UKPAR  Valaciclovir 250mg, 500mg & 1000mg Tablets PL 24668/0093
PL 24668/0096
PL 24668/0099

VALACICLOVIR 500MG TABLETS
PL 24668/0094
PL 24668/0097
PL 24668/0100

VALACICLOVIR 1000MG TABLETS
PL 24668/0095
PL 24668/0098
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UKPAR

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LAY SUMMARY

The Medicines Healthcare and products Regulatory Agency (MHRA) granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Valaciclovir 250mg Tablets (PL 24668/0093, PL 24668/0096 & PL 24668/0099), Valaciclovir 500mg Tablets (PL 24668/0094, PL 24668/0097 & PL 24668/0100) and Valaciclovir 1000mg Tablets (PL 24668/0095, PL 24668/0098 & PL 24668/0101). These are prescription only medicines (POM) used to treat the following conditions:

- Patients over 50 years of age, to treat shingles
- To treat genital Herpes simplex virus (HSV) infections
- To prevent recurrent genital Herpes simplex virus (HSV) infections in patients who have at least 6 recurrences per year.
- To prevent cytomegalovirus (CMV) infection and disease after organ transplant

Valaciclovir Tablets contains the active ingredient valaciclovir hydrochloride, which is an antiviral. Valaciclovir is a prodrug, which is converted by esterases to the active drug aciclovir. Aciclovir inhibits herpes virus DNA synthesis.

Valaciclovir 250mg Tablets and Valaciclovir 500mg Tablets are considered to be generic versions of the reference products Valtrex® 250mg Tablets (PL) and Valtrex® 500mg tablets (PL) licensed to The Wellcome Foundation Limited. Data from the Valaciclovir 250mg Tablets were extrapolated to the Marketing Authorisation applied for Valaciclovir 1000mg Tablets.

These applications are based on reference products with a valid UK licence. No new safety issues arose as a result of this application. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Valaciclovir 250mg, 500mg and 1000mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
VALACICLOVIR 250MG TABLETS
PL 24668/0093
PL 24668/0096
PL 24668/0099

VALACICLOVIR 500MG TABLETS
PL 24668/0094
PL 24668/0097
PL 24668/0100

VALACICLOVIR 1000MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Valaciclovir 250mg Tablets (PL 24668/0093, PL 24668/0096 & PL 24668/0099) Valaciclovir 500mg Tablets (PL 24668/0094, PL 24668/0097 & PL 24668/0100) and Valaciclovir 1000mg (PL 24668/0095, PL 24668/0098 & PL 24668/0101) on 10th August 2009. The products are prescription only medicines.

Valaciclovir 250mg and Valaciclovir 500mg Tablets and their duplicate licences, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, have been shown to be generic medicinal products of the original products Valtrex® 250mg Tablets (PL) and Valtrex® 500mg tablets (The Wellcome Foundation Limited, UK). Valaciclovir 1000mg and its duplicate licences were submitted as abridged application according to Article 10.3 of Directive 2001/83/EC. These licences refer to Valtrex® 250mg Tablets in the bioequivalence studies.

The products contain the active ingredient valaciclovir. Valaciclovir is a prodrug, which is converted by esterases to the active drug aciclovir. Aciclovir inhibits herpes.

These applications for Valaciclovir 250mg, 500mg and 1000mg tablets were submitted at the same time and depend on the bioequivalence study comparing the applicant’s 250mg product with Valtrex® 250mg Tablets (The Wellcome Foundation Limited, UK). Consequently, all sections of this scientific discussion refer to all three products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Valaciclovir hydrochloride

Nomenclature
rINN: Valaciclovir, hydrochloride
Chemical name: L-Valine 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester hydrochloride

Description
White to cream coloured powder

Molecular formula
C_{13}H_{20}N_{6}O_{4}.HCl

Molecular weight
360.8

CAS Number
124832-27-5

Structure

![image of structure]

General properties
Valaciclovir hydrochloride is freely soluble in water, sparingly soluble in methanol and dimethylformamide, and practically insoluble in ethanol, diisopropyl ether, acetonitrile, ethyl acetate, methylene chloride, toluene, chloroform and acetone. The pKa of valaciclovir hydrochloride is 7.32. The active substance has one stereochemical centre and is levorotatory. Valaciclovir hydrochloride is reported to exist in various hydrate/polymorphic forms. Valaciclovir hydrochloride produced by Matrix is a hydrate, having a water content in between 4.5% to 9.5%.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.
All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, valaciclovir hydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Certificates of Analysis have been provided for any working standards used.

The applicant has demonstrated that the active ingredient from this source is adequately controlled in accordance with the European Pharmacopoeia monograph for valaciclovir hydrochloride.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuffs.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely magnesium stearate, povidone K30 and microcrystalline cellulose. All the ingredients in the tablet core comply with relevant Ph Eur monographs.

The tablet coating contains: hypromellose, hydroxypropyl cellulose, titanium dioxide and macrogol. The ingredients within the tablet coating comply with relevant Ph Eur monographs.

**Pharmaceutical development**

Satisfactory pharmaceutical development studies have been conducted and support the suitability of the product composition proposed for its intended use.

**Dissolution Profiles**

Dissolution profiles of the drug products were found to be similar to those for the reference products.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided.

Satisfactory batch formulae have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on four batches of each of the 250mg and 500mg strength and two of the 1000mg strength. The results are satisfactory.

**Finished product specification**

The finished product specifications proposed for the products are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data
have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
These products are packaged in aluminium/polyvinylchloride (PVC) blister strips or high density polyethylene (HDPE) bottles with sealed plastic caps composed of low-density PE (LDPE). All three strengths of tablet packed in either blister strips or HDPE bottles are presented in pack sizes of 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 tablets. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with EU legislation regarding contact with food. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

All primary packaging complies with EU legislation, Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set, which is satisfactory. The precaution ‘Do not store above 30°C’ has been included.

**Bioequivalence**
Two bioequivalence studies have been presented. Please see clinical assessment report for more details.

**Product Information**
**Summary of Product Characteristics**
The proposed Summary of Product Characteristics for each product is pharmaceutically satisfactory.

**Patient Information Leaflet/Carton**
The patient information leaflet/carton has been prepared in-line with the details registered for the cross-reference product. A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**Conclusion**
The data submitted with these applications are acceptable. It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

1.1. Clinical Background

Valaciclovir is the L-valine ester of antiviral drug aciclovir and available only as an oral formulation. Valaciclovir as prodrug undergoes rapid and extensive by first-pass intestinal and/or hepatic metabolism to aciclovir and valine. Aciclovir has demonstrated in vitro and in vivo antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV.

1.3. Indications

The following indications are taken from the submitted SPC (submitted by the applicant in April 2008):

Therapeutic indications

- In immunocompetent patients:
  - Treatment of herpes zoster in patients aged over 50 years: valaciclovir reduces the duration of severe infection and accordingly the proportion of patients with zoster-associated pain.
  - Valaciclovir is indicated for the treatment of initial and recurrent genital herpes simplex infections.
  - Valaciclovir is indicated for the prevention of recurrent genital herpes simplex infections in patients with at least 6 recurrences per year.

- Valaciclovir is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, in particular after renal transplantation, except after lung transplantation.

1.4. Posology and method of administration

The following posology and method of administration are taken from the submitted SPC:

Posology and method of administration

Route of administration
Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water), with or without food.
Adults

Herpes zoster infections

Prevention of zoster-associated pain:
• 1000 mg of valaciclovir 3 times daily for 7 days

Treatment should be initiated as soon as possible after the beginning of the infection, within 72 hours of the appearance of skin lesions.

Herpes simplex infections

Treatment of genital herpes simplex infections in immunocompetent patients:
• 500 mg twice daily for 10 days for the initial episode
• 1000 mg per day in one or two divided doses for 5 days for recurrent episodes

Treatment should be initiated as soon as possible in the course of infection, preferably at the prodromal stage or when lesions begin to appear.

Suppression of recurrent genital herpes simplex infections:
• 500 mg per day in one or two divided doses
(Better results have been obtained by dividing the daily dose into two, i.e. by administering 250 mg twice daily, when the administration of a single 500 mg dose per day failed, or if the recurrences were frequent or very symptomatic). For this indication, the need for treatment must be re-evaluated after 6 to 12 months.

Adults and adolescents aged 12 years and above

Cytomegalovirus infections

Prophylaxis of infections and diseases caused by cytomegalovirus (CMV):
• 2000 mg of valaciclovir 4 times daily

Treatment should be initiated as soon as possible after the organ transplant. The dose of valaciclovir should be adapted according to the creatinine clearance (see second table below). The duration of treatment is usually 90 days, although longer treatment may be necessary in high risk patients.

Elderly

Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

Renal impairment

Prevention of zoster-associated pain, suppression and treatment of genital herpes simplex infections:
The dosage should be adjusted according to the creatinine clearance:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| 15-30 ml/min         | • Prevention of zoster-associated pain: 1000 mg twice daily  
                        • Suppression and treatment of genital herpes simplex infections: No dosage adjustment is required. |
| < 15 ml/min          | • Prevention of zoster-associated pain: 1000 mg once daily  
                        • Treatment of genital herpes simplex infections: 500 mg per day  
                        • Suppression of genital herpes simplex infections: 250 mg per day  
                        In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed. |

Patients on haemodialysis should receive the same dose as patients with creatinine clearance <10 ml/min. On dialysis days, the dose should be given after dialysis.

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV)*

The dosage should be adjusted according to the creatinine clearance, which must be assessed frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-75 ml/min</td>
<td>1500 mg 4 times daily</td>
</tr>
<tr>
<td>25-50 ml/min</td>
<td>1500 mg 3 times daily</td>
</tr>
<tr>
<td>10-25 ml/min</td>
<td>1500 mg twice daily</td>
</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>1500 mg daily</td>
</tr>
</tbody>
</table>

In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.

*Hepatic impairment*

Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment. However, clinical experience is limited. For the higher doses recommended for the prevention of infections and diseases caused by CMV, see section 4.4.
Children below the age of 12 years

Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

GCP Aspects
The bioequivalence study was inspected by the Austrian authorities and the performance of the study is fully GCP compliant.

Orphan Medicinal Products
n/a

Paediatric Development Programme
n/a

Scientific Advice
n/a

2. Clinical Pharmacology

2.1. Pharmacokinetics
The applicant presents clinical and non-clinical overviews that include descriptions of the pharmacokinetics of valaciclovir.
Assessor’s overall conclusions on pharmacokinetics: the pharmacokinetic characteristics of valaciclovir have been well studied in the past. There would be no particular concerns for a generic formulation provided that it can be demonstrated that this product meets the criteria for a generic medicine.

2.2. Bioequivalence

Study design
The submitted Bioequivalence study has a randomized, open label (laboratory blinded), two periods, two treatments, two sequence, single-dose crossover study design and was conducted under fasting conditions with wash out period of 3 days between the two periods.
The 26 subjects were enrolled and housed for 37 hours (13 hours prior to test and reference product administration to 24 hours post dosing.
After supervised overnight fast for approximately 10 hours, the 500 mg of test and reference product were administered with 240 ml of water. Water was not permitted 1 hour before dosing and until 2 hours post-dosing, but was allowed at all other times. 24 subjects completed the study.
Collection of blood samples
A total of 21 (1x6ml) blood samples were collected during each period. The blood samples were collected within 1 hour before dosing and up to 24 hours post-dose in vacationers containing K2EDTA.

Assessor’s comment:
According to the NfG on the Investigation of Bioequivalence and Bioavailability CPMP/EWP/QWP/1401/98 the study design is appropriate. Washout period of 3 days is considered adequate as this period exceeds more than 5-fold of half-life of aciclovir (elimination half-life of around 3 hrs for aciclovir). This period is long enough to avoid any carry over effect to the second period.

The study was conducted under fasting conditions. This is acceptable since literature and the SPC given no recommendation for administration of the drug in relation to food and food intake does not affect the absorption of the active substance.

The sampling period of 24 hours and sampling scheme is sufficient and adequate to the expected PK parameters.

Test product
Valaciclovir 500mg tablets.

Reference product
Valtrex® 500mg tablets, manufactured by Glaxo Wellcome S.A, Spain, Licence Holder in UK: GlaxoSmithKline UK.

**Assessor’s comment:**
The reference product is from the EU market and in the line with current guidelines (CPMP/EWP/QWP/1401/98 Note for Guidance on the Investigation of Bioavailability and Bioequivalence). All dissolution profiles are similar.

**Population(s) studied**
Main criteria for inclusion:

Healthy adults subjects of either sex between 18-55 years of age (inclusive), having a body mass index (BMI) between 18.5 and 24.9kg/m², without evidence of underlying disease or abnormal laboratory values at the screening, who voluntarily consented to participate in the study.

A total of 26 healthy adults were included and randomized to one of the study groups.

The pharmacokinetics and statistical analysis was done on 24 subjects.

**Analytical methods**
The LC MS/MS method for the determination of aciclovir in human plasma was validated as per method validation.

**Assessor’s comment:**
In the BE study, measured plasma concentration of aciclovir were inside the analytical range.
The analytical methods are acceptable.

**Pharmacokinetic Variables**
Primary parameters:
\[ \text{AUC}_{0-t}, \text{AUC}_{0-\infty} \text{ and } C_{\text{max}} \]
Secondary parameters:
The ratio of \( \text{AUC}_{0-t} \) to \( \text{AUC}_{0-\infty} \)
$T_{\text{max}}$, $K_e$, residual area, $T_{1/2}$,

Safety:
Descriptive only.

**Assessor's comment:**
In the accordance with the NfG on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 the PK-variables are adequate.

**Statistical methods**
26 subjects were included and randomized to one of the two groups. The following subjects were excluded from PK and statistical evaluation for the given reason:

As subject 7 and 16 did not check in for the period II they were dropped from study

Pharmacokinetic parameters $AUC_{0-\infty}$, $t_{1/2}$, $K_e$ were not reported for subject 12 period I due to non-linear terminal log-linear phase.

Individual plasma concentration data were descriptively characterized to obtain average pharmacokinetic profiles of aciclovir. Descriptive statistics including arithmetic mean, median, minimum, maximum, standard deviation and coefficient of variation were calculated for pharmacokinetic parameters listed above. Additionally geometric mean was calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$.

Analysis of variance (ANOVA) was carried out using the log-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ values.

The ANOVA model included sequence, formulation (treatment) and period as fixed effects and subjects nested within sequence as random effect. The sequence effect and all other main effects were tested at the 5% level of significance.

Study endpoints were 90% confidence intervals for the ratio of means obtained from log-transformed pharmacokinetic parameters for aciclovir $AUC_{0-\infty}$, $AUC_{0-t}$ and $C_{\text{max}}$ of the test to the reference formulations. The parametric 90% confidence intervals of relative means $C_{\text{max}}$ and $AUC_{0-t}$ were to be between 0.80 and 1.25.

**Assessor's comment:**
The statistical methods are considered adequate.

During the assessment PK data were analysed using ANOVA models as they were described by the applicant. $AUC_{0-t}$—ratio of test over reference product was estimated to be 1.00 with CI of (0.97-1.05). Similar, for $C_{\text{max}}$ this was 0.96 with a CI (0.90-1.02). Thus both parameters were found to be well within acceptance region. Therefore, the results obtained for $AUC_{0-\infty}$, $AUC_{0-t}$ and $C_{\text{max}}$ of aciclovir were found to be in accordance with the results reported by the applicant.

The protocol required 24 subjects to complete the study. There were no major protocol deviations.
Results

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} median range) for aciclovir

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-24} hrs hrs*µg/ml</th>
<th>AUC\text{0-∞} hrs*µg/ml</th>
<th>C\text{max} µg/ml</th>
<th>t\text{max} hrs</th>
<th>T\text{1/2} hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>11.20 (SD=2.59)</td>
<td>11.55 (SD=2.75)</td>
<td>3.02 (SD=0.71)</td>
<td>1.50 (0.75-2.50)</td>
<td>3.16 (2.69-4.53)</td>
</tr>
<tr>
<td>Reference</td>
<td>11.12 (SD=2.26)</td>
<td>11.46 (SD=2.31)</td>
<td>3.12 (SD=0.59)</td>
<td>1.75 (1.00-2.75)</td>
<td>3.07 (2.41-4.39)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.95-1.05)</td>
<td>0.99 (0.95-1.04)</td>
<td>0.96 (0.90-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-subjects CV (%)</td>
<td>9.58</td>
<td>9.50</td>
<td>13.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-subjects CV (%)</td>
<td>19.91</td>
<td>19.92</td>
<td>17.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC\text{0-∞} area under the plasma concentration-time curve from time zero to infinity
AUC\text{0-t} area under the plasma concentration-time curve from time zero to t hours
C\text{max} maximum plasma concentration
T\text{max} time for maximum concentration
T\text{1/2} half-life

Period and sequence effects

The individual tests for period and the sequence effects obtained by the ANOVA models revealed no statistically significant results.

Regarding AUC, mean residual areas for both the test and reference products were less than 20%.

However, it was unclear -with regard to evidence of non-linearity of valaciclovir pharmacokinetics over the therapeutic dose range - if the outcome of this study on the 500mg strength could be extrapolated to the 250 mg and 1000 mg Valaciclovir strength.

In response, the applicant has submitted an additional bioequivalence study comparing the bioavailability between 250 mg Valaciclovir tablets, test product and the reference product Valtrex ® 250mg Tablets, GlaxoSmithKline, UK.

A randomised, open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study of Valaciclovir 250mg tablets (test product) and Valtrex 250mg tablets (reference tablets) in healthy adult subjects under fasting conditions.

A total of 32 healthy adults were studied. The analytical methods, pharmacokinetic variables and the statistical methods used were the same as described previously.

The results in Table 2 show the pharmacokinetic parameters for aciclovir.
The results in Table 4 show the pharmacokinetic parameters for Valaciclovir.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-&lt;infty&lt;/sub&gt;</td>
<td>0.99</td>
<td>0.93</td>
<td>1.05</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-&lt;infty&lt;/sub&gt;</td>
<td>1.01</td>
<td>0.96</td>
<td>1.07</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.19</td>
<td>1.07</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Based on this study it can be concluded that Valaciclovir 250mg test product is bioequivalent to Valtrex® 250mg tablets reference products.

The BE-study with 250 mg for C<sub>max</sub> the point estimate for the ratio of Test/Reference is 1.19 and the 90%-confidence interval [1.07;1.33] is not entirely covered by the acceptance region of [0.80;1.25] With regard to the Draft Guideline on the investigation of bioequivalence London, 24 July 2008, CPMP/EWP/QWP/1401/98 Rev. 1, recommends in case the pro-drug or active metabolites display non-linear pharmacokinetics (or it is difficult to conclude linear pharmacokinetics from available data), it is recommended to demonstrate bioequivalence for the main active metabolite. In such case, the parent compound does not need to be measured provided that it is inactive from efficacy and safety perspectives. Moreover, some pro-drugs may have low plasma concentrations, be quickly eliminated and have high variability, resulting in difficulties in demonstrating bioequivalence for parent compound in a reasonably sized bioequivalence study. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound.

The use of the metabolite aciclovir (active moiety) to prove bioequivalence is considered acceptable and a full analysis of PK parameters of valaciclovir can be accepted as supportive.

It is considered that the data from the BE-Study carried out with 250 and 500 mg can be extrapolated to the 1000 mg valaciclovir strength.

**Safety**

Overall, the two formulations were well tolerated, with no apparent differences in safety profiles.
One adverse event (AE) was reported following administration of the test product. The AE was mild in intensity and resolved completely.

**2.3. Pharmacodynamics**
The applicant presents clinical and non-clinical overviews that include descriptions of the pharmacodynamics of valaciclovir.
Assessor’s overall conclusions on pharmacodynamics: the pharmacodynamic characteristics of valaciclovir have been well studied in the past. There would be no particular concerns for a generic formulation provided that it can be demonstrated that this product meets the criteria for a generic medicine.

3. Clinical Efficacy

The applicant presents a clinical overview of clinical studies of efficacy with fluconazole.
Assessors’ overall conclusions on clinical efficacy: this is acceptable for this type of application.
Provided that there are not any issues in the Quality Assessment then the applicant’s formulation may be assumed to be a generic medicinal product in comparison to the reference product. If so then no significant differences should be expected in terms of clinical efficacy.

4. Clinical Safety

The applicant presents a discussion of safety based on the information provided in the SPC.
Assessor’s overall conclusions on clinical safety: this is acceptable for this type of application.
Provided that there are not any issues in the Quality Assessment then the applicant’s formulation may be assumed to be a generic medicinal product in comparison to the reference product. If so then no significant differences should be expected in terms of clinical safety.

5. Expert Reports

The non-clinical overview has been written by a suitably qualified person.

6. Product Literature

The SPC & PIL are acceptable. Post-marketing data is not available. The medical product has not yet been marketed in any country.

7. Overall Conclusions

Risk Benefit
The overall risk benefit may only be considered positive.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Valaciclovir 250mg, 500mg and 1000mg are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Valaciclovir 250mg Tablets and Valtrex®250mg Tablets and Valaciclovir (The Wellcome Foundation Limited, UK). Given that linear kinetics apply between the 250mg tablet and the 500mg and 1000mg strength tablets; that the formulae for the tablets are proportional and that similar dissolution results have been shown for the three strengths, separate bioequivalence studies using the 500mg and 1000mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with valaciclovir hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**VALACICLOVIR 250MG TABLETS**  
PL 24668/0093  
PL 24668/0096  
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PL 24668/0095  
PL 24668/0098  
PL 24668/0101  

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 2nd August 2007</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 17th October 2008</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 12th May 2008, 23rd February 2009 and 20th March 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 19th November 2008, 6th March 2009 and 25th May 2009 for the clinical sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 10th August 2009.</td>
</tr>
</tbody>
</table>
VALACICLOVIR 250MG TABLETS
PL 24668/0093
PL 24668/0096
PL 24668/0099

VALACICLOVIR 500MG TABLETS
PL 24668/0094
PL 24668/0097
PL 24668/0100

VALACICLOVIR 1000MG TABLETS
PL 24668/0095
PL 24668/0098
PL 24668/0101

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tbody>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valaciclovir 250 mg Film-Coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 250 mg valaciclovir (as valaciclovir hydrochloride monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Oval, white, biconvex, film-coated tablets, 13.8 x 6.9 mm with VC1 on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• In immunocompetent patients:
  – Treatment of herpes zoster in patients aged over 50 years: valaciclovir reduces the duration of severe infection and accordingly the proportion of patients with zoster-associated pain.
  – Valaciclovir is indicated for the treatment of initial and recurrent genital herpes simplex infections.
  – Valaciclovir is indicated for the prevention of recurrent genital herpes simplex infections in patients with at least 6 recurrences per year.

• Valaciclovir is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, in particular after renal transplantation, except after lung transplantation.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration
Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water), with or without food.

Adults

Herpes zoster infections
Prevention of zoster-associated pain:
• 1000 mg of valaciclovir 3 times daily for 7 days

Treatment should be initiated as soon as possible after the beginning of the infection, within 72 hours of the appearance of skin lesions.

Herpes simplex infections
Treatment of genital herpes simplex infections in immunocompetent patients:
• 500 mg twice daily for 10 days for the initial episode
• 1000 mg per day in one or two divided doses for 5 days for recurrent episodes

Treatment should be initiated as soon as possible in the course of infection, preferably at the prodromal stage or when lesions begin to appear.

Suppression of recurrent genital herpes simplex infections:
• 500 mg per day in one or two divided doses
(Better results have been obtained by dividing the daily dose into two, i.e. by administering 250 mg twice daily, when the administration of a single 500 mg dose per day failed, or if the recurrences were frequent or very symptomatic).

For this indication, the need for treatment must be re-evaluated after 6 to 12 months.

**Adults and adolescents aged 12 years and above**

**Cytomegalovirus infections**

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV):*

- 2000 mg of valaciclovir 4 times daily

Treatment should be initiated as soon as possible after the organ transplant.

The dose of valaciclovir should be adapted according to the creatinine clearance (see second table below).

The duration of treatment is usually 90 days, although longer treatment may be necessary in high risk patients.

**Elderly**

Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

**Renal impairment**

*Prevention of zoster-associated pain, suppression and treatment of genital herpes simplex infections:*

The dosage should be adjusted according to the creatinine clearance:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage</th>
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</thead>
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<tr>
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</tr>
<tr>
<td></td>
<td>Suppression and treatment of genital herpes simplex infections: No dosage adjustment is required.</td>
</tr>
<tr>
<td>&lt; 15 ml/min</td>
<td>Prevention of zoster-associated pain: 1000 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Treatment of genital herpes simplex infections: 500 mg per day</td>
</tr>
<tr>
<td></td>
<td>Suppression of genital herpes simplex infections: 250 mg per day</td>
</tr>
<tr>
<td></td>
<td>In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.</td>
</tr>
</tbody>
</table>

Patients on haemodialysis should receive the same dose as patients with creatinine clearance <10 ml/min. On dialysis days, the dose should be given after dialysis.

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV)*

The dosage should be adjusted according to the creatinine clearance, which must be assessed frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
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<tr>
<td>50-75 ml/min</td>
<td>1500 mg 4 times daily</td>
</tr>
<tr>
<td>25-50 ml/min</td>
<td>1500 mg 3 times daily</td>
</tr>
<tr>
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</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>1500 mg daily</td>
</tr>
</tbody>
</table>

In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.
**Hepatic impairment**
Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained).
Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment. However, clinical experience is limited.
For the higher doses recommended for the prevention of infections and diseases caused by CMV, see section 4.4.

**Children below the age of 12 years**
Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

### 4.3 CONTRAINDICATIONS
Hypersensitivity to valaciclovir, aciclovir or to any of the excipients.

### 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 renal impairment and the elderly**
The dose should be adapted according to the creatinine clearance (see section 4.2). The elderly and patients with a history of renal impairment are also at increased risk of developing neurological disorders (see section 4.8). If neurological disorders occur, the treatment must be stopped. Upon reintroduction, the dosage must be reduced.

**Use of high doses of valaciclovir in hepatic impairment**
There are no data available on the use of high doses (8 g per day) in patients with hepatic impairment. Therefore caution should be exercised when administering high doses of valaciclovir to these patients.

**Use in genital herpes**
Therapy with valaciclovir reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices (particularly the use of condoms).

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The combination of valaciclovir with nephrotoxic medicinal products, in particular immunosuppressants like ciclosporin, tacrolimus, mycophenolate mofetil, must be taken into account, especially in case of impaired renal function, and warrants regular monitoring. This applies for aminoglycosides, organoplatins, iodinated contrast media, methotrexate, pentamidine, foscarnet as well.

Aciclovir is eliminated primarily unchanged in the urine via active tubular secretion. Any medicinal products administered concurrently that compete with this mechanism for elimination (e.g. cimetidine, probenecid or mycophenolate mofetil) may increase aciclovir plasma concentrations following valaciclovir administration. In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with these kinds of products. However, following 1 g valaciclovir, no dosage adjustment is necessary at this dose of 1 g because of the wide therapeutic index of aciclovir. Alternative products, which do not interact with other substances excreted primarily via the kidney, may be considered for the management of excess gastric acid production and urate-lowering therapy when administering high-dose valaciclovir.
4.6 PREGNANCY AND LACTATION

Pregnancy

Data on a large number of exposed pregnancies indicate no adverse effects of aciclovir, the active metabolite of valaciclovir, on pregnancy or on the health of the fetus/newborn child. However, only epidemiological studies would allow to substantiate the lack of harmfulness of the agent on pregnancy. Studies in animals have not shown reproductive toxicity in a single species at high doses (see section 5.3).

Valaciclovir should not be used during pregnancy unless clearly necessary.

There is no data to justify the long-term use of valaciclovir in recurrent herpes in pregnant women, in particular at the end of pregnancy.

Lactation

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk (see section 5.2).

If systemic treatment of the mother is necessary for a serious infection, breast-feeding should be discontinued owing to the risk of infection. Otherwise, local treatment should be used so breastfeeding can be continued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Valaciclovir has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

The adverse events are ranked under headings of frequency, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
- Very rare: thrombocytopenia, leucopenia / neutropenia (especially in immunocompromised patients).

Immune system disorders
- Very rare: anaphylaxis.

Psychiatric disorders
- Rare: altered consciousness, confusion, hallucinations.
- Very rare: agitation, psychotic symptoms.

Nervous system disorders
- Common: headache.
- Rare: dizziness, somnolence, decreased consciousness.
- Very rare: tremor, ataxia, dysarthria, convulsions, encephalopathy, coma.

The above events are usually seen in patients with renal impairment receiving doses greater than those recommended or in patients with other predisposing factors (especially the elderly, see section 4.4).

These neurological disorders are common in transplant recipients receiving high doses of valaciclovir for the prophylaxis of infections and diseases caused by CMV.

Respiratory, thoracic and mediastinal disorders
- Uncommon: dyspnoea.
Gastrointestinal disorders
• Common: nausea.
• Rare: abdominal discomfort, vomiting, diarrhoea.

Hepato-biliary disorders
• Very rare: reversible increases of bilirubin and serum hepatic enzyme levels.

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders
• Uncommon: rash, including photosensitivity.
• Rare: pruritus.
• Very rare: urticaria, angioedema.

Renal and urinary disorders
Rare: renal impairment.
Very rare: increased blood urea and creatinine, acute renal failure, sometimes with crystal precipitation in the tubule lumen, in particular in elderly or renally impaired patients when the doses used exceed those recommended.

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced human immunodeficiency virus (HIV) disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

4.9 OVERDOSE
Valaciclovir is rapidly and completely metabolised to aciclovir.

The intravenous administration of a high dose of aciclovir (80 mg/kg) corresponds to a valaciclovir dose of approximately 15 g.

Symptoms
Few cases of overdose have been reported with valaciclovir.

The oral administration of doses of aciclovir up to 20 g did not lead to adverse events.

The accidental and repeated oral administration of high doses of aciclovir over a period of several days led to gastrointestinal (nausea and vomiting) and neurological (headache and confusion) disorders.

The intravenous administration of a high dose of aciclovir caused an increase in serum creatinine levels with renal impairment secondary to the precipitation of crystals in the tubule lumen.

Neurological disorders (confusion, hallucinations, agitation, epilepsy and coma) have been described following intravenous overdose.

The use of doses unadapted to renal function in the renally impaired has been observed to cause altered consciousness, from confusion with hallucinations to coma.

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 excl. reverse transcriptase inhibitors
ATC code: J05A B11

Valaciclovir is the L-valine ester of aciclovir, the active antiviral. It is rapidly and completely metabolised to aciclovir by a 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.

The phosphorylation process is completed (conversion from mono- to di- and 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.

This dual selectivity ensures that aciclovir does not interfere with the metabolism of healthy cells. Extensive monitoring of clinical isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

Resistance is normally due to a thymidine kinase deficient phenotype, which results in a virus that is profoundly disadvantaged in the natural host. Infrequently, 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.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, valaciclovir is well absorbed and rapidly and almost completely metabolized to aciclovir by a marked first pass effect, which is mainly hepatic. After administration of single 250 mg and 2000 mg doses, the maximal aciclovir concentrations obtained are 10 and 37 mc mol/l (2.2 to 8.3 µg/ml) and are reached approximately 1 to 2 hours after dosing. The bioavailability of acyclovir from valaciclovir is 54%; it is not affected by food intake. Maximum plasma valaciclovir concentrations are only 4% of those of aciclovir. Valaciclovir cannot be detected within 3 hours of administration. The plasma profiles of valaciclovir and aciclovir are similar after single and multiple dosing.

Binding of aciclovir and valaciclovir to plasma proteins is very low (approximately 15%). Aciclovir distributes rapidly into all tissues, especially the liver, kidneys, muscles, lungs. It also diffuses into vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

In patients with normal renal function, the elimination half-life of aciclovir after single and repeat doses is approximately 3 hours. In patients with end-stage renal disease, the average elimination halflife of aciclovir after valaciclovir administration is approximately 14 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is mainly eliminated as aciclovir and its metabolite, 9-(carboxymethoxymethyl)-guanine, in the urine.
In elderly, cirrhotic and HIV-positive patients, the pharmacokinetic profile of aciclovir after administration of valaciclovir is not significantly different. In non-dialysed severely renally impaired patients, the maximum concentration of aciclovir is approximately doubled and its elimination half-life is increased by a factor of 5. In organ transplant recipients treated with 2000 mg of valaciclovir 4 times daily, the maximum plasma concentrations of aciclovir are similar or greater than those obtained in healthy volunteers receiving the same dose. The areas under the curve are appreciably greater. At the end of pregnancy, the area under the curve of the plasma concentration of aciclovir versus time for 1000 mg of valaciclovir is approximately twice greater than after administration of 1200 mg/day of aciclovir. Pregnancy does not modify the pharmacokinetic characteristics of valaciclovir.

With a maternal valaciclovir dosage of 500 mg twice daily, the amount of substance excreted in breast milk 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

Mutagenicity:
The results of mutagenicity tests in vitro and in vivo indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity:
Valaciclovir was not carcinogenic in bio-assays performed in mice and rats.

Teratogenicity
Valaciclovir is not teratogenic in rats and rabbits.

Fertility
Orally administered valaciclovir did not modify the fertility of male or female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
Microcrystalline cellulose
Povidone
Magnesium stearate

Tablet coating (Opadry White Y-5-7068):
Hypermellose
Hydroxypropyl Cellulose
Titanium dioxide (E171)
Macrogol

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C

6.5 NATURE AND CONTENTS OF CONTAINER
Aluminium/PVC blister: 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets
HDPE bottles with sealed plastic cap (LDPE-closure): 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets

Not all pack sizes may be marketed.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0093
PL 24668/0096
PL 24668/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/08/2009

10 DATE OF REVISION OF THE TEXT
10/08/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valaciclovir 500 mg Film-Coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 500 mg valaciclovir (as valaciclovir hydrochloride monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Oval, white, biconvex, film-coated tablets, 17.6 x 8.8 mm with VC2 on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
- In immunocompetent patients:
  - Treatment of herpes zoster in patients aged over 50 years: valaciclovir reduces the duration of severe infection and accordingly the proportion of patients with zoster-associated pain.
  - Valaciclovir is indicated for the treatment of initial and recurrent genital herpes simplex infections.
  - Valaciclovir is indicated for the prevention of recurrent genital herpes simplex infections in patients with at least 6 recurrences per year.

- Valaciclovir is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, in particular after renal transplantation, except after lung transplantation.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration
Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water), with or without food.

Adults

Herpes zoster infections
Prevention of zoster-associated pain:
- 1000 mg of valaciclovir 3 times daily for 7 days

Treatment should be initiated as soon as possible after the beginning of the infection, within 72 hours of the appearance of skin lesions.

Herpes simplex infections
Treatment of genital herpes simplex infections in immunocompetent patients:
- 500 mg twice daily for 10 days for the initial episode
- 1000 mg per day in one or two divided doses for 5 days for recurrent episodes

Treatment should be initiated as soon as possible in the course of infection, preferably at the prodromal stage or when lesions begin to appear.

Suppression of recurrent genital herpes simplex infections:
- 500 mg per day in one or two divided doses
(Better results have been obtained by dividing the daily dose into two, i.e. by administering 250 mg twice daily, when the administration of a single 500 mg dose per day failed, or if the recurrences were frequent or very symptomatic).

For this indication, the need for treatment must be re-evaluated after 6 to 12 months.

**Adults and adolescents aged 12 years and above**

**Cytomegalovirus infections**

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV):*

- 2000 mg of valaciclovir 4 times daily

Treatment should be initiated as soon as possible after the organ transplant. The dose of valaciclovir should be adapted according to the creatinine clearance (see second table below).

The duration of treatment is usually 90 days, although longer treatment may be necessary in high risk patients.

**Elderly**

Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

**Renal impairment**

*Prevention of zoster-associated pain, suppression and treatment of genital herpes simplex infections:*

The dosage should be adjusted according to the creatinine clearance:

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<th>Creatinine clearance</th>
<th>Dosage</th>
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<td>&lt; 15 ml/min</td>
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<td>• Treatment of genital herpes simplex infections: 500 mg per day</td>
</tr>
<tr>
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<td>• Suppression of genital herpes simplex infections: 250 mg per day</td>
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In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.

Patients on haemodialysis should receive the same dose as patients with creatinine clearance <10 ml/min. On dialysis days, the dose should be given after dialysis.

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV)*

The dosage should be adjusted according to the creatinine clearance, which must be assessed frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment.

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In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.
**Hepatic impairment**
Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained).
Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment. However, clinical experience is limited.
For the higher doses recommended for the prevention of infections and diseases caused by CMV, see section 4.4.

**Children below the age of 12 years**
Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

**4.3 CONTRAINDICATIONS**
Hypersensitivity to valaciclovir, aciclovir or to any of the excipients.

**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 renal impairment and the elderly**
The dose should be adapted according to the creatinine clearance (see section 4.2). The elderly and patients with a history of renal impairment are also at increased risk of developing neurological disorders (see section 4.8). If neurological disorders occur, the treatment must be stopped. Upon reintroduction, the dosage must be reduced.

**Use of high doses of valaciclovir in hepatic impairment**
There are no data available on the use of high doses (8 g per day) in patients with hepatic impairment. Therefore caution should be exercised when administering high doses of valaciclovir to these patients.

**Use in genital herpes**
Therapy with valaciclovir reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices (particularly the use of condoms).

**4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**
The combination of valaciclovir with nephrotoxic medicinal products, in particular immunosuppressants like ciclosporin, tacrolimus, mycophenolate mofetil, must be taken into account, especially in case of impaired renal function, and warrants regular monitoring. This applies for aminoglycosides, organoplatins, iodinated contrast media, methotrexate, pentamidine, foscarnet as well.

Aciclovir is eliminated primarily unchanged in the urine via active tubular secretion. Any medicinal products administered concurrently that compete with this mechanism for elimination (e.g. cimetidine, probenecid or mycophenolate mofetil) may increase aciclovir plasma concentrations following valaciclovir administration. In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with these kinds of products. However, following 1 g valaciclovir, no dosage adjustment is necessary at this dose of 1 g because of the wide therapeutic index of aciclovir. Alternative products, which do not interact with other substances excreted primarily via the kidney, may be considered for the management of excess gastric acid production and urate-lowering therapy when administering high-dose valaciclovir.
4.6 PREGNANCY AND LACTATION

Pregnancy
Data on a large number of exposed pregnancies indicate no adverse effects of aciclovir, the active metabolite of valaciclovir, on pregnancy or on the health of the fetus/newborn child. However, only epidemiological studies would allow to substantiate the lack of harmfulness of the agent on pregnancy.

Studies in animals have not shown reproductive toxicity in a single species at high doses (see section 5.3)

Valaciclovir should not be used during pregnancy unless clearly necessary.

There is no data to justify the long-term use of valaciclovir in recurrent herpes in pregnant women, in particular at the end of pregnancy.

Lactation
Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk (see section 5.2).

If systemic treatment of the mother is necessary for a serious infection, breast-feeding should be discontinued owing to the risk of infection. Otherwise, local treatment should be used so breastfeeding can be continued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Valaciclovir has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

The adverse events are ranked under headings of frequency, using the following convention:
very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
- Very rare: thrombocytopenia, leucopenia / neutropenia (especially in immunocompromised patients).

Immune system disorders
- Very rare: anaphylaxis.

Psychiatric disorders
- Rare: altered consciousness, confusion, hallucinations.
- Very rare: agitation, psychotic symptoms.

Nervous system disorders
- Common: headache.
- Rare: dizziness, somnolence, decreased consciousness.
- Very rare: tremor, ataxia, dysarthria, convulsions, encephalopathy, coma.

The above events are usually seen in patients with renal impairment receiving doses greater than those recommended or in patients with other predisposing factors (especially the elderly, see section 4.4).

These neurological disorders are common in transplant recipients receiving high doses of valaciclovir for the prophylaxis of infections and diseases caused by CMV.

Respiratory, thoracic and mediastinal disorders
- Uncommon: dyspnoea.

Gastrointestinal disorders
- Common: nausea.
- Rare: abdominal discomfort, vomiting, diarrhoea.
Hepato-biliary disorders

- Very rare: reversible increases of bilirubin and serum hepatic enzyme levels.

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders

- Uncommon: rash, including photosensitivity.
- Rare: pruritus.
- Very rare: urticaria, angioedema.

Renal and urinary disorders

Rare: renal impairment.
Very rare: increased blood urea and creatinine, acute renal failure, sometimes with crystal precipitation in the tubule lumen, in particular in elderly or renally impaired patients when the doses used exceed those recommended.

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced human immunodeficiency virus (HIV) disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

4.9 OVERDOSE

Valaciclovir is rapidly and completely metabolised to aciclovir.

The intravenous administration of a high dose of aciclovir (80 mg/kg) corresponds to a valaciclovir dose of approximately 15 g.

Symptoms

Few cases of overdose have been reported with valaciclovir.

The oral administration of doses of aciclovir up to 20 g did not lead to adverse events.

The accidental and repeated oral administration of high doses of aciclovir over a period of several days led to gastrointestinal (nausea and vomiting) and neurological (headache and confusion) disorders.

The intravenous administration of a high dose of aciclovir caused an increase in serum creatinine levels with renal impairment secondary to the precipitation of crystals in the tubule lumen.
Neurological disorders (confusion, hallucinations, agitation, epilepsy and coma) have been described following intravenous overdose.

The use of doses unadapted to renal function in the renally impaired has been observed to cause altered consciousness, from confusion with hallucinations to coma.

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 excl. reverse transcriptase inhibitors
ATC code: J05A B11

Valaciclovir is the L-valine ester of aciclovir, the active antiviral. It is rapidly and completely metabolised to aciclovir by a 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.

The phosphorylation process is completed (conversion from mono- to di- and 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.

This dual selectivity ensures that aciclovir does not interfere with the metabolism of healthy cells. Extensive monitoring of clinical isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

Resistance is normally due to a thymidine kinase deficient phenotype, which results in a virus that is profoundly disadvantaged in the natural host. Infrequently, 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.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, valaciclovir is well absorbed and rapidly and almost completely metabolized to aciclovir by a marked first pass effect, which is mainly hepatic. After administration of single 250 mg and 2000 mg doses, the maximal aciclovir concentrations obtained are 10 and 37 mcg/ml (2.2 to 8.3 µg/ml) and are reached approximately 1 to 2 hours after dosing. The bioavailability of acyclovir from valaciclovir is 54%; it is not affected by food intake. Maximum plasma valaciclovir concentrations are only 4% of those of aciclovir. Valaciclovir cannot be detected within 3 hours of administration. The plasma profiles of valaciclovir and aciclovir are similar after single and multiple dosing.

Binding of aciclovir and valaciclovir to plasma proteins is very low (approximately 15%). Aciclovir distributes rapidly into all tissues, especially the liver, kidneys, muscles, lungs. It also diffuses into vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

In patients with normal renal function, the elimination half-life of aciclovir after single and repeat doses is approximately 3 hours. In patients with end-stage renal disease, the average elimination halflife of aciclovir after valaciclovir administration is approximately 14 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is mainly eliminated as aciclovir and its metabolite, 9-(carboxymethoxymethyl)-guanine, in the urine.
In elderly, cirrhotic and HIV-positive patients, the pharmacokinetic profile of aciclovir after administration of valaciclovir is not significantly different. In non-dialysed severely renally impaired patients, the maximum concentration of aciclovir is approximately doubled and its elimination half-life is increased by a factor of 5. In organ transplant recipients treated with 2000 mg of valaciclovir 4 times daily, the maximum plasma concentrations of aciclovir are similar or greater than those obtained in healthy volunteers receiving the same dose. The areas under the curve are appreciably greater. At the end of pregnancy, the area under the curve of the plasma concentration of aciclovir versus time for 1000 mg of valaciclovir is approximately twice greater than after administration of 1200 mg/day of aciclovir. Pregnancy does not modify the pharmacokinetic characteristics of valaciclovir.

With a maternal valaciclovir dosage of 500 mg twice daily, the amount of substance excreted in breast milk 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

Mutagenicity:
The results of mutagenicity tests in vitro and in vivo indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity:
Valaciclovir was not carcinogenic in bio-assays performed in mice and rats.

Teratogenicity
Valaciclovir is not teratogenic in rats and rabbits.

Fertility
Orally administered valaciclovir did not modify the fertility of male or female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core
Microcrystalline cellulose
Povidone
Magnesium stearate

Tablet coating (Opadry White Y-5-7068):
Hypromellose
Hydroxypropyl Cellulose
Titanium dioxide (E171)
Macrogol

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Al/PVC blister: 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets
HDPE bottles with sealed plastic cap (LDPE-closure): 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets

Not all pack sizes may be marketed.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0094
PL 24668/0097
PL 24668/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT
October 2008
1 NAME OF THE MEDICINAL PRODUCT
Valaciclovir 1000 mg Film-Coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 1000 mg valaciclovir (as valaciclovir hydrochloride monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Oval, white, biconvex, film-coated tablets, 22.0 x 11.0 mm with VC3 on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• In immunocompetent patients :
  — Treatment of herpes zoster in patients aged over 50 years: valaciclovir reduces the duration of severe infection and accordingly the proportion of patients with zoster-associated pain.
  — Valaciclovir is indicated for the treatment of initial and recurrent genital herpes simplex infections.
  — Valaciclovir is indicated for the prevention of recurrent genital herpes simplex infections in patients with at least 6 recurrences per year.

• Valaciclovir is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, in particular after renal transplantation, except after lung transplantation.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration
Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water), with or without food.

Adults

Herpes zoster infections
Prevention of zoster-associated pain:
• 1000 mg of valaciclovir 3 times daily for 7 days

Treatment should be initiated as soon as possible after the beginning of the infection, within 72 hours of the appearance of skin lesions.

Herpes simplex infections
Treatment of genital herpes simplex infections in immunocompetent patients:
• 500 mg twice daily for 10 days for the initial episode
• 1000 mg per day in one or two divided doses for 5 days for recurrent episodes

Treatment should be initiated as soon as possible in the course of infection, preferably at the prodromal stage or when lesions begin to appear.

Suppression of recurrent genital herpes simplex infections:
• 500 mg per day in one or two divided doses
(Better results have been obtained by dividing the daily dose into two, i.e. by administering 250 mg twice daily, when the administration of a single 500 mg dose per day failed, or if the recurrences were frequent or very symptomatic). For this indication, the need for treatment must be re-evaluated after 6 to 12 months.

_Adults and adolescents aged 12 years and above_

_Cytomegalovirus infections_

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV):*

- 2000 mg of valaciclovir 4 times daily

Treatment should be initiated as soon as possible after the organ transplant.

The dose of valaciclovir should be adapted according to the creatinine clearance (see second table below).

The duration of treatment is usually 90 days, although longer treatment may be necessary in high risk patients.

_Elderly_

Dosage modification is not required unless renal function is significantly impaired (see Renal impairment, below). Adequate hydration must be maintained.

_Renal impairment_

*Prevention of zoster-associated pain, suppression and treatment of genital herpes simplex infections:*

The dosage should be adjusted according to the creatinine clearance:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| 15-30 ml/min         | • Prevention of zoster-associated pain: 1000 mg twice daily  
                        | • Suppression and treatment of genital herpes simplex infections: No dosage adjustment is required.                                         |
| < 15 ml/min          | • Prevention of zoster-associated pain: 1000 mg once daily  
                        | • Treatment of genital herpes simplex infections: 500 mg per day  
                        | • Suppression of genital herpes simplex infections: 250 mg per day  
                        | In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.  |

Patients on haemodialysis should receive the same dose as patients with creatinine clearance <10 ml/min. On dialysis days, the dose should be given after dialysis.

*Prophylaxis of infections and diseases caused by cytomegalovirus (CMV)*

The dosage should be adjusted according to the creatinine clearance, which must be assessed frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-75 ml/min</td>
<td>1500 mg 4 times daily</td>
</tr>
<tr>
<td>25-50 ml/min</td>
<td>1500 mg 3 times daily</td>
</tr>
<tr>
<td>10-25 ml/min</td>
<td>1500 mg twice daily</td>
</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>1500 mg daily</td>
</tr>
</tbody>
</table>

In patients on haemodialysis, the dose must be administered after the haemodialysis has been performed.
**Hepatic impairment**
Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained).
Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment. However, clinical experience is limited.
For the higher doses recommended for the prevention of infections and diseases caused by CMV, see section 4.4.

**Children below the age of 12 years**
Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

### 4.3 CONTRAINDICATIONS
Hypersensitivity to valaciclovir, aciclovir or to any of the excipients.

### 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 renal impairment and the elderly
The dose should be adapted according to the creatinine clearance (see section 4.2). The elderly and patients with a history of renal impairment are also at increased risk of developing neurological disorders (see section 4.8). If neurological disorders occur, the treatment must be stopped. Upon reintroduction, the dosage must be reduced.

#### Use of high doses of valaciclovir in hepatic impairment
There are no data available on the use of high doses (8 g per day) in patients with hepatic impairment. Therefore caution should be exercised when administering high doses of valaciclovir to these patients.

#### Use in genital herpes
Therapy with valaciclovir reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices (particularly the use of condoms).

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The combination of valaciclovir with nephrotoxic medicinal products, in particular immunosuppressants like ciclosporin, tacrolimus, mycophenolate mofetil, must be taken into account, especially in case of impaired renal function, and warrants regular monitoring. This applies for aminoglycosides, organoplatin, iodinated contrast media, methotrexate, pentamidine, foscarnet as well.

Aciclovir is eliminated primarily unchanged in the urine via active tubular secretion. Any medicinal products administered concurrently that compete with this mechanism for elimination (e.g. cimetidine, probenecid or mycophenolate mofetil) may increase aciclovir plasma concentrations following valaciclovir administration. In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with these kinds of products. However, following 1 g valaciclovir, no dosage adjustment is necessary at this dose of 1 g because of the wide therapeutic index of aciclovir. Alternative products, which do not interact with other substances excreted primarily via the kidney, may be considered for the management of excess gastric acid production and urate-lowering therapy when administering high-dose valaciclovir.
4.6 PREGNANCY AND LACTATION

**Pregnancy**

Data on a large number of exposed pregnancies indicate no adverse effects of aciclovir, the active metabolite of valaciclovir, on pregnancy or on the health of the fetus/newborn child. However, only epidemiological studies would allow to substantiate the lack of harmfulness of the agent on pregnancy. Studies in animals have not shown reproductive toxicity in a single species at high doses (see section 5.3)

Valaciclovir should not be used during pregnancy unless clearly necessary.

There is no data to justify the long-term use of valaciclovir in recurrent herpes in pregnant women, in particular at the end of pregnancy.

**Lactation**

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk (see section 5.2).

If systemic treatment of the mother is necessary for a serious infection, breast-feeding should be discontinued owing to the risk of infection. Otherwise, local treatment should be used so breastfeeding can be continued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Valaciclovir has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

The adverse events are ranked under headings of frequency, using the following convention:

very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

**Blood and the lymphatic system disorders**

- Very rare: thrombocytopenia, leucopenia / neutropenia (especially in immunocompromised patients).

**Immune system disorders**

- Very rare: anaphylaxis.

**Psychiatric disorders**

- Rare: altered consciousness, confusion, hallucinations.
- Very rare: agitation, psychotic symptoms.

**Nervous system disorders**

- Common: headache.
- Rare: dizziness, somnolence, decreased consciousness.
- Very rare: tremor, ataxia, dysarthria, convulsions, encephalopathy, coma.

The above events are usually seen in patients with renal impairment receiving doses greater than those recommended or in patients with other predisposing factors (especially the elderly, see section 4.4).

These neurological disorders are common in transplant recipients receiving high doses of valaciclovir for the prophylaxis of infections and diseases caused by CMV.

**Respiratory, thoracic and mediastinal disorders**

- Uncommon: dyspnoea.
**Gastrointestinal disorders**
- Common: nausea.
- Rare: abdominal discomfort, vomiting, diarrhoea.

**Hepato-biliary disorders**
- Very rare: reversible increases of bilirubin and serum hepatic enzyme levels.

These are occasionally described as hepatitis.

**Skin and subcutaneous tissue disorders**
- Uncommon: rash, including photosensitivity.
- Rare: pruritus.
- Very rare: urticaria, angioedema.

**Renal and urinary disorders**
Rare: renal impairment.

Very rare: increased blood urea and creatinine, acute renal failure, sometimes with crystal precipitation in the tubule lumen, in particular in elderly or renally impaired patients when the doses used exceed those recommended.

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced human immunodeficiency virus (HIV) disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

**4.9 OVERDOSE**
Valaciclovir is rapidly and completely metabolised to aciclovir.

The intravenous administration of a high dose of aciclovir (80 mg/kg) corresponds to a valaciclovir dose of approximately 15 g.

**Symptoms**
Few cases of overdose have been reported with valaciclovir.

The accidental and repeated oral administration of high doses of aciclovir over a period of several days led to gastrointestinal (nausea and vomiting) and neurological (headache and confusion) disorders.

The intravenous administration of a high dose of aciclovir caused an increase in serum creatinine levels with renal impairment secondary to the precipitation of crystals in the tubule lumen.

Neurological disorders (confusion, hallucinations, agitation, epilepsy and coma) have been described following intravenous overdose.

The use of doses unadapted to renal function in the renally impaired has been observed to cause altered consciousness, from confusion with hallucinations to coma.

**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 excl. reverse transcriptase inhibitors
ATC code: J05A B11

Valaciclovir is the L-valine ester of aciclovir, the active antiviral. It is rapidly and completely metabolised to aciclovir by a 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.

The phosphorylation process is completed (conversion from mono- to di- and 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.

This dual selectivity ensures that aciclovir does not interfere with the metabolism of healthy cells. Extensive monitoring of clinical isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

Resistance is normally due to a thymidine kinase deficient phenotype, which results in a virus that is profoundly disadvantaged in the natural host. Infrequently, 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.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, valaciclovir is well absorbed and rapidly and almost completely metabolized to aciclovir by a marked first pass effect, which is mainly hepatic. After administration of single 250 mg and 2000 mg doses, the maximal aciclovir concentrations obtained are 10 and 37 mc mol/l (2.2 to 8.3 µg/ml) and are reached approximately 1 to 2 hours after dosing. The bioavailability of acyclovir from valaciclovir is 54%; it is not affected by food intake. Maximum plasma valaciclovir concentrations are only 4% of those of aciclovir. Valaciclovir cannot be detected within 3 hours of administration. The plasma profiles of valaciclovir and aciclovir are similar after single and multiple dosing.

Binding of aciclovir and valaciclovir to plasma proteins is very low (approximately 15%). Aciclovir distributes rapidly into all tissues, especially the liver, kidneys, muscles, lungs. It also diffuses into vaginal secretions, cerebrospinal fluid and herpetic vesicular fluid.

In patients with normal renal function, the elimination half-life of aciclovir after single and repeat doses is approximately 3 hours. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is mainly eliminated as aciclovir and its metabolite, 9-(carboxymethoxymethyl)-guanine, in the urine.
In elderly, cirrhotic and HIV-positive patients, the pharmacokinetic profile of aciclovir after administration of valaciclovir is not significantly different. In non-dialysed severely renally impaired patients, the maximum concentration of aciclovir is approximately doubled and its elimination half-life is increased by a factor of 5. In organ transplant recipients treated with 2000 mg of valaciclovir 4 times daily, the maximum plasma concentrations of aciclovir are similar or greater than those obtained in healthy volunteers receiving the same dose. The areas under the curve are appreciably greater. At the end of pregnancy, the area under the curve of the plasma concentration of aciclovir versus time for 1000 mg of valaciclovir is approximately twice greater than after administration of 1200 mg/day of aciclovir. Pregnancy does not modify the pharmacokinetic characteristics of valaciclovir.

With a maternal valaciclovir dosage of 500 mg twice daily, the amount of substance excreted in breast milk 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
Mutagenicity:
The results of mutagenicity tests in vitro and in vivo indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity:
Valaciclovir was not carcinogenic in bio-assays performed in mice and rats.

Teratogenicity
Valaciclovir is not teratogenic in rats and rabbits.

Fertility
Orally administered valaciclovir did not modify the fertility of male or female rats.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Tablet core
Microcrystalline cellulose
Povidone
Magnesium stearate

Tablet coating (Opadry White Y-5-7068):
Hypermellose
Hydroxypropyl Cellulose
Titanium dioxide (E171)
Macrogol

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C

6.5 NATURE AND CONTENTS OF CONTAINER
Al/PVC blister: 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets
HDPE bottles with sealed plastic cap (LDPE-closure): 4, 7, 10, 14, 28, 30, 42, 50, 56, 60, 90, 100 or 500 film-coated tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th floor
94 Wigmore Street
London
W1U 3 RF

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0095
PL 24668/0098
PL 24668/0101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT
October 2008
VALACICLOVIR MG TABLETS
PL 24668/0093-0101

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valaciclovir 250mg, 500mg and 1000mg film-coated tablets

Valaciclovir (as valaciclovir hydrochloride monohydrate)

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 Valaciclovir tablets are and what they are used for
2. Before you take Valaciclovir tablets
3. How to take Valaciclovir tablets
4. Possible side effects
5. How to store Valaciclovir tablets
6. Further information

1. WHAT VALACICLOVIR TABLETS ARE AND WHAT THEY ARE USED FOR

Valaciclovir is a antiviral medicine.

It is used in the following situations:
- in patients over 50 years of age, to treat shingles,
- to treat genital Herpes simplex virus (HSV) infections,
- to prevent (suppress) recurrent genital Herpes simplex virus (HSV) infections in patients who have at least 6 recurrences per year,
- to prevent cytomegalovirus (CMV) infection and disease after organ transplant.

2. BEFORE YOU TAKE VALACICLOVIR TABLETS

Do NOT take Valaciclovir tablets:
- If you are allergic (hypersensitive) to valaciclovir, acyclovir or any of the other ingredients of Valaciclovir tablets (see section 6).

Take special care with Valaciclovir tablets:
- If you have kidney disease or are elderly, your doctor may need to adjust the usual dosage. Let your doctor know if you have kidney disease.
- Let your doctor know if you have liver disease.
- Valaciclovir does not affect your liver or kidney function.

Valaciclovir does not affect your liver or kidney function. It does not completely eliminate the risk of your sexual partner becoming contaminated. You must practice safe sex, in particular condom use, even whilst on treatment with valaciclovir.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, especially medicines for acid related stomach problems (e.g. cinzolide), gout (e.g. probenecid) or immunosuppressants (e.g. mycophenolate mofetil, ciclosporin, tacrolimus), and including medicines obtained without a prescription.

Taking Valaciclovir tablets with food and drink

Make sure you drink enough water during your treatment with valaciclovir, in order to avoid becoming dehydrated, especially if you are elderly.

Pregnancy and breastfeeding

You must not take this medicine if you are pregnant without the advice of your doctor.

If you discover that you are pregnant during treatment, consult your doctor, as only your doctor can judge whether you need to continue taking the treatment.

You should not breast-feed during treatment with valaciclovir.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Valaciclovir has no or negligible influence on the ability to drive and use machines.

3. HOW TO TAKE VALACICLOVIR TABLETS

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

The tablets should be taken by mouth with an ample amount of water.

Adults

- For the prevention of pain associated with shingles, the usual dose is four 250mg tablets (1000mg), two 500mg tablets (1000mg) or one 1000mg tablet 3 times a day for 7 days. You should start taking valaciclovir no more than 3 days after your symptoms first appeared.

- To treat a first genital Herpes simplex virus (HSV) infection, the usual dose is two 250mg tablets (500mg) or one 500mg tablet twice daily for 10 days. You should start taking valaciclovir as soon as possible at the beginning of the attack, preferably when the first signs of infection develop or at the outbreak of the rash.

- To treat recurrent genital Herpes simplex virus (HSV) infections, the usual dose is four 250mg tablets (1000mg), two 500mg tablets (1000mg) or one 1000mg tablet a day for 5 days. The dose can be taken in one or two divided doses, for instance, two 250mg tablets (500mg) or one 500mg tablet in the morning and the same in the evening. You should start taking valaciclovir as soon as possible at the beginning of the attack, preferably when the first signs of infection develop or at the outbreak of the rash.

- To prevent recurrent genital Herpes simplex virus (HSV) infections, the usual dose is two 250mg tablets (500mg) or one 500mg tablet a day. The dose can be taken in one or two divided doses, for instance, one 250mg tablet in the morning and another in the evening. The value of the treatment is to be re-assessed after 6 to 12 months.

- To prevent cytomegalovirus (CMV) infections and disease, the usual dose is eight 250mg tablets (2000mg), four 500mg tablets (2000mg) or two 1000mg tablets (2000mg) 4 times a day, usually for 90 days. The treatment should be started as early as possible after the organ transplant.

Adolescents over 12 years of age

- To prevent cytomegalovirus (CMV) infections and disease, the usual dose is eight 250mg tablets (2000mg), four 500mg tablets (2000mg) or two 1000mg tablets (2000mg) 4 times a day, usually for 90 days. The treatment should be started as early as possible after the organ transplant.

Children under 12 years of age

Valaciclovir is not recommended for use in children below the age of 12 years due to insufficient data on safety and efficacy.

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continued...
If you have impaired kidney function

The dose will be adapted by your doctor if you have impaired kidney function.

If you find that the effect of Valaciclovir tablets is too strong or too weak, contact your doctor or pharmacist.

If you take more Valaciclovir tablets than you should Informs your doctor. You may experience nausea and/or vomiting (feeling and/or being sick), headache, or confusion.

If you forget to take Valaciclovir tablets Do not take a double dose to make up for a forgotten dose.

If you stop taking Valaciclovir tablets You should take Valaciclovir tablets for as long as your doctor tells you to.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valaciclovir can cause side effects, although not everybody gets them.

- If you experience any of the following, contact your doctor or local hospital casualty department immediately:
  - Sudden difficulty in breathing, speaking and swallowing; swelling of the face, eyes, lips, tongue or throat; rash; or collapse; itchy, raised skin rash. This can be a severe allergic reaction which has been reported very rarely in the UK (less than one person in 10,000).
  - If you experience any of the following, contact your doctor immediately:
    - Frequent and/or severe infections (especially sore throat);
    - Unexplained fever;
    - Mouth and/or throat ulcer;
    - Unusual or unexplained bruising or bleeding;
    - Small, painless red spots or blackheads;
    - These can be blood disorders; reduction of white blood cells that protect against infections; reduced blood platelets that help blood to clot, which have been reported very rarely in the UK (less than one person in 10,000).
  - If you experience any of the following side effects, contact your doctor as soon as possible:
    - Stomach upset such as feeling sick, vomiting, diarrhoea and stomach ache;
    - Headache;
    - Skin rash (which may also occur after exposure to UV light or sunbathing causing a sun burn).

The following side effects have also been reported:

Common (affecting fewer than one person in 10 but more than one person in 100)

- Headache;
- Dizziness;
- Confusion;
- Hallucinations;
- Allergic reaction;
- Reduced consciousness;
- Drowsiness;
- Abdominal discomfort;
- Vomiting;
- Diarrhoea;
- Itching;
- Impaired kidney function.

Very rare (affecting fewer than one person in 10,000)

- Agitation;
- Disturbance of contact with reality (psychotic symptoms);
- Immovable or quiet in any part of the body (tremor);
- Lack of coordination (ataxia);
- Speech problems, slurred pronunciation (dysarthria);
- Seizures, convulsions;
- Disorder of the brain (encephalopathy);
- Convulsions;
- Reduced increase in blood function tests;
- Nervous system disorders;
- Stressed or severe kidney failure.

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

5. HOW TO STORE VALACICLOVIR TABLETS

Keep out of reach of children.

Do not store above 30°C.

Do not use Valaciclovir tablets after the expiry date stated on the label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via waste or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Valaciclovir tablets contain

- The active substance is valaciclovir.
- Each film-coated tablet contains: 250mg, 500mg or 1000mg of valaciclovir (an acyclovir hydrochloride monohydrate).
- The tablet ingredients are microcrystalline cellulose, povidone, magnesium stearate, hypromellose, hydroxypropyl cellulose, titanium dioxide (171) and magnesium stearate.

What Valaciclovir tablets look like and contents of the pack

Valaciclovir tablets are oral, white, biconvex and film-coated with the following size and markings:

- 250mg tablets: 13.6 x 6.5mm with VRC on one side
- 500mg tablets: 17.4 x 8.8mm with VRC on one side
- 1000mg tablets: 22.8 x 11.0mm with VCR on one side

All strengths are available in blister packs of plastic tablets in containers of: 7, 10, 14, 28, 30, 42, 50, 56, 60, 90 and 500 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Actavis UK Limited
Canute Close, London

Manufacturer

Actavis Ireland Limited
78, 152, 42, 56, 60, 90, 100 and 500 tablets.

This leaflet was last approved in May 2009
Please note that the style and layout for the labelling are PL 24668/0096 & PL 24668/0099 is the same as PL 24668/0093 (shown below)

Blister foil
Please note that the style and layout for the labelling are PL 24668/0097 & PL 24668/0100 is the same as PL 24668/0094 (shown below)

Blister foil
Please note that the style and layout for the labelling are PL 24668/0098 & PL 24668/0101 is the same as PL 24668/0095 (shown below).