European Medicines Agency

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ASSESSMENT REPORT

Famvir and associated names

INN / active substance: famciclovir

PROCEDURE No: EMEA/H/A-30/1005

Note:

Assessment Report as adopted by CHMP with all the information of a confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 27 November 2008, the European Commission presented to the European Medicines Agencya referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national Summary of Product Characteristics, Labelling and Package Leaflet of the medicinal products:

Famvir and associated names (see Annex I of CHMP Opinion)

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the December 2008 meeting. The Marketing Authorisation Holder was informed of the start of the procedure.

The CHMP appointed Dr Martina Weise (DE) as Rapporteur and Dr Steffen Thirstrup (DK) as Co-Rapporteur.

Famvir medicinal products are registered in the following EU Members States (MSs): Austria, Cyprus, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Spain, Sweden and United Kingdom and also in Iceland.

Famvir medicinal products are currently not registered in the following EU MSs: Bulgaria, Belgium, Estonia, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia.

2. Scientific discussion during the Arbitration procedure

2.1 Introduction

Famvir (famciclovir) was included in the list of products for SPC harmonization, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. Due to divergent national decisions taken by MSs concerning the authorisation of Famvir, a referral was triggered in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across the EU.

Famvir 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.

Famvir was first registered in United Kingdom on 10 December 1993 by another company for the treatment of herpes zoster with subsequent registrations in many EU MSs and worldwide. In December 2000, marketing authorisations for Famvir were transferred to Novartis in most countries.
Novartis is currently the marketing authorisation holder. Famvir is currently marketed in 17 EU/EEA countries and it is registered only via national procedures (NPs). MAHs in Europe besides Novartis are Demetriades & Papaellinas Ltd (Cyprus), Grünwalder Gesundheitsprodukte (Germany), Sandoz S.p.A. (Italy).

The scope of the Famvir referral included all licenses, belonging to Novartis group of companies and associated companies.

2.2 Critical Evaluation

Section 4 – Clinical particulars

Section 4.1 Therapeutic indication

The CHMP identified differences in Section 4.1 *Therapeutic indications* of the SPC across MSs. The indications 'herpes simplex and herpes zoster infections in immunocompromised patients', 'initial genital herpes infections', 'herpes zoster infections' and 'recurrent genital herpes infections' were not approved in all MSs.

The wording of the indications and posology was also different in the MSs where they were approved and this was subject to harmonisation.

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)."

The MAH submitted several studies to support the efficacy and safety of famciclovir in the treatment of herpes zoster and ophthalmic zoster (studies 007, 008, 086 and 098).

The MAH also presented six pivotal studies to support the indication for treatment of genital herpes; five in immunocompetent and one in immunocompromised patients (studies 004, 011, 035, 036, 040 and 083). Additionally, in suppression of recurrent genital herpes, the MAH referred to data from studies 024, 033, 049 and 102.

A breakdown 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. Moreover, the clinical relevance of the shown acute phase effects were questioned, as from a patient perspective, loss of acute phase pain would have been relevant.

In the acute treatment of herpes zoster famciclovir 750mg tid resulted in a shorter time to full crusting than placebo, and both 750mg and 500 mg tid resulted in shortened time to loss of vesicles and time to loss of ulcers.

The CHMP agreed that famciclovir resulted in a significant reduction in time to resolution of cutaneous signs of herpes zoster.

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.

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

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 (251 randomised to famciclovir and 246 to aciclovir). Treatment was started within 72 hours after onset of the zoster rash. 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). Treatment compliance (≥95%) was similar for famciclovir and aciclovir recipients.

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, these drugs appear to reduce important ocular manifestations.

The CHMP agreed that the indication treatment of ophthalmic zoster in immunocompetent patients was supported by the available data.

Safety results in Herpes Zoster

From the submitted data –not taking into account the relationship to study medication- the most common adverse events were headache and nausea (see discussions under section 4.8). Adverse events did mainly concern the gastrointestinal tract and the central nervous system (CNS). However, no clear dose effect relationship was seen and the comparative safety profile (respect to aciclovir) varied between the studies. Overall, the safety profile appeared to be acceptable. Safety results are discussed in further detail under section 4.8 Undesirable effects.

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 designedto 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 two studies, which included a total of 775 patients, 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 by the MAH 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. There were 352 patients randomised and treated. Of these patients, 313 completed the study. 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, the MAH presented one dose-finding study (study 024) and two pivotal studies (studies 033 and 049) in immunocompetent patients, and one dose findingstudy (study 102) in immunocompromised patients.
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.

There were 2 primary endpoints: the proportion of patients free from virologically confirmed lesion episodes for 6 months; and the time to first clinically confirmed lesion episode. Together, the 2 endpoints were considered as representing both virologically and clinically meaningful outcomes. The ITT population was used to assess outcomes.

In study 033, patients were randomly assigned to receive either famciclovir (125 mg t.i.d, 250 mg b.i.d., or 250 mg t.i.d.) or placebo for 52 weeks. Between 59% and 63% of famciclovir-treated patients completed the double-blind segment of the study, as compared to only 26% of placebo-treated patients. In study 049 between 57% and 63% of famciclovir-treated patients completed the double-blind segment study, as compared to only 23% of placebo-treated patients. The proportion of placebo-treated patients who entered the open-label segments of these studies and then completed was in-line with completion rates for active-treated patients. The results showed a significant effect of famciclovir with regard to suppression of recurrent genital herpes.

Study 024 was a randomised, double-blind, placebo-controlled trial conducted at 20 centres in the USA. The primary variable in this study was time to first recurrence. The results showed that both bid (*bis in die*, twice a day) regimens (125 bid 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. This was also the conclusion of *Merts et al*, 1997.

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. It was performed at a single centre in the USA. HIV-infected patients were targeted for study since they represent an immunocompromised patient population known to experience frequent reactivations of herpes simplex virus (HSV) infection.

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, the CHMP agreed that the indication suppression of recurrent genital herpes in immunocompetent and immunocompromised adults was supported by the available data.

Safety results in genital herpes

No deaths or serious adverse events (SAEs) leading to death were reported in genital herpes studies in immunocompetent patients. From the submitted safety data the most common adverse events are headache

and nausea (see discussions under section 5.2). Adverse events do mainly concern the gastrointestinal tract and the CNS. However, no clear dose effect relationship was seen.

The CHMP concluded that the clinical study data in support of the safety of long-term use of famciclovir at a dose of 500mg bid in HIV-infected patients are not satisfactory. The MAH gathered safety data in putting famciclovir in perspective with other antivirals, but the interpretation is hampered by the lack of a direct comparison and differences in study design, e.g. duration of the trial. The data generated in immunocompetent patients at a daily dose of 750mg can be considered reassuring; 143 patients received this dose for at least one year (≥351 days). Nevertheless, there is still some uncertainty with respect to the influence of the underlying condition as well as with the dose, when it is increased by 1/3 to 1000mg/d.

Post-marketing surveillance did not indicate a specific risk in this patient group/therapeutic indication. A caveat of these data is that neither dose nor duration of treatment or estimated numbers of treatment courses administered during this period are reported. However, the overall number of events is very small, which can be considered reassuring. As presently no specific risk has been identified, it does not appear appropriate to restrict/delete this indication. Therefore, the CHMP recommended the inclusion of the safety results in supressive therapy for genital herpes in immunocompromised patients in the forthcoming periodic safety update reports. All efforts should be made by the MAH to collate the information missing in the current analysis of post marketing data. The MAH committed to monitoring of future safety reports from HIV-infected patients treated with famciclovir and to the discussion of such cases in section 9.8 “Experience in special patient groups” of future three-yearly PSURs.

Safety results are discussed in further detail under section 4.8 Undesirable effects.

Section 4.2: Posology and Method of Administration

The CHMP identified divergences in section 4.2. The MAH proposed to include in the harmonised SPC the wording that was most common to the product information in the majority of MSs, as justified by available data. Specific issues regarding posology are discussed hereinafter.

HERPES ZOOSTER

HERPES ZOOSTER 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.

OTHERS: PATIENTS AT RISK OF POSTHERPETIC NEURALGIA

The MAH was asked to provide a critical discussion of all efficacy and safety data for the 500mg tid and the 750mg tid dose with respect to PHN. The studies investigating the effect of famciclovir on PHN found a reduction in the number of days till loss of pain. However, a reduction in the proportion of patients experiencing PHN was not demonstrated.

The CHMP concluded that this effect should not be included in sections 4.1 or 4.2 of the SPC.

GENITAL HERPES

GENITAL HERPES IN 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. This was evident for the time to cessation of viral shedding for all patients, which was more pronounced for the primary patients. The time to cessation of viral shedding was the most sensitive indicator of antiviral activity preceding the times to complete healing and loss of symptoms by 5 days. 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.

Although the clinical relevance of the primary endpoint (“duration of viral shedding”) was questionable, relevant secondary endpoints point in the same direction, thus the 250mg famciclovir TID regimen was considered acceptable.

- Episodic treatment of recurrent herpes

No 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.

It was noted that for the therapy of recurrent episodes of genital herpes half the dose of that for suppressive therapy was recommended (see below). This appeared paradoxical as HSV viral load can be assumed to be higher in clinically symptomatic disease than when used for prevention of recurrence. However, further to clarifications provided, the CHMP endorsed this posology.

- Suppression of recurrent herpes

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 famciclovir development program had evaluated total daily doses of famciclovir for episodic treatment of recurrent genital herpes below the levels that were subsequently shown to be most efficacious for suppressive therapy.

The CHMP, considered the above, and 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.

GENITAL HERPES IN IMMUNOCOMPROMISED ADULTS

- Episodic treatment of recurrent herpes

The CHMP noted that the available therapeutic guidelines provide divergent views regarding treatment of first episode. No clinical studies have been conducted with famciclovir in treating HIV-infected patients with an initial episode of genital herpes. Recruiting first episode patients would present a challenge as the

vast majority of HIV-infected adults also have serologic evidence of established HSV-1 and HSV-2 infections.

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). Since, anyway, a primary episode in immunocompromised patients will be a rarity, this approach was considered acceptable.

On the other hand the CHMP saw the need for antiviral treatment due to prolonged viral shedding and possibly more severe disease courses in immunocompromised patients. However, it was recognized that due to immunosuppression higher doses than those used in immunocompetent adults might be necessary. A pivotal clinical study (study 083) was conducted in HIV-infected patients with recurrent genital herpes where 500 mg bid for seven days was the recommended posology.

The MAH summarised that the combined studies of 102 and 195 extend 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).

The benefits of suppressive anti-HSV therapy in an HIV-infected patient may go beyond clinical benefits in the reduction of symptoms. A meta-analysis of 8 randomized trials involving 1792 participants and 2947 person-years of follow-up indicated that aciclovir (administered at a dosage of 3200 mg per day) offered a significant survival benefit for HIV-1–infected persons (hazard ratio, 0.78; 95% CI, 0.65–0.93) (*Ioannidis, et al* 1998). In a placebo-controlled trial, cervicovaginal HIV-1 levels were a mean of 0.35 log10 copies/ml lower among women co-infected with HIV-1 and HSV-2 receiving valaciclovir suppression (*Ouedraogo, et al* 2006). Observational data indicate that genital ulcer disease, the majority of which is due to HSV-2 infection, increases the probability of HIV-1 transmission by approximately 4-fold on a per-contact basis among monogamous HIV-1–discordant heterosexual couples (*Gray, et al* 2001). Anti-HSV viral treatment reduced HIV-1 shedding in genital herpes lesions within the first 4–5 days of therapy (*Chen, et al* 2000; Schacker, et al 1998b).

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

Dosage adjustment is recommended for patients with renal insufficiency. In renal impaired patients on haemodialysis it has been shown that a 4-hour haemodialysis resulted in approximately 75% reduction in plasma penciclovir concentrations (*Gill and Wood* 1996). Hence, penciclovir is rapidly removed from plasma during haemodialysis. The CHMP considered the MAH's re-evaluation of the available information on the pharmacokinetics of penciclovir in patients with varying degrees of renal insufficiency as well as in haemodialysis patients. An overview of the pharmacokinetics of penciclovir in haemodialysis patients was presented, and revised dose recommendations for all indications for patients with different degrees of renal impairment were provided.

Regarding the hepatic function, no dosage adjustments are required in patients with mild or moderate hepatic impairement. However, as there is no PK and efficacy data in patients with severe hepatic impairment it is not possible to reliably assess these effects and to recommend an appropriate dose of famciclovir for patients with severe hepatic impairment.

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

Section 4.3 Contraindications included proposals which were not harmonised across MSs and were not in accordance with the SPC Guideline.

Since patient populations not studied should be mentioned in section 4.4 and not in section 4.3, the latter was updated to reflect that 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 (see above).

Additionally, some MSs also had awarning stating 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, discussions were held regarding the clinical relevance of the interactions proposed since clinically relevant interactions resulting from

competition at the tubular secretion site (with probenecid or cimetidine) are unlikely with this kind of drugs and since no drug-drug interaction study was available. 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. A drug interaction study of famciclovir with probenecid has not been performed. There is, however, 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. It was shown that a single dose of probenecid increased the AUC of aciclovir by 40% (*Laskin et al* 1982). In a drug interaction study of valaciclovir (a prodrug of aciclovir) probenecid increased the Cmax and AUC of aciclovir by 22% and 48%, respectively (De Bony et al 2002). In a drug interaction study of ganciclovir, which is structurally similar to aciclovir, probenecid increased Cmax and AUC of ganciclovir by 40.1 % and 52.5%, respectively (*Cimoch et al* 1998).

In analogy with the above reports, it was hypothesized that probenecid may increase penciclovir AUC by approximately 50%. The CHMP agreed that patients traded with 500mg tid co-administered with probenecid should be monitor 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 MAH also addressed 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. Thus, this information was included in this section.

Section 4.6: Pregnancy and lactation

The CHMP having noted the wording under this section, asked the MAH to amend the SPC or otherwise justify the proposed wording, in particular to provide human data regarding male fertility as these seem to be available based on the wording in section 5.3.

The MAH provided a review of three clinical trials evaluating male fertility. There were no significant differences between famciclovir and placebo in major sperm parameters: sperm concentration, total sperm count, % motility, % abnormal morphology, and % dead sperm. All sperm parameters were comparable between treatment groups and no consistent drug-related trends were seen with famciclovir. The lack of any effect on sperm count or concentration in particular, provides strong evidence that the type of testicular toxicity seen in animals was not evident in these 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 and the wording was endorsed by the CHMP.

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. The CHMP endorsed the MAH's proposed wording with few amendments, since confusion or other central nervous system disturbances are mentioned as adverse events in section 4.8.

Section 4.8: Undesirable effects

The MAH was requested to provide a comprehensive safety summary of famciclovir taking into account also a global summary on the product safety (pooling of safety data from different studies).

The MAH analysed AEs from all pivotal efficacy and safety studies for famciclovir in treating herpes zoster and genital herpes in immunocompetent and immunocompromised patients.

In studies 007 and 008 the percentage of patients with a severe AE on active treatment (8.6% – 12.7%) was less than placebo recipients (17.1%). No dose dependency for any particular severe adverse event was apparent for recipients of famciclovir. Headache was the only severe adverse event reported by greater than 2% of the famciclovir recipients, and the frequency was less than that seen for placebo recipients.

The percentages of patients with related adverse events were similar across all active treatments and placebo groups. Headache and nausea were the more frequent adverse events noted, but their frequency was no different between famciclovir and placebo recipients. No dose dependency was apparent between adverse event and famciclovir.

In pivotal studies 004, 011 and 040 the numbers of patients who reported severe adverse event during study medication and within 30 days of end of study medication ranged from 4.2% to 9.9% and was comparable to the reports for aciclovir recipients (8.8%). The incidence of each severe adverse event was generally low and neither a consistent pattern nor dose dependency was observed. Headache was the most frequently reported severe adverse event. Nausea was the most noted AE occurring more frequently in recipients of the 125mg tid and 500mg tid doses of famciclovir, but with similar or less frequent events for recipients of the 250mg tid and 750mg tid doses of famciclovir when compared to aciclovir recipients. Dizziness and headache were frequently noted adverse events, but their frequency was similar between famciclovir and aciclovir recipients. No dose dependency was apparent between adverse event and famciclovir.

The percentage of famciclovir recipients in studies 035 and 036 with a severe adverse event ranged from 6.2% to 6.8%, slightly greater than that reported for placebo recipients (5.0%). The incidence of each severe adverse event was generally low. Headache was the most frequently reported severe AE. Overall, the percentages of patients with related adverse events were somewhat higher for recipients of famciclovir (28.4% – 30.3%) compared to placebo recipients (24.4%). Headaches, gastrointestinal adverse events and dizziness were frequently noted adverse events, and, except for headache, their frequency was similar between famciclovir and placebo recipients. No dose dependency was apparent between adverse event and famciclovir.

In studies 033 and 049 the percentage of famciclovir recipients with a severe AE ranged from 15.7% to 24.0%, and was comparable to that reported for placebo recipients (20.6%). The incidence of each severe AE was generally low. Headache was the most frequently reported severe adverse event but no dose dependency was apparent. Furthermore the percentages of patients with related adverse events were similar for recipients of famciclovir (26.1 – 30.5%) compared to placebo recipients (31.7%). Headaches and GI adverse events were frequently noted adverse events, and their frequency was similar between famciclovir and placebo recipients. No dose dependency was apparent between adverse event and famciclovir.

In study 086 7 (9.9%) in the famciclovir group and 9 (11.7%) in the aciclovir group experienced severe adverse event on dose. One famciclovir and 2 aciclovir recipients reported severe vomiting. Herpes zoster events were reported and included severe itching in 1 famciclovir recipient, severe pain in 1 aciclovir recipient and severe dissemination in a second aciclovir recipient. Only 1 patient in any treatment group reported all other on-dose severe adverse events.

Headache was the only severe AE reported by more than 2 HIV-infected patients who received famciclovir 500mg bid in study 083. Two patients who received aciclovir reported dizziness. Only 1

patient in any treatment group reported all other severe adverse event. The percentages of patients with related adverse events were higher for recipients of famciclovir 500mg bid (37.3%) than aciclovir (27.3%). Headaches and gastrointestinal adverse events were frequently noted, and their frequency was similar between famciclovir and aciclovir recipients.

In study 102 no AE were reported as related to study medication.

In study 195, 15.9% (13/82) of patients experienced at least one on-dose AE considered related to study medication. These included diarrhoea (4.9%, 4/82), nausea (3.7%, 3/82) and headache (2.4%, 2/82).

Over time additional ADRs based on post-marketing reports have been added, pruritus and urticaria, thrombocytopenia and serious skin reactions (e.g. Stevens - Johnson syndrome and toxic epidermal necrolysis, erythema multiforme), abnormal liver function tests and cholestatic jaundice. Frequencies for the ADRs were determined using post-marketing data. To calculate the frequency categories for the listed ADRs, the number of patients reporting any of these ADRs was retrieved from each of the trials which were subsequently pooled. A total pool of 4,749 patients was treated with active famciclovir across these trials. To be able to compare the active arm and placebo arm frequencies, data from placebo controlled trials was extracted, with a total of 2,946 patients receiving famciclovir and 1,042 patients received placebo. The extraction of the placebo controlled trials did not influence the overall calculated frequency categories.

The effects of famciclovir when used long-term or frequently (e.g. for suppression or treatment of recurrent episodes of genital herpes) were also discussed, in light of the rat carcinogenicity study (positive findings in females) and considering the fact that the exposure in the (negative) male rat- and mouse-study was in the range or even lower than that achieved in humans at therapeutic doses.

A cumulative search for all malignancy cases in the MAH's safety database was run using the "Malignant or unspecified tumour's standard MedDRA query (SMQ) with the data-lockpoint of 30 September 2009. The search retrieved a total of 79 cases. Thirteen of the 79 reports were poorly documented to be assessed properly and another two were consumer reports, which could not be medically validated.

Seventy-one of the 79 cases were clinical trial reports (mainly reported between 1991 and 1999). In 3 poorly documented cases the causality was not provided, whereas in 68 cases the malignancy was not suspected to be related to Famvir by the investigator. The remaining 8 spontaneous reporting cases were reported between 1994 and 1998 with only one report from 2005. Two thereof were non health-care-professional reports and could therefore not be medically validated. Another 3 had a medical history of a malignancy prior to starting Famvir, 2 had a time-to-onset of less than one week and the last case was too poorly documented to be assessed properly.
The CHMP considered that there is a need to specifically monitor and report malignancies within future PSURs. Special consideration should be given to the cumulative dose in terms of total number of famciclovir treatment cycles and doses applied at the time of event onset. The MAH committed to monitor malignancies in the PSURs.

Section 5.1: Parmacodynamic properties

The MAH was requested to provide an analysis of current data on viral resistance to famciclovir.Antiviral treatment of HSV infections with nucleoside analogues has been available for nearly three decades. Thousands of HSV isolates collected from worldwide clinical trials and surveillance programs have been tested for susceptibility to aciclovir or penciclovir. Laboratory studies searching for resistant strains of HSV have detected naturally occurring mutants but their incidence has not increased since the licensure of aciclovir/penciclovir. In immunocompetent individuals, clinical cases of resistant HSV are so rare that they are limited to individual case reports (*Griffiths* 2009). In immunocompromised patients, particularly AIDS patients or recipients of stem cell transplants, the incidence of clinically significant resistance is increased although it still remains a minority of treated patients. Nonetheless, even in this population 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, which is contrary to experience gained with many other anti-infective agents. This section of the SPC was thus revised to reflect current knowledge.

Section 5.2: Pharmacokinetic properties

The CHMP noted that wording proposed by the MAH. However, clarifications were requested, in particular regarding the characteristics of special populations, as the elderly.

The MAH discussed whether the elderly experienced more adverse events than the younger age groups treated with the same famciclovir dose due to the higher exposure of penciclovir (AUC was around 40% higher and penciclovir renal clearance around 20% lower).

The safety data from trials where elderly patients composed the majority of subjects and compared the safety results with those from trials enrolling younger patients was presented. Several clinical trials (studies 053, 067 and 109) enrolled patients whose average age was ~67 years and >40% of patients were older than 70 years of age. The daily dose for famciclovir ranged from 750mg (N=1066) to 1000mg (N=147). These studies were placebo controlled. The overall incidence of adverse events and serious adverse events were generally similar between the different daily doses of famciclovir and with those reported by placebo-treated patients. There was no pattern in the serious adverse events or adverse events leading to withdrawal that would suggest any potential for intolerance of clinical significance. Study 109 compared the safety of two different regimens of famciclovir (750mg qd and 500mg bid). No differences in adverse event or serious adverse events were apparent between these two regimens and placebo.

Studies 007 and 008 also examined the safety of famciclovir in patients with herpes zoster. These two studies enrolled patients whose combined average age was approximately 52 years and examined several dose regimens from 250mg tid to 750mg tid for famciclovir, providing a daily exposure to famciclovir of 750mg (N=134) to 2,250mg (N=273). Like Studies 053, 067 and 109, these two studies treated patients for 7 days and had a 6-month follow-up period. Overall, the nature and incidence of adverse events were generally similar across these 5 studies.

Famciclovir recipients in studies 007 and 008 reported more headaches (13.4% – 23.9%) than in Studies 053, 067 and 109 (4.1% – 6.6%); yet, the incidence of headaches in studies 007 and 008 were similar to placebo. More famciclovir recipients in studies 053, 067 and 109 reported abdominal pain (1.3% – 2.7%) than in studies 007 and 008; but, again, the reported incidence was similar to placebo in these 3 studies (3.0% – 3.5%). No patterns in serious adverse events (fatal or non-fatal) or reasons for withdrawal were evident. Studies 007 and 008 included a 750mg tid. dose regimens, which provided drug exposure greater than the recommended daily dose to treat herpes zoster (250mg tid, 500mg bid or 750mg qd). It is noteworthy that the nature and incidence of adverse events and serious adverse events for this higher dose were comparable to those observed for the placebo-treated patients.

Studies 004, 011 and 040 examined the safety of famciclovir in patients with genital herpes. The enrolled population was considerably younger (average age ~27 years) than those patients enrolled in studies 053, 067 and 109 (average age 67 years). The 3 studies in genital herpes examined doses ranging from 125mg tid to 750mg tid with duration of dosing from 5 days (study 004) to 10 days (studies 011 and 040). No serious adverse events were reported. No dose response in the nature or incidence of adverse events was observed. As in the studies targeting herpes zoster, headache and gastrointestinal symptoms were predominate adverse events reported in studies 004, 011 and 040.

A significant body of evidence has been gathered from the estimated >20 million patients who have been treated with Famvir since its first approval for clinical use in adults. All identified risks have been assessed and the safety profile has remained stable.

A breakdown of cumulative adverse event reports by system organ class and age group (18 to 64 and ≥65 years) showed strikingly similar distribution across both age groups.
The CHMP agreed with the MAH that overall no differences in the nature or frequency of adverse or serious adverse events were observed for famciclovir patients across the clinical studies regardless of the mean age of enrolled patients. For most of the events where differences were seen, there is a biological plausibility (e.g. those cardiac AEs are more common in elderly). However, the difference in psychiatric AEs is noteworthy and in line with the current wording in the SPC (possible mechanism: increased concentrations due to renal impairment).

No clear safety differences were observed for different daily doses of famciclovir with the adverse event and serious adverse event profiles being generally similar to placebo recipients.
Furthermore, the post-marketing survey showed an equal number of adverse events among the younger and the older age group (2,4 per patient), and an almost equal distribution of adverse events among the system organ classes. This section was updated accordingly.

Section 5.3 Preclinical safety data

The statement regarding the reversibility of the degenerative testicular epithelium was discussed. 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.

Study T87318-42810 was a 26-week dietary repeat dose study in rats followed by 6 and 12 week off-dose periods. Fertility was markedly reduced following pairing after 0 and 5 weeks off-dose but recovery was evident after 11 weeks.

Study T87320-42810 was a 26-week repeat oral dose toxicity study in dogs, followed by a 6-week off-dose period. In the testes, early degenerative change of the seminiferous epithelium was seen at the terminal kill. In dogs killed after the off-dose period, there was no absence of testicular change.

Study T89327-42810 was a 52-week repeat oral dose toxicity study in dogs, followed by a 12-week off-dose period. In the testes, a minimal reduction of cellularity of the seminiferous epithelium was seen in the single low dose and three high dose males with reduced testicular weight. The effect was not seen following an off-dose period of 12 weeks.
The CHMP agreed that the wording on the reversibility of the degenerative testicular epithelium should be included in this section.

Serologic determination is not readily performed in clinical practice differentiating between patients with primary disease versus recurrent episodes of genital herpes. Most clinical guidelines advise clinicians to manage these cases as potential primary episodes using higher doses than is usually recommended for episodic therapy (Kinghorn et al. 2007, Money and Steben 2008, Patel et al. 2001, Workowski and Berman 2006). Approximately two thirds of genital herpes acquisitions are asymptomatic but not necessarily totally quiescent and that the majority will develop symptomatic recurrent disease. When such patients present for the first time to a clinician, it can be difficult to differentiate between what is probably a recurrent episode and what may be an acquisition episode. Acquisitions can only be excluded when there has been no sexual exposure in the previous 3 weeks, but such a distinction is rarely clinically useful. Primary episodes can only be diagnosed serologically. On the other hand, in recurrent disease, if the current episode is established and has progressed beyond the papule stage, the patient will be advised to take nothing for this episode and to wait for the next episode to take patient initiated therapy. Therapy should be patient initiated and ideally started within the first 6 hours after an episode has recurred.

Both famciclovir and valaciclovir have been evaluated at various doses and compared to aciclovir, each other or to placebo.

Individual trials have attempted using subset analyses to look for groups that may benefit from higher doses, but no such effects have ever been reported. Further subset analyses over those currently available are of academic value will add little to these historic treatment strategies and are unlikely to impact clinical practice.

The famciclovir pivotal studies in first episode of genital herpes randomized all patients with a first episode of suspected genital herpes to receive treatment, which mimics the clinical situation. Serologic determination followed. Subset analysis by pre-existing serologic status showed that although true primary infection was associated with longer viral shedding and time to lesion healing, there were no statistically significant differences between the recommended dose for first episode of genital herpes (250 mg t.i.d. for five days) and the higher doses evaluated.

Famciclovir 125 mg b.i.d. for five days is approved for episodic treatment of recurrent genital herpes across all EU MSs in which Famvir is currently registered and Iceland.

2.3 Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4 Recommendation

As an outcome of the scientific discussion, the CHMP concluded that the maximum daily dose should be reduced to 500 mg twice daily. As a consequence the 750 mg strength currently authorised in four MSs was considered obsolete in accordance with the agreed harmonised SPC.
The CHMP recommended the withdrawal of the 750 mg film coated tablets for Famvir and associated names.

2.5 Conclusions

The basis for this arbitration procedure was a harmonisation of the SPC, labelling and package leaflet.
The CHMP having considered

- the Rapporteur and Co-Rapporteur assessment reports,
- scientific discussion within the Committee,
- comments and commitments from the Marketing Authorisation Holders,

was of the opinion that the benefit/risk ratio of Famvir and associated names is considered to be favourable. The CHMP adopted a positive Opinion recommending the harmonisation of the SPC, labelling and package leaflet as set out in Annex III of the CHMP Opinion for Famvir and associated names (see Annex I).