**ANNEX I**

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES**

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Austria | GlaxoSmithKline Pharma GmbH, Albert Schweitzer-Gasse 6, A-1140 Wien, Austria | Valtrex 1000 mg - Filmtabletten | 1000mg | film – coated tablet | Oral use |
| Austria | Sandoz GmbH Biochemiestraße 10, 6250 Kundl Austria | Valaciclovir Sandoz 1000 mg - Filmtabletten | 1000mg | film – coated tablet | Oral use |
| Austria | GlaxoSmithKline Pharma GmbH, Albert Schweitzer-Gasse 6, A-1140 Wien Austria | Valtrex 500 mg - Filmtabletten | 500mg | film – coated tablet | Oral use |
| Austria | Sandoz GmbH Biochemiestraße 10, 6250 Kundl Austria | Valaciclovir Sandoz 500 mg - Filmtabletten | 500mg | film – coated tablet | Oral use |
| Austria | GlaxoSmithKline Pharma GmbH, Albert Schweitzer-Gasse 6, A-1140 Wien, Austria | Valtrex 250 mg - Filmtabletten | 250mg | film – coated tablet | Oral use |
| Austria | Sandoz GmbH Biochemiestraße 10, 6250 Kundl Austria | Valaciclovir Sandoz 250 mg - Filmtabletten | 250mg | film – coated tablet | Oral use |
| Belgium | GlaxoSmithKline s.a. /n.v., rue du Tilleul 13, B-1332 Genval, Belgium | Zelitrex | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Belgium | GlaxoSmithKline s.a. /n.v., rue du Tilleul 13, B-1332 Genval, Belgium | Zelitrex | 250mg | film – coated tablet | Oral use |
| Bulgaria | Glaxo Group Ltd<br>Greenford Road<br>Greenford<br>Middlesex UB6 0NN<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Cyprus | Glaxo Group Limited<br>Berkeley Avenue<br>Greenford<br>Middlesex , UB6 0NN,<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Czech Republic | The Wellcome Foundation Ltd., Glaxo Wellcome House<br>Berkeley Avenue<br>Greenford<br>Middlesex<br>UB6 0NN,<br>United Kingdom | Valtrex 500 mg | 500mg | film – coated tablet | Oral use |
| Denmark | GlaxoSmithKline Pharma A/S,<br>Nykaer 68<br>2605 Broendby,<br>Denmark | Zelitrex | 1000mg | film – coated tablet | Oral use |
| Denmark | GlaxoSmithKline Pharma A/S,<br>Nykaer 68<br>2605 Broendby,<br>Denmark | Zelitrex | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Denmark | GlaxoSmithKline Pharma A/S,<br>Nykaer 68<br>2605 Broendby,<br>Denmark | Zelitrex | 250mg | film – coated tablet | Oral use |
| Estonia | Glaxo Wellcome Operations<br>Glaxo Wellcome House,<br>Berkeley Avenue, Greenford,<br>Middlesex UB6 0NN,<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Finland | The Wellcome Foundation Ltd.<br>Greenford, Middlesex,<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Finland | Orion Corporation<br>Orionintie 1<br>FI-02200 Espoo,<br>Finland | Valavir | 500mg | film – coated tablet | Oral use |
| Finland | GlaxoSmithKline Oy<br>Piispansilta 9 A,<br>02230 Espoo,<br>Finland | Valtrex | 250mg | film – coated tablet | Oral use |
| France | Laboratoire GlaxoSmithKline<br>100 route de Versailles<br>78163 Marly-le-Roi cedex,<br>France | Zelitrex 500 mg, comprimé enrobé | 500mg | film – coated tablet | Oral use |
| France | Laboratoire GlaxoSmithKline<br>100 route de Versailles<br>78163 Marly-le-Roi cedex,<br>France | Zelitrex 1000 mg, comprimé enrobé | 1000mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| France | Laboratoires BIOGARAN 15, boulevard Charles de Gaulle 92707 COLOMBES Cedex France | Valaciclovir Biogaran500 mg, comprimé enrobé | 500mg | film – coated tablet | Oral use |
| France | Laboratoire GlaxoSmithKline 100 route de Versailles 78163 Marly-le-Roi cedex, France | Valaciclovir GSK 500 mg, comprimé enrobé | 500mg | film – coated tablet | Oral use |
| France | sanofi-aventis France 1 – 13 boulevard Romain Rolland 75014 PARIS France | Valaciclovir Winthrop 500 mg, comprimé enrobé | 500mg | film – coated tablet | Oral use |
| Germany | GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany | Valtrex | 500mg | film – coated tablet | Oral use |
| Germany | GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany | Valtrex S | 500mg | film – coated tablet | Oral use |
| Germany | GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany | Valtrex S 250 mg | 250mg | film – coated tablet | Oral use |
| Greece | GlaxoSmithKline a.e.b.e, Leof. Kifissias 266, 152 32 Halandri, Athens, Greece | Valtrex | 1000mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Greece | GlaxoSmithKline a.e.b.e, Leof. Kifissias 266,<br>152 32 Halandri, Athens,<br>Greece | Valtrex | 500mg | film – coated tablet | Oral use |
| Greece | GlaxoSmithKline a.e.b.e, Leof. Kifissias 266,<br>152 32 Halandri, Athens,<br>Greece | Valtrex | 250mg | film – coated tablet | Oral use |
| Iceland | GlaxoSmithKline ehf.<br>Þverholt 14<br>105 Reykjavík,<br>Iceland | Valtrex | 500mg | film – coated tablet | Oral use |
| Iceland | GlaxoSmithKline ehf.<br>Þverholt 14<br>105 Reykjavík,<br>Iceland | Valtrex | 250mg | film – coated tablet | Oral use |
| Ireland | GlaxoSmithKline (Ireland) Ltd., Stonemasons Way,<br>Rathfarnham, Dublin 16,<br>Ireland | Valtrex 500mg Film-coated Tablet | 500mg | film – coated tablet | Oral use |
| Ireland | GlaxoSmithKline (Ireland) Ltd., Stonemasons Way,<br>Rathfarnham, Dublin 16,<br>Ireland | Valtrex 250mg Film-coated Tablet | 250mg | film – coated tablet | Oral use |
| Italy | GlaxoSmithKline S.p.A. - Via A. Fleming, 2 –<br>37135 Verona,<br>Italy | Zelitrex | 1000mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Italy | Sigma Tau Industrie Farmaceutiche Riunite S.p.A Viale Shakespeare, 47 – 00144 Roma, Italy | Talavir | 1000mg | film – coated tablet | Oral use |
| Italy | GlaxoSmithKline S.p.A. - Via A. Fleming, 2 – 37135 Verona, Italy | Zelitrex | 500mg | film – coated tablet | Oral use |
| Italy | Sigma Tau Industrie Farmaceutiche Riunite S.p.A Viale Shakespeare, 47 – 00144 Roma, Italy | Talavir | 500mg | film – coated tablet | Oral use |
| Italy | GlaxoSmithKline S.p.A. - Via A. Fleming, 2 – 37135 Verona, Italy | Zelitrex | 250mg | film – coated tablet | Oral use |
| Italy | Sigma Tau Industrie Farmaceutiche Riunite S.p.A Viale Shakespeare, 47 – 00144 Roma, Italy | Talavir | 250mg | film – coated tablet | Oral use |
| Latvia | GlaxoSmithKline Latvia SIA, Bruņinieku iela 5, Riga, LV-1001 Latria | Valtrex 500 mg film-coated tablets | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Lithuania | The Wellcome Foundation Ltd, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Luxembourg | GlaxoSmithKline s.a. /n.v., rue du Tilleul 13, B-1332 Genval, Belgium | Zelitrex | 500mg | film – coated tablet | Oral use |
| Luxembourg | GlaxoSmithKline s.a. /n.v., rue du Tilleul 13, B-1332 Genval, Belgium | Zelitrex | 250mg | film – coated tablet | Oral use |
| Malta | The Wellcome Foundation Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex,UB6 ONN, United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Netherlands | GlaxoSmithKline BV Huis ter Heideweg 62 3705 LZ Zeist, Netherlands | Zelitrex 500 mg | 500mg | film – coated tablet | Oral use |
| Netherlands | GlaxoSmithKline BV Huis ter Heideweg 62 3705 LZ Zeist, Netherlands | Zelitrex 250 mg | 250mg | film – coated tablet | Oral use |
| Norway | GlaxoSmithKline AS Forskningsveien 2A Postboks 180 Vinderen 0319 Oslo, Norway | Valtrex | 1000mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Norway | GlaxoSmithKline AS<br>Forskningsveien 2A<br>Postboks 180 Vinderen<br>0319 Oslo,<br>Norway | Valtrex | 500mg | film – coated tablet | Oral use |
| Norway | GlaxoSmithKline AS<br>Forskningsveien 2A<br>Postboks 180 Vinderen<br>0319 Oslo,<br>Norway | Valtrex | 250mg | film – coated tablet | Oral use |
| Poland | GlaxoSmithKline Export Ltd,<br>980 Great West Road,<br>Brentford, Middlesex,<br>TW8 9GS<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Portugal | Laboratórios Wellcome de Portugal, Lda, Rua Dr António Loureiro Borges, nº3<br>Arquiparque - Miraflores<br>1495-131 Algés<br>Portugal | Valtrex | 1000mg | film – coated tablet | Oral use |
| Portugal | Alter, SAEstrada Marco do Grilo<br>Zemouto - Coina<br>2830 Barreiro<br>Portugal | Valavir | 1000mg | film – coated tablet | Oral use |
| Portugal | Laboratórios Wellcome de Portugal, Lda, Rua Dr António Loureiro Borges, nº3<br>Arquiparque - Miraflores<br>1495-131 Algés<br>Portugal | Valtrex | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Portugal | Alter, SAEstrada Marco do Grilo<br>Zemouto - Coina<br>2830 Barreiro<br>Portugal | Valavir | 500mg | film – coated tablet | Oral use |
| Portugal | Laboratórios Wellcome de Portugal, Lda, Rua Dr António Loureiro Borges, nº3<br>Arquiparque - Miraflores<br>1495-131 Algés<br>Portugal | Valtrex | 250mg | film – coated tablet | Oral use |
| Portugal | Alter, SAEstrada Marco do Grilo<br>Zemouto - Coina<br>2830 Barreiro<br>Portugal | Valavir | 250mg | film – coated tablet | Oral use |
| Romania | The Wellcome Foundation Limited, Glaxo Wellcome House, Berkeley Avenue, Greenford,<br>Middlesex UB6 0NN,<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |
| Slovak Republic | GlaxoSmithKline Slovakia s.r.o.,<br>Galvaniho 7/A,<br>82104 Bratislava<br>Slovak Republic | Valtrex | 500mg | film – coated tablet | Oral use |
| Slovenia | GSK do.o., Ljubljana<br>Knezov štradon 90<br>1001 Ljubljana<br>Slovenija | Valtrex | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Spain | GlaxoSmithKline, S.A<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valtrex | 1000mg | film – coated tablet | Oral use |
| Spain | GlaxoSmithKline, S.A<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Virval | 1000mg | film – coated tablet | Oral use |
| Spain | Allen Farmacéutica S.A.<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valaciclovir Allen | 1000mg | film – coated tablet | Oral use |
| Spain | Smithkline Beecham Farma S.A.<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valherpes | 1000mg | film – coated tablet | Oral use |
| Spain | GlaxoSmithKline, S.A<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valtrex | 500mg | film – coated tablet | Oral use |
| Spain | GlaxoSmithKline, S.A Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Virval | 500mg | film – coated tablet | Oral use |
| Spain | Allen Farmacéutica S.A.<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valaciclovir Allen | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| Spain | Smithkline Beecham Farma S.A.<br>Severo Ochoa, 2 ,28760,<br>Tres Cantos Madrid<br>Spain | Valherpes | 500mg | film – coated tablet | Oral use |
| Sweden | GlaxoSmithKline AB<br>Box 516<br>169 29 Solna,<br>Sweden | Valtrex | 1 g | film – coated tablet | Oral use |
| Sweden | GlaxoSmithKline AB<br>Box 516<br>169 29 Solna,<br>Sweden | Valtrex | 500mg | film – coated tablet | Oral use |
| Sweden | GlaxoSmithKline AB<br>Box 516<br>169 29 Solna,<br>Sweden | Valtrex | 250mg | film – coated tablet | Oral use |
| United Kingdom | The Wellcome Foundation Ltd<br>Glaxo Wellcome House<br>Berkeley Avenue<br>Greenford<br>Middlesex<br>UB6 0NN,<br>United Kingdom<br>Trading as;<br>GlaxoSmithKline UK<br>Stockley Park West<br>Uxbridge<br>Middlesex<br>UB11 1BT<br>United Kingdom | Valtrex | 500mg | film – coated tablet | Oral use |

| **Member State EU/EEA** | **Marketing Authorisation Holder** | **(Invented) name** | **Strength** | **Pharmaceutical Form** | **Route of administration** |
|---|---|---|---|---|---|
| United Kingdom | The Wellcome Foundation Ltd<br>Glaxo Wellcome House<br>Berkeley Avenue<br>Greenford<br>Middlesex<br>UB6 0NN,<br>United Kingdom<br>Trading as;<br>GlaxoSmithKline UK<br>Stockley Park West<br>Uxbridge<br>Middlesex<br>UB11 1BT<br>United Kingdom | Valtrex | 250mg | film – coated tablet | Oral use |

# ANNEX II

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

## SCIENTIFIC CONCLUSIONS

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

Valtrex is an oral tablet containing valaciclovir (VACV), the esterified prodrug of the antiherpetic compound Aciclovir (ACV).
Aciclovir is a potent and selective inhibitor of a number of herpes viruses, including the human pathogens herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV). Aciclovir inhibits herpes virus DNA polymerase. Valaciclovir is rapidly and almost completely converted to acyclovir and L-valine via intestinal and hepatic first-pass metabolism. Valaciclovir achieves high bioavailability of aciclovir allowing less frequent dosing.

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 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. The CHMP adopted a List of Questions on 20 November 2008 and other three Lists of outstanding issues.

GlaxoSmithKline agreed with the European Medicines Agency 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.

### Section 4.1 Therapeutic Indications

The CHMP discussed the wording for the following indications taking into account the Marketing Authorisation Holder (MAH) proposals, the current national SPCs and scientific knowledge:
1- Varicella zoster virus (VZV) infections – herpes zoster,
2- Herpes simplex virus (HSV) infections
3- Cytomegalovirus (CMV) infections

<u>Indication 1 Varicella zoster virus (VZV) infections – herpes zoster</u>
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.

<u>Indication 2 - Herpes simplex virus (HSV) infections</u>
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, 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.

*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
The prophylaxis of cytomegalovirus was 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, particularly bone marrow transplant (BMT), solid organ transplantation recipients, and immunosuppressed patients as those with HIV.
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 and the second one was a smaller trial (Study 123-031) in adult heart transplant recipients.
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 MAH presented two studies in order to support the safety use of VACV (Study 123-016 and Study 123-039). The safety profile of prophylactic IV treatment with ganciclovir and oral treatment with VACV were comparable and were both similar to that of the placebo group. The reported adverse events (AEs) were listed events and no new and significant safety signals could be identified.
The MAH stated that valaciclovir offered proven efficacy for prophylaxis of CMV infection and disease and influenced positively other outcomes such as graft rejection and opportunistic infections.
The CHMP noted that these findings would support an additional effect of VACV although this can not be addressed as a primary indication for treatment but can be annotated in section 5.1.

The CHMP also asked the MAH 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 endorses the following wording:
*"Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents"*

**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.

*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.
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 also 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 acyclovir 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 acyclovir 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. Acyclovir bioavailability from valaciclovir decreases somewhat with increasing dose. Thus, in addition to altered acyclovir 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 acyclovir 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 are 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 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 not to 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 **t**he amount of experience accumulated with valacicovir 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 revised section 4.8 in line with the SPC guideline.
The MAH was requested to consider adverse events irrespective of statistical significance

The MAH revised section 4.8 accordingly. 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 was assigned based on the overall frequency observed in clinical trials.
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 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 prevalence of aciclovir-resistant HSV has remained low and stable despite increasing clinical use of antiviral agents directed at herpes viruses for nearly three decades. A unique combination of virus-, host- and drug-related factors explains why resistance has not emerged in the general population and also why the use of valaciclovir is unlikely to increase the prevalence of aciclovir-resistant HSV.
HSV resistance to aciclovir, the active metabolite of valaciclovir, as determined by plaque reduction assay has been determined to be less than 1% in immunocompetent subjects and approximately 5-6% in immunocompromised subjects. These data give confidence that the potential for development of resistance has not diminished the established benefit/risk profile of valaciclovir.
The incidence of aciclovir resistance is stable, has not changed in the nearly three decades aciclovir has been available, and is not different between treated patients and untreated subjects.

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 taking into account 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.

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

Whereas

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

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

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Valtrex and associated names (see Annex I).

**ANNEX III**

**SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Valtrex and associated names (see Annex I) 250 mg film-coated tablets
Valtrex and associated names (see Annex I) 500 mg film-coated tablets
Valtrex and associated names (see Annex I) 1000 mg film-coated tablets

[See Annex I - To be completed nationally]

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains valaciclovir hydrochloride equivalent to 250 mg valaciclovir
Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir
Each tablet contains valaciclovir hydrochloride equivalent to 1000 mg valaciclovir

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

250 mg tablet
White, biconvex, elongated tablet with a white to off-white core, marked "GX CE7" in blue ink on one side.

500 mg tablet
White, biconvex, elongated tablet with a white to off-white core, engraved "GX CF1" on one side.

1000 mg tablet
White, biconvex, elongated tablet with a white to off-white core, with a partial scorebar on both sides and marked "GX CF2" in blue ink on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Valtrex is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see sections 4.4).

Valtrex is indicated for the treatment of herpes zoster in adult patients with mild or moderate immunosuppression (see section 4.4).

*Herpes simplex virus (HSV) infections*

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 (see section 4.4)

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

*Cytomegalovirus (CMV) infections*:

Valtrex is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents (see section 4.4)

## 4.2 Posology and method of administration

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

Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.

*Immunocompetent Adults*
The dose in immunocompetent patients is 1000 mg three times daily for seven days (3000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

*Immunocompromised Adults*
The dose in immunocompromised patients is 1000 mg three times daily for at least seven days (3000 mg total daily dose) and for 2 days following crusting of lesions. This dose should be reduced according to creatinine clearance (see Renal impairment below).

In immunocompromised patients, antiviral treatment is suggested for patients presenting within one week of vesicle formation or at any time before full crusting of lesions.

*Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)*

*Immunocompetent Adults and Adolescents (≥12 years)*
The dose is 500 mg of Valtrex to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

For recurrent episodes, treatment should be for three to five days. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms. Valtrex can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.

*Herpes labialis*
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. This dose should be reduced according to creatinine clearance (see Renal impairment below). When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

*Immunocompromised Adults*
For the treatment of HSV in immunocompromised adults, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. This dose should be reduced according to creatinine clearance (see Renal impairment below). For maximum clinical benefit, the treatment should be started within 48 hours. A strict monitoring of the evolution of lesions is advised.

*Suppression of recurrences of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)*

*Immunocompetent Adults and Adolescents (≥12 years)*
The dose is 500 mg of Valtrex to be taken once daily. Some patients with very frequent recurrences (≥ 10/year in absence of therapy) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily). This dose should be reduced according to creatinine clearance (see Renal impairment below).Treatment should be re-evaluated after 6 to 12 months of therapy.

*Immunocompromised Adults*
The dose is 500 mg of Valtrex twice daily. This dose should be reduced according to creatinine clearance (see Renal impairment below). Treatment should be re-evaluated after 6 to 12 months of therapy.

*Prophylaxis of cytomegalovirus (CMV) infection and disease in adults and adolescents (≥12 years)*

The dosage of Valtrex is 2000 mg four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see Renal impairment below).

The duration of treatment will usually be 90 days, but may need to be extended in high-risk patients.

Special populations

Children
The efficacy of Valtrex in children below the age of 12 years has not been evaluated.

Elderly
The possibility of renal impairment in the elderly must be considered and the dose should be adjusted accordingly (see Renal impairment below). Adequate hydration should be maintained.

Renal impairment
Caution is advised when administering Valtrex to patients with impaired renal function. Adequate hydration should be maintained. The dose of Valtrex should be reduced in patients with impaired renal function as shown in Table 1 below.

In patients on intermittent haemodialysis, the Valtrex dose should be administered after the haemodialysis has been performed. The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after renal transplantation or engraftment. The Valtrex dosage should be adjusted accordingly.

Hepatic impairment
Studies with a 1000 mg dose of valaciclovir in adult patients show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in adult patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dose adjustment; however, clinical experience is limited. For higher doses (4000 mg or more per day), see section 4.4.

Table 1: DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

| **Therapeutic Indication** | **Creatinine Clearance (mL/min)** | **Valaciclovir Dosage** [a] |
|---|---|---|
| Varicella-Zoster Virus (VZV) Infections | | |
| *Treatment of herpes zoster (shingles)* in immunocompetent and immunocompromised adults | ≥ 50<br>30 to 49<br>10 to 29<br>10 | 1000 mg three times daily<br>1000 mg twice daily<br>1000 mg once daily<br>500 mg once daily |
| Herpes Simplex Virus (HSV) Infections | | |
| *Treatment of HSV infections* | | |
| - immunocompetent adults and adolescents | ≥ 30<br>< 30 | 500 mg twice daily<br>500 mg once daily |
| - immunocompromised adults | ≥ 30<br>< 30 | 1000 mg twice daily<br>1000 mg once daily |
| *Treatment of herpes labialis (cold sores) in immunocompetent adults and adolescents (alternative 1-day regimen)* | ≥50<br>30 to 49<br>10 to 29<br><10 | 2000mg twice in one day<br>1000 mg twice in one day<br>500 mg twice in one day<br>500 mg single dose |
| S*uppression of HSV infections* | | |
| - immunocompetent adults and adolescents | ≥ 30<br>< 30 | 500 mg once daily [b]<br>250 mg once daily |
| - immunocompromised adults | ≥ 30<br>< 30 | 500 mg twice daily<br>500 mg once daily |
| Cytomegalovirus (CMV) Infections | | |
| *CMV prophylaxis in solid organ transplant recipients in adults and adolescents* | ≥75<br>50 to <75<br>25 to <50<br>10 to <25<br><10 or on dialysis | 2000 mg four times daily<br>1500 mg four times daily<br>1500 mg three times daily<br>1500 mg twice daily<br>1500 mg once daily |

[a] For patients on intermittent haemodialysis, the dose should be given after dialysis on dialysis days.
[b]For HSV suppression in immunocompetent subjects with a history of ≥10 recurrences/year, better results may be obtained with 250 mg twice daily.

## 4.3 Contraindications

Hypersensitivity to valaciclovir or aciclovir or any of the excipients (see section 6.1).

## 4.4 Special warnings and precautions for use

Hydration status
Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Use in patients with renal impairment and in elderly patients
Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both

elderly patients and patients with renal impairment are at increased risk of developing neurological side-effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Use of higher doses of valaciclovir in hepatic impairment and liver transplantation
There are no data available on the use of higher doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg to these patients.

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

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

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

Use in ocular HSV infections
Clinical response should be closely monitored in these patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is unlikely to be sufficient.

Use in CMV infections

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV-positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that valaciclovir should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).

## 4.5 Interaction with other medicinal products and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Following 1000 mg valaciclovir, cimetidine and probenecid reduce aciclovir renal clearance and increase the AUC of aciclovir by about 25% and 45%, respectively, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65%. Other medicinal products (including e.g. tenofovir) administered concurrently that

compete with or inhibit active tubular secretion may increase aciclovir concentrations by this mechanism. Similarly, valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving higher aciclovir exposures from valaciclovir (e.g., at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with drugs which inhibit active renal tubular secretion.

Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate motefil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
A limited amount of data on the use of valaciclovir and a moderate amount of data on the use of aciclovir in pregnancy is available from pregnancy registries (which have documented the pregnancy outcomes in women exposed to valaciclovir or to oral or intravenous aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy, respectively) and postmarketing experience indicate no malformative or foeto/neonatal toxicity. Animal studies do not show reproductive toxicity for valaciclovir (see section 5.3). Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Breastfeeding
Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. However, at therapeutic doses of valaciclovir, no effects on the breastfed newborns/infants are anticipated since the dose ingested by the child is less than 2% of the therapeutic dose of intravenous aciclovir for treatment of neonatal herpes (see Section 5.2). Valaciclovir should be used with caution during breast feeding and only when clinically indicated.

Fertility
Valaciclovir did not affect fertility in rats dosed by the oral route. At high parenteral doses of aciclovir testicular atrophy and aspermatogenesis have been observed in rats and dogs. No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 to 1000 mg aciclovir.

## 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. The clinical status of the patient and the adverse reaction profile of Valtrex should be borne in mind when considering the patient`s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

## 4.8 Undesirable effects

The most common adverse reactions (ARs) reported in at least one indication by patients treated with Valtrex in clinical trials were headache and nausea. More serious ARs such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure and neurological disorders are discussed in greater detail in other sections of the label.

Undesirable effects are listed below by body system organ class and by frequency.

The following frequency categories are used for classification of adverse effects:

| | |
|---|---|
| Very common | ≥ 1/10, |
| Common | ≥1/100 to < 1/10, |
| Uncommon | ≥ 1/1,000 to < 1/100, |
| Rare | ≥ 1/10,000 to < 1/1000, |
| Very rare | < 1/10,000 |

Clinical trial data have been used to assign frequency categories to ARs if, in the trials, there was evidence of an association with valaciclovir.

For ARs identified from postmarketing experience, but not observed in clinical trials, the most conservative value of point estimate ("rule of three") has been used to assign the AR frequency category. For ARs identified as associated with valaciclovir from post-marketing experience, and observed in clinical trials, study incidence has been used to assign the AR frequency category. The clinical trial safety database is based on 5855 subjects exposed to valaciclovir in clinical trials covering multiple indications (treatment of herpes zoster, treatment/suppression of genital herpes & treatment of cold sores).

Clinical Trial Data

Nervous system disorders
Very common: Headache

Gastrointestinal disorders
Common: Nausea

Post Marketing Data

Blood and lymphatic system disorders
Uncommon: Leucopenia, thrombocytopenia
Leucopenia is mainly reported in immunocompromised patients.

Immune system disorders
Rare: Anaphylaxis

Psychiatric and nervous system disorders

| | |
|---|---|
| Common: | Dizziness |
| Uncommon: | Confusion, hallucinations, decreased consciousness, tremor, agitation |
| Rare: | Ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms. |

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8000 mg daily) of Valtrex for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea

Gastrointestinal disorders

| | |
|---|---|
| Common: | Vomiting, diarrhoea. |
| Uncommon: | Abdominal discomfort |

Hepato-biliary disorders
Uncommon: Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).

Skin and subcutaneous tissue disorders

| | |
|---|---|
| Common: | Rashes including photosensitivity, pruritus. . |
| Uncommon: | Urticaria |
| Rare: | Angioedema |

Renal and urinary disorders

| | |
|---|---|
| Uncommon: | Renal pain |
| Rare: | Renal impairment, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended doses). |

Renal pain may be associated with renal failure.

Intratubular precipitation of aciclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see section 4.4).

Additional information on special populations

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised adult patients, particularly those with advanced HIV disease, receiving high doses (8000 mg daily) of valaciclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

## 4.9 Overdose

Symptoms and Signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB11.

Mechanism of action

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue.

Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase.

Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr

Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus-infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of UL97. This requirement for activation of aciclovir by a virus-specific enzyme largely explains its selectivity.

The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype which results in a virus which is disadvantaged in the natural host. Reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent host and is found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

**Clinical studies**

Varicella Zoster Virus Infection
Valtrex accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and, in patients older than 50 years, also post-herpetic neuralgia. Valtrex reduces the risk of ocular complications of ophthalmic zoster.

Intravenous therapy generally is considered standard for zoster treatment in immunocompromised patients; however, limited data indicate a clinical benefit of valaciclovir in the treatment of VZV infection (herpes zoster) in certain immunocompromised patients, including those with solid organ cancer, HIV, autoimmune diseases, lymphoma, leukaemia and stem cell transplants.

Herpes Simplex Virus Infection

Valaciclovir for ocular HSV infections should be given according to applicable treatment guidelines.

Studies of valaciclovir treatment and suppression for genital herpes were performed in HIV/HSV coinfected patients with a median CD4 count of > 100cells/mm3. Valaciclovir 500 mg twice daily was superior to 1000 mg once daily for suppression of symptomatic recurrences Valaciclovir 1000 mg twice daily for treatment of recurrences was comparable to oral aciclovir 200 mg five times daily on herpes episode duration. Valaciclovir has not been studied in patients with severe immune deficiency.

The efficacy of valaciclovir for the treatment of other HSV skin infections has been documented. Valaciclovir has shown efficacy in the treatment of herpes labialis (cold sores), mucositis due to chemotherapy or radiotherapy, HSV reactivation from facial resurfacing, and herpes gladiatorum. Based on historical aciclovir experience, valaciclovir appears to be as effective as aciclovir for the treatment of erythema multiforme, eczema herpeticum and herpetic whitlow.

Valaciclovir has been proven to reduce the risk of transmission of genital herpes in immunocompetent adults when taken as suppressive therapy and combined with safer sex practices. A double blind, placebo controlled study was conducted in 1,484 heterosexual, immunocompetent adult couples discordant for HSV-2 infection. Results showed significant reductions in risk of transmission: 75 % (symptomatic HSV-2 acquisition), 50 % (HSV-2 seroconversion), and 48 % (overall HSV-2 acquisition) for valaciclovir compared to placebo. Among subjects participating in a viral shedding sub-study, valaciclovir significantly reduced shedding by 73 % compared to placebo (see section 4.4 for additional information on transmission reduction).

Cytomegalovirus Infection (see section 4.4)
CMV prophylaxis with valaciclovir in subjects receiving solid organ transplantation (kidney, heart) reduces the occurrence of acute graft rejection, opportunistic infections and other herpes virus infections (HSV, VZV). There is no direct comparative study versus valganciclovir to define the optimal therapeutic management of solid organ transplant patients.

## 5.2 Pharmacokinetic properties

Absorption

Valaciclovir is a prodrug of aciclovir. The bioavailability of aciclovir from valaciclovir is about 3.3 to 5.5-fold greater than that historically observed for oral aciclovir. After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as valaciclovir hydrolase. The bioavailability of aciclovir from 1000 mg valaciclovir is 54%, and is not reduced by food. Valaciclovir pharmacokinetics is not dose-proportional. The rate and extent of absorption decreases with increasing dose, resulting in a less than proportional increase in Cmax over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Aciclovir pharmacokinetic (PK) parameter estimates following single doses of 250 to 2000 mg valaciclovir to healthy subjects with normal renal function are shown below.

| Aciclovir PK Parameter | | 250 mg (N=15) | 500 mg (N=15) | 1000 mg (N=15) | 2000 mg (N=8) |
|---|---|---|---|---|---|
| $C_{max}$ | micrograms/mL | 2.20 ± 0.38 | 3.37 ± 0.95 | 5.20 ± 1.92 | 8.30 ± 1.43 |
| $T_{max}$ | hours (h) | 0.75 (0.75–1.5) | 1.0 (0.75–2.5) | 2.0 (0.75–3.0) | 2.0 (1.5–3.0) |
| AUC | h.micrograms/mL | 5.50 ± 0.82 | 11.1 ± 1.75 | 18.9 ± 4.51 | 29.5 ± 6.36 |

$C_{max}$ = peak concentration; $T_{max}$ = time to peak concentration; AUC = area under the concentration-time curve. Values for $C_{max}$ and AUC denote mean ± standard deviation. Values for $T_{max}$ denote median and range.

Peak plasma concentrations of unchanged valaciclovir are only about 4% of peak aciclovir levels, occur at a median time of 30 to 100 min post-dose, and are at or below the limit of quantification 3 h after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. Herpes zoster, herpes simplex and HIV infection do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir compared with healthy adults. In transplant recipients receiving valaciclovir 2000 mg 4 times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Distribution

Binding of valaciclovir to plasma proteins is very low (15%). CSF penetration, determined by CSF/plasma AUC ratio, is independent of renal function and was about 25% for aciclovir and the metabolite 8-OH-ACV, and about 2.5% for the metabolite CMMG.

Biotransformation

After oral administration, valaciclovir is converted to aciclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9(carboxymethoxy)methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolized by cytochrome P450 enzymes.

Elimination

Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the aciclovir metabolite CMMG (about 14% of the recovered dose). The metabolite 8-OH-ACV is detected only in small amounts in urine (< 2% of the recovered dose). Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 h.

**Special Populations**

Renal impairment
The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, at severe renal impairment compared with normal renal function.

Hepatic impairment
Pharmacokinetic data indicate that hepatic impairment decreases the rate of conversion of valaciclovir to aciclovir but not the extent of conversion. Aciclovir half-life is not affected.

Pregnant women
A study of the pharmacokinetics of valaciclovir and aciclovir during late pregnancy indicates that pregnancy does not affect the pharmacokinetics of valaciclovir.

Transfer into breast milk
Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (Cmax) in breast milk ranged from 0.5 to 2.3 times the corresponding maternal aciclovir serum concentrations. The median aciclovir concentration in breast milk was 2.24 micrograms/ml (9.95 micromoles/L). With a maternal valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral aciclovir dosage of about 0.61 mg/kg/day. The elimination half-life of aciclovir from breast milk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breast milk, or infant urine.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Valaciclovir did not affect fertility in male or female rats dosed by the oral route.

Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolised to aciclovir. Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal abnormalities and maternal toxicity were observed at subcutaneous doses that produced plasma aciclovir levels of 100 micrograms/mL (>10-fold higher than 2000 mg single dose valaciclovir in humans with normal renal function).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Microcrystalline cellulose
Crospovidone
Povidone
Magnesium stearate
Colloidal silicon dioxide

Film coat
Hypromellose
Titanium dioxide
Macrogol
Polysorbate 80 (500 and 1000 mg tablets only)
Blue printing ink FT203 containing brilliant blue (E133) (250 mg and 1000 mg tablets only)
Carnauba wax

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

250 mg tablets, 1000 mg tablets
Two years

500 mg tablets
Three years

### 6.4 Special precautions for storage

Store below 30°C.

### 6.5 Nature and contents of container

Polyvinyl chloride / aluminium foil blister packs.

250 mg tablets
Packs of 60 tablets

500 mg tablets
Packs of 10, 30, 42, 90 or 112 tablets
Not all pack sizes may be marketed.

1000 mg tablets

Packs of 21 tablets

### 6.6 Special precautions for disposal

No special requirements

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

**LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

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

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains valaciclovir hydrochloride equivalent to 250 mg valaciclovir.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets
60 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Store below 30°C.

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

## 15. INSTRUCTIONS ON USE

[To be completed nationally]

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 3. EXPIRY DATE

EXP {MM YYYY}

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
10 tablets
30 tablets
42 tablets
90 tablets
112 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP {MM YYYY}

## 9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

## 15. INSTRUCTIONS ON USE

[To be completed nationally]

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 3. EXPIRY DATE

EXP {MM YYYY}

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Valtrex and associated names (see Annex I) 1000 mg film-coated tablets
[See Annex I - To be completed nationally]
Valaciclovir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains valaciclovir hydrochloride equivalent to 1000 mg valaciclovir

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets
21 tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Store below 30°C.

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

## 12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

## 15. INSTRUCTIONS ON USE

[To be completed nationally]

## 16. INFORMATION IN BRAILLE

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

**1. NAME OF THE MEDICINAL PRODUCT**

Valtrex and associated names (see Annex I) 1000 mg film-coated tablets
[See Annex I - To be completed nationally]
Valaciclovir

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

**3. EXPIRY DATE**

EXP {MM YYYY}

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Valtrex and associated names (see Annex 1) 250 mg film-coated tablets**
**Valtrex and associated names (see Annex 1) 500 mg film-coated tablets**
**Valtrex and associated names (see Annex 1) 1000 mg film-coated tablets**
[See Annex I – To be completed nationally]
Valaciclovir

**Read all of this leaflet carefully before you start taking this medicine.**

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

**In this leaflet:**



## 1. What Valtrex is and what it is used for

Valtrex belongs to a group of medicines called antivirals. It works by killing or stopping the growth of viruses called herpes simplex (HSV), varicella zoster (VZV) and cytomegalovirus (CMV).
Valtrex can be used to:

- treat shingles (in adults)
- treat HSV infections of the skin and genital herpes (in adults and adolescents over 12 years old). It is also used to help prevent these infections from returning.
- treat cold sores (in adults and adolescents over 12 years old)
- prevent infection with CMV after organ transplants (in adults and adolescents over 12 years old)
- treat and prevent HSV infections of the eye

## 2. Before you take Valtrex

**Don’t take Valtrex**

- if you are allergic (hypersensitive) to valaciclovir or aciclovir or any of the other ingredients (listed in Section 6).
- Don’t take Valtrex if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Valtrex.

**Take special care with Valtrex**
**Check with your doctor or pharmacist before taking Valtrex if:**

- **you have kidney problems**
- **you have liver problems**
- **you are over 65 years of age**
- **your immune system is weak**

**If you are not sure if the above apply to you, talk to your doctor or pharmacist before taking Valtrex.**

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

**Taking other medicines**
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Tell your doctor or pharmacist if you are taking any other medicines that affect the kidneys. These include: aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, tacrolimus, cimetidine and probenecid.

Always tell your doctor or pharmacist about other medicines if you are taking Valtrex for treatment of shingles or after having an organ transplant.

**Pregnancy and breast-feeding**
Valtrex is not usually recommended for use during pregnancy. If you are pregnant, or think you could be, or if you are planning to become pregnant, don't take Valtrex without checking with your doctor. Your doctor will weigh up the benefit to you against the risk to your baby of taking Valtrex while you're pregnant or breastfeeding.

**Driving or using machines**
Valtrex can cause side effects that affect your ability to drive.
→ Don't drive or use machines unless you are sure you're not affected.

## 3. How to take Valtrex

Always take Valtrex exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The dose that you should take will depend on why your doctor has prescribed Valtrex for you. Your doctor will discuss this with you.

Treatment of shingles

- The usual dose is 1000 mg (one 1000 mg tablet or two 500 mg tablets) three times a day.
- You should take Valtrex for seven days.

Treatment of cold sores

- The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) twice a day.
- The second dose should be taken 12 hours (no sooner than 6 hours) after the first dose
- You should take Valtrex for one day (two doses) only.

Treatment of HSV infections of the skin and genital herpes

- The usual dose is 500 mg (one 500 mg tablet or two 250 mg tablets) twice a day.
- For the first infection you should take Valtrex for five days or for up to ten days if your doctor tells you to. For recurrent infection the duration of treatment is normally 3-5 days.

Helping to prevent HSV infections from returning after you have had them

- The usual dose is one 500 mg tablet once a day.
- Some people with frequent recurrences may benefit from taking one 250 mg tablet twice a day.
- You should take Valtrex until your doctor tells you to stop.

To stop you being infected with CMV (*Cytomegalovirus*)

- The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) four times a day.
- You should take each dose about 6 hours apart.
- You will usually start taking Valtrex as soon as possible after your surgery.
- You should take Valtrex for around 90 days after your surgery, until your doctor tells you to stop.

Your doctor may adjust the dose of Valtrex if:

- you are over 65 years of age
- you have a weak immune system
- you have kidney problems.

➔ Talk to your doctor before taking Valtrex if any of the above apply.

**Taking this medicine**

- Take this medicine by mouth.
- Swallow the tablets whole with a drink of water.
- Take Valtrex at the same time each day.
- Take Valtrex according to instructions from your doctor or pharmacist.

**People over 65 years of age or with kidney problems**

**It is very important while you are taking Valtrex that you drink water regularly** during the day. This will help to reduce side effects that can affect the kidney or nervous system. Your doctor will closely monitor you for signs of these. Nervous system side effects might include feeling confused or agitated, or feeling unusually sleepy or drowsy.

**If you take more Valtrex than you should**

Valtrex is not usually harmful, unless you take too much over several days. If you take too many tablets you may feel sick, vomit, or be confused, agitated or unusually sleepy. Talk to your doctor or pharmacist if you take too much Valtrex. Take the medicine pack with you.

**If you forget to take Valtrex**

- If you forget to take Valtrex, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose.
- Don’t take a double dose to make up for a forgotten dose.

## 4. Possible side effects

Like all medicines, Valtrex can cause side effects in some people. The following side effects may happen with this medicine:

**Conditions you need to look out for**

- severe allergic reactions (*anaphylaxis*). These are rare in people taking Valtrex. Rapid development of symptoms including:
- flushing, itchy skin rash
- swelling of the lips, face, neck and throat, causing difficulty in breathing (*angiodema*)
- fall in blood pressure leading to collapse.

➔ If you have an allergic reaction, stop taking Valtrex and see a doctor straight away.

**Very Common** (affects more than 1 in 10 people):
- headache

**Common** (affects up to 1 in 10 people)
- feeling sick
- dizziness
- vomiting
- diarrhoea
- skin reaction after exposure to sunlight (*photosensitivity*).
- rash

**Uncommon** (affects up to 1 in 100 people)
- feeling confused
- seeing or hearing things that aren't there (*hallucinations*)
- feeling very drowsy
- tremors
- feeling agitated

These nervous system side effects usually occur in people with kidney problems, the elderly or in organ transplant patients taking high doses of 8 grams or more of Valtrex a day. They usually get better when Valtrex is stopped or the dose reduced.

<u>Other uncommon side effects:</u>
- shortness of breath (*dyspnoea*)
- stomach discomfort
- rash, sometimes itchy, hive-like rash (*urticaria*)
- low back pain (kidney pain)

<u>Uncommon side effects that may show up in blood tests:</u>
- reduction in the number of white blood cells (*leucopenia*)
- reduction in the number of *blood platelets* which are cells that help blood to clot (*thrombocytopenia*)
- increase in substances produced by the liver.

**Rare** (affects up to 1 in 1,000 people)
- unsteadiness when walking and lack of coordination (*ataxia*)
- slow, slurred speech (*dysarthria*)
- fits (convulsions)
- altered brain function (*encephalopathy*)
- unconsciousness (*coma*)
- confused or disturbed thoughts

These nervous system side effects usually occur in people with kidney problems, the elderly or in organ transplant patients taking high doses of 8 grams or more of Valtrex a day. They usually get better when Valtrex is stopped or the dose reduced.

Other rare side effects:

- kidney problems where you pass little or no urine.

## 5. How to store Valtrex

- Keep out of the reach and sight of children.
- Do not use Valtrex after the expiry date which is stated on the carton. The expiry date (Exp.) refers to the last day of that month.
- Store below 30°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help protect the environment.

## 6. Further information

### What Valtrex contains

- The active substance is valaciclovir. Each tablet contains 250 mg, 500 mg or 1000 mg of valaciclovir (as valaciclovir hydrochloride).

The other ingredients are:

Tablet core
Microcrystalline cellulose
Crospovidone
Povidone
Magnesium stearate
Colloidal silicon dioxide

Film coat
Hypromellose
Titanium dioxide
Macrogol
Polysorbate 80 (500 and 1000 mg tablets only)
Blue printing ink FT203 containing brilliant blue (E133) (250 mg and 1000 mg tablets only):
Carnauba wax

### What Valtrex tablets look like and contents of the pack

Valtrex tablets are contained in polyvinyl chloride/aluminium foil blister packs.

Valtrex Tablets 250 mg are supplied to you in cartons containing 60 film-coated tablets. They are white and marked with “GX CE7” on one side.

Valtrex Tablets 500 mg are supplied in cartons containing 10, 30, 42, 90 or 112 film-coated tablets. They are white and marked with “GX CF1” on one side.

Valtrex Tablets 1000 mg are supplied in cartons containing 21 film-coated tablets. They are white and marked with “GX CF2” on one side.

**Marketing Authorisation Holder and Manufacturer**

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

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

Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Germany, Greece, Iceland, Ireland, Latvia, Lithuania, Malta, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom: Valtrex

France, Belgium, Denmark, Italy, Luxembourg, Netherlands: Zelitrex

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

[To be completed nationally]