European Medicines Agency

London, 22 April 2010
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ASSESSMENT REPORT

Valtrex and associated names

INN / active substance: valaciclovir

PROCEDURE No: EMEA/H/A-30/1004

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 October 2008 the European Commission presented to the EMEA a 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:

Valtrex 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 November 2008 meeting. The Marketing Authorisation Holder was informed of the start of the procedure.

The CHMP appointed Dr Tomas Salmonson (SE) as Rapporteur and Dr Pierre Demolis (FR) as Co-Rapporteur.

Valtrex and associated names are registered in all EU Member States (including Iceland and Norway) as listed in Annex I and currently not registered in Hungary.

2. Scientific discussion during the Arbitration procedure

2.1 Introduction

Valtrex is an oral tablet containing valaciclovir (VACV), the esterified prodrug of the antiherpetic compound Aciclovir (ACV). The Marketing Authorization Holder is GlaxoSmithKline and associated companies. Aciclovir is a potent and selective inhibitor of a number of herpes viruses, including the human pathogens herpes simplex virus (HSV) type 1 and 2, varicella zoster virus (VZV), and cytomegalovirus (CMV). Aciclovir inhibits herpes virus DNA polymerase once it has been phosphorylated to the active triphosphate form. Valaciclovir is rapidly and almost completely converted to aciclovir and L-valine via intestinal and hepatic first-pass metabolism. Valaciclovir achieves high bioavailability of aciclovir (3 to 5 fold higher than with oral aciclovir), allowing less frequent dosing. At higher doses, plasma exposure of aciclovir following oral Valaciclovir administration is similar to that measured after intravenous aciclovir.

Valtrex (and associated names) has been included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended.

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned products (and its associated names), the European Commission notified the CHMP/Agency Secretariat of an official referral under Article 30(2) of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise the SPCs across the EU.

In addition, as agreed with the EMEA, GSK have also taken this opportunity to harmonise the CMC quality data (Module 3) during this Article 30 referral.

The areas of disharmony mainly pertain to sections 4.1, 4.2, 4.3 and 4.6 of the SPC.

2.2 Critical Evaluation

The antiviral drugs aciclovir and valaciclovir have augmented the possibilities for treatment of herpes zoster and herpes simplex. The prognosis of disease has improved by early treatment, similarly the intensity and duration of pain associated with herpes zoster can be reduced. These antiviral drugs have generally have a known safety profile. However, serious neurological adverse events, even fatal, with hallucinations, confusion, tremor, mycoclonus and coma have been reported with the use of valaciclovir. Individuals with initial normal renal function may experience acute renal dysfunction during treatment caused by precipitation

of aciclovir crystals in renal tubuli followed by acute tubular necrosis and acute renal failure. These events appear to be dose-related. Elderly patients, preferably women, with renal dysfunction by age and/or impaired renal function caused by nausea, vomiting and insufficient nutrition and fluid imbalance are particularly vulnerable. Thus, careful adjustment of the dosage is considered indispensable. Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered management option in the event of symptomatic overdose.

Section 4.1 Therapeutic Indication

Valtrex is indicated for:

1- Varicella zoster virus (VZV) infections – herpes zoster
2- Cytomegalovirus (CMV) infections
3- Herpes simplex virus (HSV) infections

Indication 1- Varicella zoster virus (VZV) infections herpes zoster

The following indication was agreed:
"Valtrex is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults.
Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression".

The CHMP endorsed the MAH's proposal to delete "*Valtrex accelerates the resolution of pain….and postherpetic neuralgia"* and the information was moved under section 5.1.

Regarding the prevention of ocular complications, present in some MS SPC, the CHMP noted that it is a secondary benefit of the treatment of VZV infection, therefore this part of the indication was covered by a statement in section 5.1

Indication 2 - Herpes simplex virus (HSV) infections

Regarding herpes simplex there were differences between Member States regarding site of infection and recommendations for treatment, suppression or prevention.

HSV Treatment
The MAH, in order to prove the safety and efficacy of valaciclovir for the treatment of HSV, evaluated the product in a clinical development programme of six studies focusing on genital herpes (HSV-2) infection.

These studies showed that valaciclovir was superior to placebo and/or as effective as aciclovir in reducing episode duration, viral shedding and lesion healing time.

HSV Suppression for Outbreak Reduction (recurrent episodes of genital herpes simples)
The MAH in order to demonstrate efficacy in the suppression of genital herpes recurrences presented two Studies (123-026 and 123-037). Valaciclovir was significantly more effective than placebo in delaying the time to first genital herpes recurrence (Patel, 1997; Reitano, 1998). A recent meta-analysis (Lebrun-Vignes, 2007) provided additional supportive data for this indication.

Genital Herpes Suppression for Transmission Risk Reduction
The MAH presented the Study HS2AB3009 to demonstrate the efficacy of valaciclovir suppressive therapy (500 mg once daily).

The CHMP concluded that the indication about prophylaxis for transmission of genital herpes with VACV can not be regarded to as indication itself but rather to be associated with the treatment of initial and

recurrent treatment of genital herpes. This information is included in section 4.4 of the SPC.

Treatment and Suppression of HSV-Related Ocular Infections
The MAH presented several studies to evaluate the efficacy of oral aciclovir for HSV keratitis after penetrating keratoplasty (Barney, 1994; van Rooij, 1995, and 2003).

The approved dosages were based on comparative estimates of systemic aciclovir exposure (Weller, 2000). The results of the Weller study showed that valaciclovir is comparable to aciclovir in the prevention of herpes keratitis during long term follow-up after surgery.

The CHMP considered that only studies of limited size and unknown quality have been reported. Furthermore, the safety of the potentially higher intraocular concentrations of aciclovir after valaciclovir use in infected eyes has not been satisfactorily addressed. The CHMP concluded that the only ocular use that should be noted is the *treatment of ophthalmic zoster*.

The CHMP agreed to include a reference to ocular HSV in section 5.1 "*Valtrex reduces the risk of ocular complications of ophthalmic zoster"*.

Herpes labialis infections (HSV-1)
The MAH to support this proposed indication presented two randomised, placebo controlled studies (HS230027 and HS0028) [Spruance, 2003] evaluating the efficacy and safety of one dosing regimen of VACV, 2000 mg twice daily for 1 day, compared to placebo. Based on the results of these two studies the International Herpes Management forum (IHMF) [Gilbert, 2007] recommends short course, high dose therapy for treatment of herpes labialis as an alternative to other approved regimens.

The MAH provided several key documents describing Study HS230027 and Study HS230028, and data analysis supporting short-course, high-dose therapy in immunocompetent adolescents and adults. These include also a Clinical Overview describing safety and efficacy of the pivotal efficacy trials. The CHMP agreed that for herpes labialis, valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents.

The CHMP considered *Herpes labialis* covered by the indication "*Treatment and suppression of HSV infections of the skin and mucous membranes*", and concluded that does not deserve to be specified in section 4.1 of the SPC although the short course dosage shall be mentioned in Section 4.2.

The CHMP agreed the removal of several more specific indication statements (i.e., herpes labialis, ocular HSV infections, reduction of transmission).

Several indications were not approved in all Member States, in particular for *immunocompromised* patients. The safety and efficacy of valaciclovir for the treatment of HSV in immunocompromised patients was evaluated in Study 123-008 but there are limited data available to demonstrate the efficacy and the optimal dosage of VACV for treating HSV in immunocompromised patients.

The MAH responded that is not recommending inclusion of an indication for valaciclovir in the treatment of HSV in immunocompromised patients.

HSV Suppression in HIV-infected Patients
Studies 123-007 and HS230018 were conducted to evaluate the safety and efficacy of valaciclovir in the suppression of recurrent ano-genital HSV episodes in HIV-infected subjects (Conant, 2002).

The CHMP endorsed the following wording for the treatment of herpes simplex virus:
"Valtrex is indicated

- *for the treatment and suppression of HSV infections of the skin and mucous membranes including*

- treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults
- treatment of recurrences of genital herpes in immunocompetent adults and adolescents, and in immunocompromised adults
- suppression of recurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults

- *Treatment and suppression of recurrent ocular HSV infections.*

Indication 3 Cytomegalovirus (CMV) infections
Prophylaxis of cytomegalovirus is not approved in some Member States.

Cytomegalovirus is a leading cause of virus-associated birth defects, including mental retardation and deafness and may cause severe and fatal diseases in immunocompromised individuals. Approximately 12% of CMV-seropositive bone marrow transplant (BMT) recipients who are not given pre-emptive antiviral therapy will develop CMV disease. Similarly, CMV disease is a leading infectious cause of morbidity in solid organ transplantation and the mortality rate in untreated renal transplant patients with CMV disease is around 65%. Transplant recipients who are CMV-seronegative and receive an organ from a CMV-seropositive donor have a particularly high risk of developing CMV disease. Other immunosuppressed patients as those with HIV are also susceptible and in patients with AIDS, CMV most commonly manifests itself as necrotising retinitis.

The MAH pointed out that Valaciclovir is approved in the majority of Member States for prophylaxis of cytomegalovirus (CMV) infection and disease following organ transplantation. Valaciclovir has been investigated as prophylaxis for the suppression of CMV infection in both the solid organ and bone marrow transplant (BMT) settings, with demonstrated efficacy and a favourable safety profile. The MAH contended that the clinical data from the trials are robust and justify inclusion of this indication in the harmonised SPC for all Member States.

The valaciclovir dosage for CMV prophylaxis in organ transplant recipients (2g four times a day) was selected with the goal of providing a similar systemic exposure to aciclovir to that from the approved regimen of intravenous aciclovir for CMV prophylaxis in bone marrow transplant patients. Oral valaciclovir produces lower aciclovir peak concentrations compared with comparable intravenous aciclovir doses while providing similar daily systemic exposures (AUC) and more convenient dosing.

Prophylaxis of cytomegalovirus in Solid Organ Transplantation
The MAH completed two studies to determine the safety and efficacy of VACV compared to ACV or placebo for the prophylaxis of CMV infection and disease in solid organ transplant.

The first one was a pivotal trial (Study 123-012) in renal transplant patients (Lowance, 1999) and the second one was a smaller trial (Study 123-031) in adult heart transplant recipients (Egan, 2002).

In study 123-012 the results indicate that prophylaxis with oral VACV in renal transplant patients reduced the incidence or delayed the onset of CMV disease in both the seropositive and the seronegative recipients. The results of Study 123-031 showed a significant difference in time to development of CMV antigenemia and similar delays of acute rejection and fewer opportunistic or other herpes infections in favour of VACV.

The CHMP noted that these findings support an additional effect of VACV prophylaxis on preventing CMV infection/disease, although this can not be addressed as a primary indication for treatment.

Prophylaxis of cytomegalovirus in Bone marrow transplantation
Two studies were conducted by the MAH to support this indication. Study 123-016, a randomized, double-blind, multicenter study and Study 123-039 an open-label, randomized, multicenter study.

Safety data indicate that the safety profile of prophylactic IV treatment with ganciclovir and oral treatment with VACV, respectively, in BMT patients were comparable. The safety profile of the two active treatment

groups did not differ significantly and were both similar to that of the placebo group. The reported AEs were listed events and no new and significant safety signals could be identified in relation to any of the treatment regimens.

CMV following organ transplantation remains a major problem, both as a direct cause of CMV disease and indirectly as a risk factor for acute graft rejection, opportunistic infections and death. Valaciclovir offers proven efficacy for prophylaxis of CMV infection and disease and has also been shown to influence positively other outcomes such as graft rejection and opportunistic infections.

Even though these resulting effects of reduction of acute graft rejection, opportunistic infections and other herpes infections (HSV, VZV) by treatment with VACV are supported by the provided documentation the primary effect of valaciclovir is prevention of CMV infection and disease and the observed positive influence on other outcomes are secondary effects.

The CHMP considered that as a consequence of the prophylactic treatment and thus be annotated in section 5.1. The MAH accepted the CHMP's proposal to annotate these additional benefits from CMV prophylaxis with valaciclovir in Section 5.1 and to modify the indication statement for CMV prophylaxis as follows: *Section 4.1"Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (see section 4.4)"*.

The posology is overall uniformly recommended and should be approved:
The dosage of Valtrex is 2 g four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance. The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.

The modified indication statement regarding prophylaxis of CMV infection and disease following organ transplantation is endorsed by the CHMP. Inclusion of the recommended associated wording in section 5.1 indicating the anticipated effect of VACV prophylaxis in organ transplanted subject is considered appropriate.

In the absence of direct comparison, it is unclear to what extent the use of valaciclovir might not represent a potential loss of chance as compared to valganciclovir in the prophylaxis of CMV infection and disease following organ transplantation. The MAH was asked to give reassurance that the benefit/risk of valaciclovir can be regarded as similar to that of valganciclovir, currently widely used in clinical practice.

The MAH, to show the safety and efficacy of valaciclovir for the prophylaxis of CMV disease in transplant recipients, presented four randomized, controlled clinical trials: Lowance, 1999; Egan, 2002; Ljungman, 2002; Winston, 2003.

The Lowance study demonstrated that prophylactic treatment with valaciclovir is a safe and effective way to prevent CMV disease after renal transplantation.

Results from Egan study indicated that high-dose valaciclovir significantly delayed the incidence of CMV antigenemia and had positive effects on time to CMV infections, symptoms and disease compared to low-dose oral aciclovir.

The Ljungman study demonstrated that valaciclovir was significantly more effective than oral aciclovir in reducing the incidence of CMV infection ($P < 0.0001$), and the safety of oral valaciclovir was similar to that of high-dose oral aciclovir.

The authors of Winston study concluded that oral valaciclovir can be an effective alternative to IV ganciclovir for prophylaxis of CMV disease after bone marrow transplant.

The CHMP considering the above trials results endorsed the use of valaciclovir for the prophylaxis of CMV infection. However, the use of valaciclovir in prophylaxis of transplant should be restricted to solid organ transplant.

The CHMP endorsed the following amendment to section 5.1.
"There is no direct comparative study versus valganciclovir to define the optimal therapeutic management of solid organ transplant patients."

The CHMP proposed the removal of several more specific indication statements (i.e., herpes labialis, ocular HSV infections, reduction of transmission)

Section 4.2 Posology and method of administration

There were differences in Section 4.2 between Member States. Some Member States have recommendations of a higher dose than other member states in specific situations.

Immunocompromised
The MAH responded that higher doses of valaciclovir usually are recommended for dosing in immunocompromised subjects relative to immunocompetent subjects for a common indication.

Herpes labialis
The MAH gained approval in some Member States for the use of valaciclovir at a higher dose and shorter course (2g twice daily for one day) for the treatment of herpes labialis (Clinical practice recommendation of the International Herpes management Forum (IHMF) [Gilbert, 2007]).The CHMP considered that herpes labialis should not be a specific treatment indication, however the dosage for herpes labialis could be mentioned under this section. The included study reports have shown that no additional clinical benefit was found with 2-day vs. 1-day treatment (Spruance, 2003). However, the 1-day valaciclovir regimen offers patients a convenient dosing alternative compared to available topical therapies and longer-course aciclovir and valaciclovir regimens.

The CHMP endorsed the following:
"For herpes labialis (cold sores), valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose."

Renal impairment
Some Member States have revised the dose recommendations in patients with renal impairment in treatment of herpes zoster based on safety signals.

Only one MS has revised the dose recommendations for Valtrex for patients with renal impairment after considering concerns on the risk of central nervous system (CNS), adverse effects in patients taking valaciclovir or aciclovir and the potential need to modify recommended dosages in patients with renal impairment.

The CHMP proposed to reduce doses in renal impairment but the MAH was of the opinion that the precautionary statements regarding use in the elderly and patients with renal impairment, the maintenance of adequate hydration, and adherence to the recommended dosage reductions for patients with renal impairment were adequate and appropriate.

The MAH stated that the pivotal studies of valaciclovir for treatment of HSV and VZV infections and for suppression of HSV recurrences had enrolment criteria that excluded most subjects with significant renal impairment. The criteria varied among studies, but excluded subjects with either serum creatinine greater than the upper limit of normal (Scr > ULN), Scr > 1.5 mg/dL (~133 uM), or with creatinine clearance less than 35 mL/min. The data were therefore not sufficient for subgroup analyses of efficacy and safety.

The MAH had no data indicating that patients with renal impairment have an altered PK/PD relationship compared with patients with normal renal function such that they would require higher aciclovir exposure for comparable treatment effect.

Thus the effectiveness of different valaciclovir doses in patients with similar degrees of renal function could not been compared.

The CHMP concluded that there was no data to suggest that patients with renal impairment need higher exposure for treatment effect. The CHMP recommended a cut-off at 10 ml/min in this case (resulting in an estimated exposure of 39-63 at <10 ml/min and 43-77 at CLcr 10-30 ml/min).

The CHMP agreed a reduced dosage in renal impairment.

The CHMP requested the MAH to further discuss the proposed dose adjustment for *renal impairment* at one-day treatment of *herpes labialis*. The dose is reduced by 50% already at CLcrea 30-49 ml/min, while for varicella-zoster infections, which have a normal dose in about the same range as that proposed for *herpes labialis*, the dose is reduced by 33% at CLcrea 30-49 ml/min.

The MAH provided the dosage adjustment rationale for the treatment of herpes labialis in subjects with renal impairment. Two randomized, double-blind, placebo-controlled safety and efficacy studies were described to support the use of valaciclovir in the treatment of cold sores (herpes labialis). Creatinine clearance estimates were similar between treatments and between the two studies.

Dosage selection for treatment of cold sores was based on administration of high-dose valaciclovir during prodrome, targeting plasma concentrations to exceed the *in vitro* IC99, based on the hypothesis that optimal antiviral effect would be obtained from high systemic exposure during the time that viral replication dominates temporarily over the host immune response. Accordingly, evaluation of valaciclovir dosage regimens for patients with renal impairment were primarily derived such that *peak aciclovir concentrations* (Cmax) would approximate those from 2000mg bid one-day dosing in subjects with CLcr from 50 to 120 mL/min. Estimates for total area under the aciclovir concentration-time curve (AUC) are also considered.

Estimations of relationships between aciclovir pharmacokinetics and renal function are obtained from subjects in Studies P66-01, P66-02, P66-09 and P66-10 who received valaciclovir 1000mg doses.

Aciclovir bioavailability from valaciclovir decreases somewhat with increasing dose. Thus, in addition to altered aciclovir pharmacokinetics in renal impairment, this factor also needs to be taken into account in developing dosage adjustments based on Cmax and/or AUC.

Based on results from study P66-09, estimates of relative bioavailability of aciclovir from different valaciclovir dose levels were assumed to be independent of renal function.

For the proposed valaciclovir dosage regimens, predicted total aciclovir AUCs for subjects with severe renal impairment are greater than those expected in subjects with less severe renal impairment. However, the primary safety concerns with aciclovir pertain primarily to reversible acute effects on renal function due to the potential for crystallization in renal tubules. Although rare, this is thought to be associated with high peak concentrations rather than AUC. Additionally, the model results chosen for predictions of Cmax and AUC were conservative by their provision of higher estimates for subjects with severe renal impairment. Given that expected peak concentrations in this group appear to be near the low end of the range for subjects with CLcr $\geq$ 50 mL/min and that only a single dose would be administered, assurance is provided regarding the appropriateness of the proposed regimens. Pharmacokinetic variability (% CV) in Cmax and AUC are expected to be similar for different doses and degrees of renal impairment.

The CHMP noted that the suggested dose reductions for renal impairment at treatment of herpes labialis were somewhat different from that for other indications, since the dose is halved already at CLcrea 30-49 ml/min, despite the relatively low dose. For other indications where the normal dose is in the lower range,

dose reductions in renal impairment are not made until CLcrea is below 30 ml/min, since at these exposure levels, the expected increase in exposure at CLcrea 30-49 ml/min is not considered a great safety risk.

The CHMP asked for the rationale behind the proposed doses in herpes labialis due to a concern that a dose reduction already at CLcrea 49 ml/min might possibly lead to underexposure. However, the modelled data presented indicated that the Cmax (suggested to be important for the short-term treatment of herpes labialis) and the AUC will still be sufficient in the group with CLcrea 30-49 ml/min. It should be kept in mind that the modelling is based on some not very strong relationships, e.g. Cmax as a function of creatinine clearance. Nevertheless, given the relatively benign indication, a conservative approach might be appropriate to reduce the potential safety risk.

Immunocompromised
The MAH stated that higher doses of valaciclovir usually are recommended for dosing in immunocompromised subjects relative to immunocompetent subjects for a common indication.

As requested by the CHMP, the MAH reconsidered the use of valaciclovir for zoster treatment in immunocompromised patients and reviewed treatment guidelines. The French guidelines recommend valaciclovir 1000 mg 3 times daily (TID) with close follow-up [Yeni, 2008]. The IDSA (Infectious disease society of America) recommends valaciclovir 1000 mg TID [Dworkin, 2007] and the European Conference on Infections in Leukemia recommends the same valaciclovir dosage for at least 7 days [Styczynski, 2009].

The CDC advocates that prompt antiviral therapy should be instituted in all immune-suppressed herpes zoster patients within 1 week of rash onset or any time before full crusting of lesions. Oral valaciclovir 1000 mg TID for 7-10 days is a recommended treatment option for acute localized dermatomal herpes zoster in HIV-infected patients**.** If cutaneous lesions are extensive or if visceral involvement is suspected, IV aciclovir should be initiated and continued until clinical improvement is evident [Balfour, 1983]. A switch from IV aciclovir to oral antiviral therapy (to complete a 10-14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving [CDC, 2009].

The MAH stated that published reviews and guidelines support the use of valaciclovir for the treatment of herpes zoster in immunocompromised subjects with localized dermatomal infection, and suggested a dose of 1000 mg three times daily.

The CHMP endorsed the wording and considered acceptable the posology 1000 mg three times daily.

Section 4.3 Contraindications

Some Member States have an additional contraindication for pregnancy and lactation. Some Member States have an additional contraindication for virus resistant to aciclovir**.**

The MAH retained an appropriate cautionary statement in the Pregnancy and Lactation Section 4.6 in the harmonised EU SPC. The MAH believed that the use of valaciclovir in pregnancy should not be contraindicated.

The CHMP endorsed the proposal from the MAH considering it in line with currently applicable guidelines and accurately reflects data available.

The CHMP endorsed the MAH's proposal to not include the insertion of viral resistance in the Section 4.3. Viral resistance differs from a condition where the drug must not be given for safety reasons and a distinction is to be made between safety risks versus reduced efficacy.

The CHMP endorsed also contraindications regarding hypersensitivity to ACV, VACV or formulations of VACV.

Section 4.6 Pregnancy

The level of information differs across Members States. Similar type of data is presented but the level of factual detail varies significantly. Recommendations for use also show differences.

The benefit and risk assessment of the use of valaciclovir in specific indications and in specific individual pregnant or lactating women falls within the remit of the treating physician.

The CHMP endorsed the MAH proposal to state, under this section, that valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risks.

As requested, the MAH conducted a review of available information since closure of the Pregnancy Registry. In addition, the MAH assessed reports of pregnancy and pregnancy outcomes available in the MAH's Worldwide Clinical Safety Database. The extent of exposure in this population is difficult to quantify. Analysis of the published literature showed no new significant safety concerns for the babies or the mothers. A significant proportion of the congenital anomalies described in the articles were consistent with the known foetal adverse effects of intra-uterine infection with CMV.

The CHMP found the new proposal acceptable. However, minor changes to the text were recommended as such as the amount of experience accumulated with valaciclovir and aciclovir in pregnancy was quantified (designated as limited or moderate, respectively), the historical corresponding numbers from the final study report of the Pregnancy Registry were inserted to illustrate the data available.

Section 4.8 Undesirable Effects

The CHMP asked the MAH to substantiate all proposed frequencies and to submit, with adequate supportive data, a new section 4.8 more in line with the SPC guideline.

Clinical trial data
Data from valaciclovir (VACV) clinical trials were used to estimate the frequency category of those events identified by the MAH as drug related based on clinical trial data. For those adverse events with evidence of a drug association, the excess frequency in the study drug group was used to determine the frequency grouping. Based on these data, an AE frequency category of "common" has been assigned to the following AEs: headache and nausea.

Postmarketing data
Spontaneous data has been used as the basis for assigning frequency categories for AEs not identified as being possibly drug related from clinical trial data.

Since there was no robust denominator when using spontaneous reports, an AE frequency/category of "unknown" has been assigned to the following AEs: leucopenia, thrombocytopenia, anaphylaxis, dizziness, confusion, hallucinations, decreased consciousness, agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma, dyspnoea, abdominal discomfort, vomiting, diarrhoea, reversible increases in liver function tests (e.g. bilirubin, liver enzymes), rashes including photosensitivity, pruritus, urticaria, angioedema, renal impairment, acute renal failure, and renal pain.

The MAH accepted the SPC changes proposed by the CHMP, apart from the removal of "tremor, ataxia, dysarthria, psychotic symptoms" from the description of neurological disorders, as removal of these events would not reflect the full AE profile of valaciclovir.

The MAH also wished to retain all the neurological AEs listed in Section 4.8 as these are known Adverse Drug Reactions (ADRs) with valaciclovir treatment. Based on the above information, the MAH proposed a revision to Section 4.8.

The CHMP noted that in post marketing experience (spontaneous reporting), according to the SPC guidelines, the number of spontaneous reports should not be stated because this number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used to assign frequency category. In case a particular adverse reaction has not been observed in a specific number exposed to the product in clinical trials and studies then the upper limits of the 95% confidence interval for the point estimate should be used for indication of the frequency category.

The MAH noted evidence of a causal association with valaciclovir, regardless of statistical significance. For AEs identified from spontaneous reporting, the frequency will be referred to as "not known" as requested. For AEs identified from clinical trials, a frequency category has been assigned based on the overall frequency observed in clinical trials. Therefore the frequency category for "nausea" is common (>1/10 to <1/100) and the frequency category for "headache" will be very common (>1/10).

The MAH, as requested, included an introductory statement in Section 4.8 to clarify the sample size/exposure from clinical trials. The sample size of the clinical trial database is based on pooled data from valaciclovir pivotal studies for 4 different indications. These studies were selected as most representative of the product safety profile for the general population exposed to valaciclovir and cover approximately 5855 subjects. The 5855 subjects are comprised as follows: herpes zoster treatment (n=967); genital herpes treatment (n=1160 high dose and n=1203 low dose); genital herpes suppression (n=1009 high dose and n=269 low dose); cold-sore treatment (n=609 high dose and n=638 low dose).

The MAH, as requested, re-calculated the adverse reactions (ARs) frequency categories for those reactions identified from post-marketing data to take into account the revised SPC guidelines.

The MAH also clarified that the clinical trial database, composed of pooled clinical trials data for four indications, as described above, was used to re-calculate the frequencies of ARs identified in the post marketing setting. The selection of the studies included in this clinical trial database reflects the product safety profile for the general population exposed to valaciclovir.

The MAH presented, in a table of the document responses, the recalculated AR frequencies for those ARs identified from post-marketing experience and the supporting analyses. In situations where there were different incidences across studies, the most conservative approach was taken i.e. frequency category was based on the higher incidence.

The CHMP asked the MAH to give an estimate of the frequency of resistance in immunocompetent and immunocompromised across clinical trials to be put in perspective to post marketing data.

The MAH replied that the antiviral agents directed at herpes viruses have been used clinically for over twenty-five years and the prevalence of aciclovir-resistant HSV has remained low and stable in post-marketing experience.

HSV resistance to aciclovir, the active metabolite of valaciclovir, is less than 1% in immunocompetent subjects and approximately 5-6% in immunocompromised subjects (as measured by plaque reduction assay). The incidence of aciclovir resistance is stable, has not changed in the nearly three decades and is not different between treated patients and untreated subjects.

These data give confidence that the potential for development of resistance has not diminished the established benefit/risk profile of valaciclovir.

Antiviral resistance in immunocompetent patients
According to several surveys, the isolation of HSV resistant to aciclovir or other antiherpetic agents is rare in the immunocompetent population (<1%) [Bacon, 2003; Christophers, 1998; Field, 2001]. Data from extensive surveys conducted in the UK and US provide baseline information on the susceptibility of HSV isolates from immunocompetent individuals who have not been exposed to aciclovir [Collins, 1991; Christophers, 1998; Hill, 1993; Hill, 1995]. The prevalence of resistant virus in these surveys was 0.3% and

2.5% for untreated subjects. Overall, in the same surveys, the prevalence of resistant virus was similar among isolates from aciclovir-treated subjects (0.5% and 3.2%) and untreated individuals (0.3% and 2.5%).

Additionally, a collaborative surveillance system for aciclovir-resistant HSV has been established in the US through the CDC and the Task Force on Herpes Simplex Virus Resistance to estimate the prevalence of aciclovir-resistant genital HSV among immunocompetent patients with sexually transmitted diseases (STD) and patients infected with human immunodeficiency virus (HIV) [Reyes, 2003; Gnann, 1999]. The results of this surveillance between 1996 and 1998 for treated immuno-competent patients (1644 isolates) were comparable to other surveys (aciclovir resistance in 0.18% of isolates). Most recently, a survey for penciclovir resistance reported two resistant isolates out of 1035 isolates (0.19%) obtained from 2 of 585 (0.34%) immunocompetent, treated patients [Sarisky, 2002]. Notably, both resistant isolates were transient in that subsequent isolates from these patients were susceptible to penciclovir and aciclovir.

There has been debate as to whether development of resistance is associated with prior aciclovir use. The Fife's study in1994 reported that the frequency of resistance has not changed from the time before the availability of aciclovir and does not appear to increase in immunocompetent subjects maintained on antiherpetic suppressive therapy for several years.

The in vitro sensitivity of HSV-2 isolates to aciclovir was evaluated in three completed clinical studies of valaciclovir in immunocompetent subjects [Fife, 2008; Sperling, 2008; Martens, 2009]. In the first study, Fife and colleagues enrolled 384 newly infected subjects with HSV-2, and collected swab samples at screen and during genital herpes recurrence visits. A total of 221 HSV-2 culture samples were tested for aciclovir-sensitivity and three possible aciclovir-resistant isolates (1.4%) were initially reported. Upon repeat assay however, the three isolates initially reported as resistant were all susceptible to aciclovir. One of these isolates was obtained at screening (before administration of study drug); the other two isolates were from a single subject and were obtained from recurrence visits for outbreaks while on placebo [Fife, 2008]. In the other two clinical studies, HSV-2 isolates obtained from subjects not responding to a routine course of episodic treatment for recurrent genital herpes were analyzed for aciclovir sensitivity [Sperling, 2008; Martens, 2009]. In these combined studies, all isolates obtained (7 isolates from 5 subjects) were sensitive to aciclovir with IC50 values less than 2.0 μg/ml [Sperling, 2008; Martens, 2009].

Antiviral resistance in immunocompromised patients
Isolation of HSV resistant to aciclovir occurs more frequently in immunocompromised compared to immunocompetent individuals [Field, 2001; Bacon, 2003]. Almost 30 years ago, Wade et al. reported a prevalence rate of aciclovir-resistant HSV ranging from 2% to 9% in bone marrow transplant recipients treated with aciclovir [Wade, 1983]. Similar results were reported by Englund and colleagues [Englund, 1990]. With the increase in the immunocompromised population due to HIV infection and AIDS, reports of resistant isolates have increased while the actual frequency of resistance has not [Erlich, 1989; Kimberlin, 1996; Bacon, 2003]. More recently, a CDC surveillance study reported an incidence of aciclovir-resistant HSV strains of 5.3% in this population [Reyes, 2003]. Similar results have been obtained in other studies (Table 3) and underscore the fact that the prevalence of resistant HSV in this population is stable. The MAH conducted a study, HS230018, in HIV-infected subjects and a similar incidence of aciclovir-resistance was observed (three aciclovir-resistant isolates (3/50, 6.0%) [DeJesus, 2003].

There is no evidence that the incidence of aciclovir resistance in immunocompromised subjects is increasing. Moreover, it appears that the development of aciclovir-resistance in immunocompromised subjects does not pose a risk for the development of resistance in immunocompetent subjects [Field, 2001].

Use of prophylactic antiviral regimens reduces the number of replicating viruses which, in turn, is thought to decrease the likelihood of viral mutations [Ambinder, 1984]. It has been proposed that the increased incidence of aciclovir resistant HSV strains in HIV-infected subjects may be due to increased replication of attenuated strains allowed by decreased immune function [Field, 2001; Bacon, 2003]. Therefore, it has been hypothesized by some investigators that use of suppressive anti-herpetic therapy in HIV-infected subjects may actually decrease the probability of resistance [Severson, 1999]; this hypothesis does not yet have experimental confirmation.

Transmission of resistant HSV
To date there has been no unequivocal evidence of transmission of an aciclovir-resistant HSV strain from person to person, although this remains a theoretical possibility. A single publication [Kost, 1993] reports a case study in which transmission of a resistant HSV strain is described as a possibility; however, paired source and patient isolates required for proof of transmission were not available for analysis The absence of documented transmission of aciclovir-resistant HSV is in contrast to other virus and drug combinations such as HIV and antiretrovirals as described by Romano et al. [Romano, 2002]. One of the reasons for this paucity of data may be that almost all aciclovir-resistant mutants are TK-deficient (95% on average) and such mutants have reduced pathogenicity and greatly impaired ability to reactivate from latency in animal models [Coen, 1994]. Therefore, the great majority of resistant strains are likely to be less biologically competent in the normal human infection and transmission cycle. While very rare strains of aciclovir resistant HSV which retain pathogenicity have been reported, there is no evidence that they have established additional infections in the population[Hwang, 1994; Horsburgh, 1998; Swetter, 1998], even though one was isolated more than a decade ago [Grey, 2003].

Alternative treatment for aciclovir-resistant infection
Aciclovir-resistant HSV infections have been treated successfully with foscarnet [Safrin, 1991; Safrin, 1994; Chatis, 1989; Jones, 1995] and with cidofovir [Lalezari, 1994; Lalezari, 1997; Snoeck, 1994]. These agents act directly at the level of DNA polymerase and do not require phosphorylation by TK; both are effective in vitro against both TK-deficient and TK-altered HSV mutants [Gaudreau, 1998]. However, a few DNA polymerase mutants resistant to aciclovir are also cross-resistant to foscarnet and cidofovir.

Antiviral resistance modeling
Blower and colleagues developed an antiviral epidemic mathematics model of HSV-2 to predict levels of antiviral drug resistance that would emerge if treatment rates for genital herpes were substantially increased [Blower, 1998]. The model represents the linked transmission dynamics of drug-sensitive and drug-resistant HSV-2 in an immunocompetent community where patients receive either episodic therapy or no therapy. HSV-2 resistance could emerge within three scenarios: (1) susceptible individuals could acquire drug-resistant infection through sexual contact with an individual who has drug-resistant HSV-2, (2) HSV-2 resistance could develop due to acquired permanent resistance, or (3) HSV-2 resistance could occur due to acquired transient resistance. Predictions were based upon the assumptions that drug-resistant and drug-sensitive viruses differed only in their transmissibility and that drug-sensitive strains are more infectious than drug-resistant strains [Blower, 1998, Gershengorn, 2000].

Assuming that antiviral usage is high, only low levels of drug resistance are predicted to emerge even over a period of decades. Under the assumption that drug-resistant strains will only be attenuated in their ability to infect, it was predicted that only 7 in 1,000 individuals at 25 years are expected to be shedding drug-resistant strains and that even after 25 years of high antiviral usage, 4.5 cases of HSV-2 would be prevented for each prevalent case of drug-resistant HSV-2 [Blower, 1998; Gershengorn, 2000]. Assuming that drug-resistant strains will be less infectious and less likely to reactivate, only 5 out of 10,000 individuals are predicted to be shedding drug-resistant virus; furthermore, after 25 years, 52 cases of HSV-2 would be prevented for each prevalent case of drug-resistant HSV-2 [Gershengorn, 2003]. Thus, increasing episodic treatment rates (in an immunocompetent population) would mildly, yet significantly, decrease the incidence of HSV-2 infections. The actual impact of increased treatment rates on the incidence of new infections has not been determined, and in the model of White and Garnett [White, 1999], decreased incidence was not demonstrated. Importantly, and in contrast to the analogous situation with HIV and antiretroviral drugs, the prevalence of drug-resistant HSV-2 strains would remain low, even after several decades [Blower, 1998; Gershengorn, 2000; Gershengorn, 2003]. A very similar conclusion was reached in modelling of increased rates of topical treatment of herpes labialis, in which significant increases in resistance prevalence were not predicted for decades following the treatment increase [Lipsitch, 2000].

The CHMP concluded that the MAH has provided a comprehensive account for the frequency of resistance in immunocompetent and immunocompromised individuals across the clinical trials.

The conclusion summarises that the prevalence of aciclovir resistant HSV has not changed significantly during the last three decades. The HSV resistance in the immunocompetent is low; less than 1% and in the immunosuppressed subjects ~5-6% which similarly is considered to be low. These observations support safety of treatment of HSV in both groups although the possibility of increasing resistance should continuously be observed.

Section 5.1 Pharmacodynamic properties

The CHMP agreed to insert under this section a reference to valaciclovir to reduce the risk of transmission of genital herpes in immunocompetent adults when taken as suppressive therapy and combined with safer sex practices.

The success of chemotherapy or transplantation is often compromise by infection during the period of immunosuppression after treatment or surgery reactivation of latent viruses is particularly common (Bustamante, 1991; Houglund, 2001).

The CHMP noted that, the studies supporting the safe and efficacy use of valaciclovir were performed in HIV-patients only, and for the most in patients without severe CD4 depletion. However, valaciclovir showed efficacy in the treatment of herpes labialis (cold sores), mucositis due to chemotherapy or radiotherapy, HSV reactivation from facial resurfacing, and herpes gladiatorum.

Other Sections of the SPC

The CHMP asked the MAH to evaluate all other sections of the nationally approved EU SPCs and suggest appropriate changes in the text where divergences exist.

The MAH did a proposal for the harmonisation of valaciclovir SPCs taking into account the whole pharmaceutical presentations and all the dosages currently approved in at least one European MSs. Specific documentation was submitted to support some therapeutic indications, taking into account some updated data.

The CHMP found satisfactory the responses and the justification presented by the MAH.
As requested by the MAH, the Quality Module has been also harmonised.

2.3 Risk Management Plan

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

2.4 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,

the CHMP was of the opinion that the benefit/risk ratio of Valtrex 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 Valtrex and associated names (see Annex I).