated posology recommendations were harmonised. Commitments to be undertaken by the MAH were agreed. Based on the above, the CHMP considers the benefit/risk ratio of Famvir to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- the scope of the referral was the harmonisation of the Summary of Products Characteristics, labelling and package leaflet.

- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Famvir and associated names (see Annex I). The CHMP recommended also the revocation of the 750 mg film coated tablets for Famvir and associated names.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Famvir and associated names (see Annex I) 125 mg film-coated tablets
Famvir and associated names (see Annex I) 250 mg film-coated tablets
Famvir and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Varicella zoster virus (VZV) infections – herpes zoster
Famvir is indicated for
- the treatment of herpes zoster and ophthalmic zoster in immunocompetent adults (see section 4.4)
- the treatment of herpes zoster in immunocompromised adults (see section 4.4)

Herpes simplex virus (HSV) infections – genital herpes
Famvir is indicated for
- the treatment of first and recurrent episodes of genital herpes in immunocompetent adults
- the treatment of recurrent episodes of genital herpes in immunocompromised adults
- the suppression of recurrent genital herpes in immunocompetent and immunocompromised adults

Clinical studies have not been conducted in HSV-infected patients immunocompromised for other causes than HIV-infection (see section 5.1).

4.2 Posology and method of administration

Herpes zoster in immunocompetent adults
500 mg three times daily for seven days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Herpes zoster in immunocompromised adults
500 mg three times daily for ten days.

Treatment should be initiated as soon as possible after a diagnosis of herpes zoster.

Genital herpes in immunocompetent adults

First episode of genital herpes: 250 mg three times daily for five days. Initiation of treatment is recommended as soon as possible after a diagnosis of first episode of genital herpes.

Episodic treatment of recurrent genital herpes: 125 mg twice daily for five days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Recurrent genital herpes in immunocompromised adults
Episodic treatment of recurrent genital herpes: 500 mg twice daily for seven days. Initiation of treatment is recommended as soon as possible after onset of prodromal symptoms (e.g. tingling, itching, burning, pain) or lesions.

Suppression of recurrent genital herpes in immunocompetent adults
250 mg twice daily. Suppressive therapy should be discontinued after a maximum of 12 months of continuous antiviral therapy to reassess recurrence frequency and severity. The minimum period of reassessment should include two recurrences. Patients who continue to have significant disease may restart suppressive therapy.

Suppression of recurrent genital herpes in immunocompromised adults
500 mg twice daily.

Patients with renal impairment
Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to doses in patients with impaired renal function. Dose recommendations for adult patients with renal impairment are provided in Table 1.

Table 1 Dose recommendations for adult patients with renal impairment

Indication and nominal dose regimen	Creatinine clearance [ml/min]	Adjusted dose regimen
Herpes zoster in immunocompetent adults		
500 mg three times daily for 7 days	≥ 60	500 mg three times daily for 7 days
	40 to 59	500 mg twice daily for 7 days
	20 to 39	500 mg once daily for 7 days
	< 20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis during 7 days
Herpes zoster in immunocompromised adults		
500 mg three times daily for 10 days	≥ 60	500 mg three times daily for 10 days
	40 to 59	500 mg twice daily for 10 days
	20 to 39	500 mg once daily for 10 days
	< 20	250 mg once daily for 10 days
	Haemodialysis patients	250 mg following each dialysis during 10 days
Genital herpes in immunocompetent adults – first episode of genital herpes		
250 mg three times daily for 5 days	≥ 40	250 mg three times daily for 5 days
	20 to 39	250 mg twice daily for 5 days
	< 20	250 mg once daily for 5 days
	Haemodialysis patients	250 mg following each dialysis during 5 days
Genital herpes in immunocompetent adults – episodic treatment of recurrent genital herpes		
125 mg twice daily for 5 days	≥ 20	125 mg twice daily for 5 days
	< 20	125 mg once daily for 5 days
	Haemodialysis patients	125 mg following each dialysis during 5 days
Genital herpes in immunocompromised adults – episodic treatment of recurrent genital herpes		
500 mg twice daily for 7 days	≥ 40	500 mg twice daily for 7 days
	20 to 39	500 mg once daily for 7 days
	< 20	250 mg once daily for 7 days
	Haemodialysis patients	250 mg following each dialysis during 7 days
Suppression of recurrent genital herpes in immunocompetent adults		

250 mg twice daily	≥ 40	250 mg twice daily
	20 to 39	125 mg twice daily
	< 20	125 mg once daily
	Haemodialysis patients	125 mg following each dialysis
Suppression of recurrent genital herpes in immunocompromised adults		
500 mg twice daily	≥ 40	500 mg twice daily
	20 to 39	500 mg once daily
	< 20	250 mg once daily
	Haemodialysis patients	250 mg following each dialysis

Patients with renal impairment on haemodialysis
Since 4 h haemodialysis resulted in up to 75% reduction in plasma penciclovir concentrations, famciclovir should be administered immediately following dialysis. The recommended dose regimens for haemodialysis patients are included in Table 1.

Patients with hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for patients with severe hepatic impairment (see sections 4.4 and 5.2).

Elderly patients (≥ 65 years)
Dose modification is not required unless renal function is impaired.

Children and adolescents
Famvir is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Method of administration
Famvir can be taken without regard to meals (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to penciclovir.

4.4 Special warnings and precautions for use

Use in patients with renal impairment
In patients with impaired renal function dose adjustment is necessary (see sections 4.2 and 4.9).

Use in patients with hepatic impairment
Famciclovir has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of famciclovir may occur.

Use for zoster treatment
Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.
Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes
Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, transmission is still possible. Therefore, in addition to therapy with famciclovir, it is recommended that patients use safer sex practices.

Other
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on famciclovir
No clinically significant interactions have been identified.

Concurrent use of probenecid may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir, by competing for elimination.

Therefore, patients receiving famciclovir at a dose of 500 mg three times daily co-administered with probenecid, should be monitored for toxicity. If patients experience severe dizziness, somnolence, confusion or other central nervous system disturbances, a dose reduction of famciclovir to 250 mg three times daily may be considered.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifen has been shown to be a potent inhibitor of this enzyme *in vitro*. Co-administration of raloxifene could affect the formation of penciclovir and thus the efficacy of famciclovir. When raloxifen is co-administered with famciclovir the clinical efficacy of the antiviral therapy should be monitored.

4.6 Pregnancy and lactation

Pregnancy
There is a limited amount of data (less than 300 pregnancy outcomes) from the use of famciclovir in pregnant women. Based on these limited amounts of information, the cumulative analysis of both prospective and retrospective pregnancy cases did not provide evidence indicating that the product causes any specific foetal defect or congenital anomaly. Animal studies have not shown any embryotoxic or teratogenic effects with famciclovir or penciclovir (the active metabolite of famciclovir). Famciclovir should only be used during pregnancy when the potential benefits of treatment outweigh the potential risks.

Lactation
It is unknown whether famciclovir is excreted in human breast milk. Animal studies have shown excretion of penciclovir in breast milk. If the woman's condition mandates treatment with famciclovir, discontinuation of breast-feeding may be considered.

Fertility
Clinical data do not indicate an impact of famciclovir on male fertility following long-term treatment at an oral dose of 250 mg twice daily (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famvir should refrain from driving or operating machinery.

4.8 Undesirable effects

Headache and nausea have been reported in clinical studies. These were generally mild or moderate in nature and occurred at a similar incidence in patients receiving placebo treatment. All other adverse reactions were added during postmarketing.

A total of 1,587 patients have received famciclovir at recommended doses in placebo- (n=657) and active- (n=930) controlled studies. These clinical studies were retrospectively reviewed to obtain a frequency category for all adverse reactions mentioned below. For adverse reactions which have never been observed in these studies, the upper limit of the 95% confidence interval is not expected to be higher than 3/X (based on the "rule of three"), with X representing the total sample size (n=1,587).

Adverse reactions (Table 2) are ranked under headings of frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2 Adverse reactions

Blood and lymphatic system disorders		
	Rare:	Thrombocytopenia.
Psychiatric disorders		
	Uncommon:	Confusion.
	Rare:	Hallucinations.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness, somnolence.
Gastrointestinal disorders		
	Common:	Nausea, vomiting.
Hepatobiliary disorders		
	Common:	Abnormal liver function tests.
	Rare:	Cholestatic jaundice.
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus.
	Uncommon:	Urticaria, serious skin reactions* (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis).

* Never reported in clinical trials; category is based on the "rule of three"

Overall, adverse reactions reported from clinical studies with immunocompromised patients were similar to those reported in the immunocompetent population. Nausea, vomiting and abnormal liver function tests were reported more frequently, especially at higher doses.

4.9 Overdose

Overdose experience with famciclovir is limited. In the event of an overdose supportive and symptomatic therapy should be given as appropriate. Acute renal failure has been reported rarely in patients with underlying renal disease where the famciclovir dose has not been appropriately reduced for the level of renal function. Penciclovir is dialysable; plasma concentrations are reduced by approximately 75% following 4 h haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: JO5AB09

Mechanism of action
Famciclovir is the oral prodrug of penciclovir. Famciclovir is rapidly converted *in vivo* into penciclovir, which has *in vitro* activity against herpes simplex viruses (HSV types 1 and 2), varicella zoster virus, Epstein-Barr virus and cytomegalovirus.

The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to *in vivo* conversion to penciclovir. In virus-infected cells the viral thymidine kinase (TK) phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. This triphosphate persists in infected cells in excess of 12 hours and inhibits viral DNA chain elongation by competitive inhibition with deoxyguanosine triphosphate for incorporation into the growing viral DNA, thus halting virus replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Hence the probability of toxicity to mammalian host cells is low and uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir.

Resistance
Like aciclovir, the most common form of resistance encountered among HSV strains is a deficiency in the production of the thymidine kinase (TK) enzyme. Such TK deficient strains would generally be expected to be cross-resistant to both penciclovir and aciclovir.

Results from 11 worldwide clinical studies involving penciclovir (topical or intravenous formulations) or famciclovir in immunocompetent or immunocompromised patients, including studies of up to 12 months treatment with famciclovir, have shown a small overall frequency of penciclovir resistant isolates: 0.2% (2/913) in immunocompetent patients and 2.1% (6/288) in immunocompromised patients. The resistant isolates were mostly found at the start of treatment or in a placebo group, with resistance occurring on or after treatment with famciclovir or penciclovir only in two immunocompromised patients.

Clinical efficacy
In placebo-controlled and active-controlled studies both in immunocompetent and immunocompromised patients with uncomplicated herpes zoster, famciclovir was effective in the resolution of lesions. In an active-controlled clinical study, famciclovir was shown to be effective in the treatment of ophthalmic zoster in immunocompetent patients.

Efficacy of famciclovir in immunocompetent patients with first episode of genital herpes was shown in three active-controlled studies. Two placebo-controlled studies in immunocompetent patients and one-active controlled study in HIV-infected patients with recurrent genital herpes showed that famciclovir was effective.

Two placebo-controlled 12-month studies in immunocompetent patients with recurrent genital herpes showed that famciclovir-treated patients had a significant reduction of recurrences as compared to placebo-treated patients. Placebo-controlled and uncontrolled studies of up to 16 weeks duration showed that famciclovir was effective in the suppression of recurrent genital herpes in HIV-infected patients; the placebo-controlled study showed that famciclovir significantly decreased the proportion of days of both symptomatic and asymptomatic HSV shedding.

5.2 Pharmacokinetic properties

General characteristics

Absorption
Famciclovir is the oral prodrug of the antivirally active compound penciclovir. Following oral administration, famciclovir is rapidly and extensively absorbed and converted to penciclovir. Bioavailability of penciclovir after oral administration of famciclovir was 77%. Mean peak plasma concentration of penciclovir, following a 125 mg, 250 mg, 500 mg and 750 mg oral dose of famciclovir, was 0.8 microgram/ml, 1.6 micrograms/ml, 3.3 micrograms/ml and 5.1 micrograms/ml, respectively, and occurred at a median time of 45 minutes post-dose.

Plasma concentration-time curves of penciclovir are similar following single and repeat (t.i.d. and b.i.d.) dosing, indicating that there is no accumulation of penciclovir on repeated dosing with famciclovir.

The extent of systemic availability (AUC) of penciclovir from oral famciclovir is unaffected by food.

Distribution
Penciclovir and its 6-deoxy precursor are poorly (< 20%) bound to plasma proteins.

Metabolism and elimination
Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor, which are excreted in urine. No unchanged famciclovir has been detected in urine. Tubular secretion contributes to the renal elimination of penciclovir.

The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir was approximately 2 hours.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450 enzymes and inhibition of CYP3A4.

Characteristics in special populations
Patients with herpes zoster infection
Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir. The terminal plasma half-life of penciclovir in patients with herpes zoster was 2.8 h and 2.7 h, respectively, after single and repeated dosing of famciclovir.

Subjects with renal impairment
The apparent plasma clearance, renal clearance, and plasma elimination rate constant of penciclovir decreased linearly with reductions in renal function, both after single and repeated dosing. Dose adjustment is necessary in patients with renal impairment (see section 4.2).

Subjects with hepatic impairment
Mild and moderate hepatic impairment had no effect on the extent of systemic availability of penciclovir following oral administration of famciclovir. No dose adjustment is recommended for patients with mild and moderate hepatic impairment (see sections 4.2 and 4.4). The pharmacokinetics of penciclovir have not been evaluated in patients with severe hepatic impairment. Conversion of famciclovir to the active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus possibly a decrease of efficacy of famciclovir.

Elderly patients (≥ 65 years)
Based on cross-study comparisons, the mean penciclovir AUC was about 30% higher and penciclovir renal clearance about 20% lower after oral administration of famciclovir in elderly volunteers (65-79 years) compared to younger volunteers. Partly this difference may be due to differences in

renal function between the two age groups. No dose adjustment based on age is recommended unless renal function is impaired (see section 4.2).

Gender
Small differences in renal clearance of penciclovir between females and males have been reported and were attributed to gender differences in renal function. No dose adjustment based on gender is recommended.

5.3 Preclinical safety data

General toxicity
Studies on safety pharmacology and repeated dose toxicity reveal no special hazard for humans.

Genotoxicity
Famciclovir was not found to be genotoxic in a comprehensive battery of *in vivo* and *in vitro* tests designed to detect gene mutation, chromosomal damage and repairable damage to DNA. Penciclovir, in common with other substances of this class, has been shown to cause chromosomal damage, but did not induce gene mutation in bacterial or mammalian cell systems, nor was there evidence of increased DNA repair *in vitro*.

Carcinogenicity
At high doses in female rats, there was an increased incidence of mammary adenocarcinoma, a tumour commonly observed in the strain of rats used in the carcinogenicity study. There was no effect on the incidence of neoplasia in male rats or in mice of either sex.

Reproductive toxicity
Impaired fertility (including histopathological changes in the testis, altered sperm morphology, reduced sperm concentration and motility, and reduced fertility) was observed in male rats given 500 mg/kg/day. Furthermore, degenerative changes of the testicular epithelium were noted in the general toxicity studies. This finding was reversible and has also been observed with other substances of this class. Animal studies did not indicate any negative effect on female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Famvir and associated names (see Annex I) 125 mg film-coated tablets
Famvir and associated names (see Annex I) 250 mg film-coated tablets
Famvir and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

famciclovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Famvir and associated names (see Annex I) 125 mg film-coated tablets
Famvir and associated names (see Annex I) 250 mg film-coated tablets
Famvir and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

famciclovir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Famvir and associated names (see Annex I) 125 mg film-coated tablets
Famvir and associated names (see Annex I) 250 mg film-coated tablets
Famvir and associated names (see Annex I) 500 mg film-coated tablets
[See Annex I - To be completed nationally]

famciclovir

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- Famvir has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FAMVIR IS AND WHAT IT IS USED FOR

Famvir is an antiviral medicine. It stops the infecting virus from reproducing. Since the virus reproduces very early in the infection, you will benefit most from treatment if you take Famvir as soon as the first symptoms appear.

Famvir is used to treat two types of viral infections in adults:
- Shingles (herpes zoster), which is a viral infection caused by a virus called varicella zoster (the same virus that causes chickenpox). Famvir stops the virus from spreading in the body so that healing can occur faster.
- Famvir is also used for the treatment of shingles in the area around the eye or of the eye itself (ophthalmic zoster).
- Genital herpes. Genital herpes is a viral infection caused by herpes simplex virus type 1 or 2. It is normally spread by sexual contact. It causes blisters and burning or itching around the genitals, which may be painful. Famvir is used to treat genital herpes infections in adults. People who have frequent episodes of genital herpes can also take Famvir to help to prevent the attacks.

2. BEFORE YOU TAKE FAMVIR

Do not take Famvir
- If you are allergic (hypersensitive) to famciclovir, to any of the other ingredients of Famvir listed in section 6, or to penciclovir (the active metabolite of famciclovir and an ingredient of some other medicines).

Ask your doctor for advice, if you think you may be allergic.

Take special care with Famvir

- If you have kidney problems (or have had them before). Your doctor may decide to give you a lower dose of Famvir.
- If you have problems with your body's immune system.
- If you have liver problems.

If any of these applies to you, tell your doctor before you take Famvir.

Children and adolescents (below the age of 18 years)
Famvir is not recommended for use in children and adolescents.

Prevent passing genital herpes to others
If you are taking Famvir to treat or to suppress genital herpes, or you have had genital herpes in the past, you should still practise safe sex, including the use of condoms. This is important to prevent you passing the infection on to others. You should not have sex if you have genital sores or blisters.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important that you tell your doctor or pharmacist if you are taking any of the following medicines:
- Raloxifen (used to prevent and treat osteoporosis).
- Probenecid (used to treat high blood levels of uric acid associated with gout and to increase blood levels of penicillin-type antibiotics), or any other medicine that can affect your kidneys.

Taking Famvir with food and drink
You can take Famvir with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or think you may be, tell your doctor. Famvir is not to be used during pregnancy unless clearly necessary. Your doctor will discuss with you the potential risks of taking Famvir during pregnancy.

If you are breast-feeding, tell your doctor. Famvir is not to be used during breast-feeding unless clearly necessary. Your doctor will discuss with you the possible risks of taking Famvir during breast-feeding.

Driving and using machines
Famvir can cause dizziness, drowsiness or confusion. **Do not drive or use machines** if you have any of these symptoms while taking Famvir.

Important information about some of the ingredients of Famvir
If you have been told by your doctor that you have an intolerance to some sugars, e.g. lactose, contact your doctor before taking this medicine. Famvir 125 mg, 250 mg and 500 mg (country specific) tablets contain lactose.

3. HOW TO TAKE FAMVIR

Always take Famvir exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- The daily dose and length of treatment will depend on the type of viral infection you have – see below. Your doctor will prescribe the correct dose for you.
- For the best results start the medicine as soon as possible after the first signs and symptoms appear.

- Do not have sexual contact with anyone if you have symptoms of genital herpes – even if you have started treatment with Famvir. This is because you could pass the herpes infection to your partner.
- If you have or have had kidney problems, your doctor may decide to give you a lower dose of Famvir.

Dose for shingles
If you have a normal immune system, the recommended dose is
- one tablet of 500 mg, three times a day, for seven days

If you have a reduced immune system, the recommended dose is
- one tablet of 500 mg three times a day, for ten days.

Dose for genital herpes
The dose depends on the state of your immune system, and the stage of your infection.

If you have a normal immune system, the doses are as follows:

For the *first outbreak*, the recommended dose is:
- one tablet of 250 mg three times a day, for five days.

To *treat further outbreaks*, the recommended dose is:
- one tablet of 125 mg twice a day, for five days.

To *prevent future outbreaks*, the recommended dose is:
- one tablet of 250 mg twice a day.

Your doctor will tell you how long you need to continue taking your tablets.

If you have a reduced immune system, the doses are as follows:

To *treat the current outbreak*, the recommended dose is:
- one tablet of 500 mg twice a day, for seven days.

To *prevent future outbreaks*, the dose is
- one tablet of 500 mg twice a day.

Your doctor will tell you how long you need to continue taking your tablets.

If you take more Famvir than you should
If you have taken more tablets than you have been told to take, or if someone else accidentally takes your medicine, go to your doctor or hospital for advice immediately. Show them your pack of tablets.

Taking too much Famvir may affect the kidneys. In people who already have kidney problems it may, rarely, lead to kidney failure if their dose is not correctly lowered.

If you forget to take Famvir
If you forget to take a dose of Famvir, you should take it as soon as you remember. Then take your next dose as scheduled. However, do not take two doses within a time interval of less than 1 hour, in that case you should skip the missed dose. Furthermore, do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Famvir can cause side effects, although not everybody gets them. The side effects caused by Famvir are usually mild to moderate in intensity.

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)

Serious side effects of Famvir are:
- **Severe blistering** of the skin or mucous membranes of the lips, eyes, mouth, nasal passages or genitals (these could be signs of a serious allergic skin reaction, for frequency see below).
- **Unexplained bruising**, reddish or purplish patches on the skin or **nosebleeds** (these could be signs of a decrease in the number of blood platelets, for frequency see below).

Contact a doctor or go to the emergency department at your nearest hospital straight away if you get any of these effects.

Very common side effects
- Headache

Common side effects
- Feeling sick (nausea)
- Vomiting
- Dizziness
- Drowsiness
- Rash
- Pruritus
- Liver function test giving abnormal results

Uncommon side effects
- Confusion
- Severe skin reactions

Rare side effects
- Hallucinations (seeing or hearing things that are not really there)
- Yellowing of the skin and/or eyes
- Low platelet count

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FAMVIR

- Keep out of the reach and sight of children.
- Do not use Famvir after the expiry date which is stated on the label after the expiry date. The expiry date refers to the last day of that month.
- [To be completed nationally]
- Do not use Famvir if you notice the pack is damaged or shows signs of tampering.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Famvir contains

[To be completed nationally]

What Famvir looks like and contents of the pack

Film–coated tablets
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]