Public Assessment Report

Decentralised Procedure

Valaciclovir 500mg and 1000mg Film-coated Tablets

Valaciclovir hydrochloride monohydrate

UK/H/2217/001-2/DC

UK licence no: PL 18909/0328-9

Arrow Generics Limited
Lay Summary

On 22nd July 2010, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisations to Arrow Generics Limited for the medicinal products Valaciclovir 500mg and 1000mg Film-coated Tablets. These licences were granted via the Decentralised Procedure (DCP), with the UK as the RMS. After the national phase, licences were granted in the UK on 29th July 2010.

These are prescription-only medicines (POM) used to treat:
- Shingles (in adults)
- HSV infections of the skin and genital herpes (in adults and adolescents over 12 years old). It is also used to help prevent the following infections from returning.
- Cold sores (in adults and adolescents over 12 years old)
- Prevent infection with CMV after organ transplants (in adults and adolescents over 12 years of old)
- Infections in the eye

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

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Valaciclovir 500mg and 1000mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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Module 6  Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Valaciclovir 500mg and 1000mg Film-coated Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1 and Article 10.3 (hybrid)</td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Form</strong></td>
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<td><strong>MA Holder</strong></td>
<td>Arrow Generics Limited</td>
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<tr>
<td></td>
<td>Unit 2 Eastman Way</td>
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<td></td>
<td>Stevenage</td>
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<td>Hertfordshire</td>
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<td>Spain, France, Ireland, Italy, Malta, Norway, Poland,</td>
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<td>Portugal, Sweden, Slovenia, Slovakia and the</td>
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<td>UK/H/2217/001-2/DC</td>
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Module 2

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 valaciclovir hydrochloride monohydrate equivalent to 500 mg valaciclovir.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablet

White to off-white, capsule shaped coated tablet with ‘VA 500’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Varicella zoster virus (VZV) infections – herpes zoster
Valaciclovir is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see sections 4.4).

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

Herpes simplex virus (HSV) infections
Valaciclovir is indicated for the treatment and suppression of HSV infections of the skin and mucous membranes including treatment of first-episode of genital herpes in immunocompetent patients, recurrences of genital herpes in immunocompetent and immunocompromised patients, suppression of recurrent genital herpes in immunocompetent and immunocompromised patients.

Treatment and suppression of recurrent ocular HSV infections (see section 4.4)

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

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

4.2 Posology and method of administration
Varicella zoster virus (VZV) infections – herpes zoster
Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.

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

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

In immunocompromised patients, antiviral treatment is suggested for patients presenting within one week of vesicle formation or at any time before full crusting of lesions.
Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)

Immunocompetent Adults and Adolescents (≥12 years)

The dose is 500 mg of Valaciclovir to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

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

Herpes labialis

For herpes labialis (cold sores), valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose. This dose should be reduced according to creatinine clearance (see Renal impairment below). When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

Immunocompromised Adults

For the treatment of HSV in immunocompromised patients, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. This dose should be reduced according to creatinine clearance (see Renal impairment below). For maximum clinical benefit, the treatment should be started within 48 hours. A strict monitoring of the evolution of lesions is advised.

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

Immunocompetent Adults and Adolescents (≥12 years)

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

Immunocompromised Adults

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

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

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

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

Special populations

Children

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

Elderly

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

Renal impairment

Caution is advised when administering Valaciclovir to patients with impaired renal function. Adequate hydration should be maintained. The dose of Valaciclovir should be reduced in patients with impaired renal function as shown in Table 1 below.
In patients on intermittent haemodialysis, the Valaciclovir dose should be administered after the haemodialysis has been performed. The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after renal transplantation or engraftment. The Valaciclovir dosage should be adjusted accordingly.

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

Table 1: DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

<table>
<thead>
<tr>
<th>Therapeutic Indication</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Valaciclovir Dosagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella-Zoster Virus (VZV) Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of herpes zoster (shingles) in immunocompetent and immunocompromised adults</td>
<td>≥50</td>
<td>1000 mg three times daily</td>
</tr>
<tr>
<td></td>
<td>30 to 49</td>
<td>1000 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>10 to 29</td>
<td>1000 mg once daily</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>500 mg once daily</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Therapeutic Indication</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Valaciclovir Dosagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes Simplex Virus (HSV) Infections</td>
<td></td>
<td></td>
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<tr>
<td>Treatment of HSV infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- immunocompetent adults and adolescents</td>
<td>≥30</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>500 mg once daily</td>
</tr>
<tr>
<td>- immunocompromised adults</td>
<td>≥30</td>
<td>1000 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>1000 mg once daily</td>
</tr>
<tr>
<td>Treatment of herpes labialis (cold sores) in immunocompetent adults and adolescents (alternative 1-day regimen)</td>
<td>≥50</td>
<td>2000mg twice in one day</td>
</tr>
<tr>
<td></td>
<td>30 to 49</td>
<td>1000 mg twice in one day</td>
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<tr>
<td></td>
<td>10 to 29</td>
<td>500 mg twice in one day</td>
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<tr>
<td></td>
<td>&lt;10</td>
<td>500 mg single dose</td>
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<table>
<thead>
<tr>
<th>Therapeutic Indication</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Valaciclovir Dosagea</th>
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<tbody>
<tr>
<td>Suppression of HSV infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- immunocompetent adults and adolescents</td>
<td>≥30</td>
<td>500 mg once dailyb</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>250 mg once daily</td>
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<tr>
<td>- immunocompromised adults</td>
<td>≥30</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>500 mg once daily</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Therapeutic Indication</th>
<th>Creatinine Clearance (mL/min)</th>
<th>Valaciclovir Dosagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus (CMV) Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV prophylaxis in solid organ transplant recipients in adults and adolescents</td>
<td>≥75</td>
<td>2000 mg four times daily</td>
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<tr>
<td></td>
<td>50 to &lt;75</td>
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<tr>
<td></td>
<td>&lt;10 or on dialysis</td>
<td>1500 mg once daily</td>
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</table>

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

4.3 Contraindications
Hypersensitivity to valaciclovir, aciclovir or any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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

Use in patients with renal impairment and in elderly patients
Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side-effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

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

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

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

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

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

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

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

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).
4.5 Interaction with other medicinal products and other forms of interaction
The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Valaciclovir should be borne in mind when considering the patient’s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.
4.8 Undesirable effects

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

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

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

- Very common (≥1/10)
- Common (≥1/100, <1/10)
- Uncommon (≥1/1,000, ≤1/100)
- Rare (≥1/10,000, ≤1/1,000)
- Very rare (≤1/10,000).

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

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

Clinical Trial Data

Nervous system disorders
Very common: Headache

Gastrointestinal disorders
Common: Nausea

Post Marketing Data

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

Immune system disorders
Rare: Anaphylaxis

Psychiatric and nervous system disorders
Common: Dizziness,
Uncommon: Confusion, hallucinations, decreased consciousness, tremor, agitation
Rare: Ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms.

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8g daily) of Valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea

Gastrointestinal disorders
Common: Vomiting, diarrhoea.
Uncommon: Abdominal discomfort

Hepato-biliary disorders
Uncommon: Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).
Skin and subcutaneous tissue disorders
Common: Rashes including photosensitivity, pruritus.
Uncommon: Urticaria
Rare: Angioedema

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

Renal pain may be associated with renal failure.

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors.
ATC code: J05AB11

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

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

Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

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

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

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

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

**Clinical Studies**

**Varicella Zoster Virus Infection**
Valaciclovir accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and, in patients older than 50 years, also post-herpetic neuralgia. Valaciclovir reduces the risk of ocular complications of ophthalmic zoster. Intravenous therapy generally is considered standard for zoster treatment in immunocompromised patients; however, limited data indicate a clinical benefit of valaciclovir in the treatment of VZV infection (herpes zoster) in certain immunocompromised patients, including those with solid organ cancer, HIV, autoimmune diseases, lymphoma, leukaemia and stem cell transplants.

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

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

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

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

5.2 **Pharmacokinetic properties**

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

<table>
<thead>
<tr>
<th>Aciclovir PK Parameter</th>
<th>250 mg (N=15)</th>
<th>500 mg (N=15)</th>
<th>1000 mg (N=15)</th>
<th>2000 mg (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax micrograms/mL</td>
<td>2.20 ± 0.38</td>
<td>3.37 ± 0.95</td>
<td>5.20 ± 1.92</td>
<td>8.30 ± 1.43</td>
</tr>
<tr>
<td>Tmax hours (h)</td>
<td>0.75 (0.75–1.5)</td>
<td>1.0 (0.75–2.5)</td>
<td>2.0 (0.75–3.0)</td>
<td>2.0 (1.5–3.0)</td>
</tr>
<tr>
<td>AUC h.micrograms/mL</td>
<td>5.50 ± 0.82</td>
<td>11.1 ± 1.75</td>
<td>18.9 ± 4.51</td>
<td>29.5 ± 6.36</td>
</tr>
</tbody>
</table>

Cmax = peak concentration; Tmax = time to peak concentration; AUC = area under the concentration-time curve. Values for Cmax and AUC denote mean ± standard deviation. Values for Tmax denote median and range.

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

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

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

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

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

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

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

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

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

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

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

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

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
**Tablet core:**
- Microcrystalline cellulose,
- Crospovidone,
- Povidone,
- Talc,
- Magnesium stearate.

**Tablet coating:**
- Polyvinyl alcohol,
- Titanium dioxide (E-171),
- Macrogol,
- Talc

6.2 **Incompatibilities**
Not Applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
The medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
Aclar/PVC/aluminium foil blister packs containing 4, 6, 10, 20, 21, 24, 30, 42, 50, 60, 80, 90 and 112 tablets.

Not all pack sizes may be marketed
6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage, Herts
SG1 4SZ

8 MARKETING AUTHORIZATION NUMBER(S)
PL 18909/0328

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
22/07/2010

10 DATE OF REVISION OF THE TEXT
22/07/2010
1 NAME OF THE MEDICINAL PRODUCT
Valaciclovir 1000 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains valaciclovir hydrochloride monohydrate equivalent to 1000 mg valaciclovir.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablet.

White capsule shaped coated tablets with ‘VA 1000’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Varicella zoster virus (VZV) infections – herpes zoster
Valaciclovir is indicated for the treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults (see sections 4.4).

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

Herpes simplex virus (HSV) infections
Valaciclovir is indicated for the treatment and suppression of HSV infections of the skin and mucous membranes including treatment of first-episode of genital herpes in immunocompetent patients recurrences of genital herpes in immunocompetent and immunocompromised patients suppression of recurrent genital herpes in immunocompetent and immunocompromised patients

Treatment and suppression of recurrent ocular HSV infections (see section 4.4)

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

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

4.2 Posology and method of administration
Varicella zoster virus (VZV) infections – herpes zoster
Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.

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

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

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

Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)
Immunocompetent Adults and Adolescents (≥12 years)
The dose is 500 mg of Valaciclovir to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).
For recurrent episodes, treatment should be for three to five days. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms. Valaciclovir can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.

**Herpes labialis**
For herpes labialis (cold sores), valaciclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose. This dose should be reduced according to creatinine clearance (see Renal impairment below). When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

**Immunocompromised Adults**
For the treatment of HSV in immunocompromised patients, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. This dose should be reduced according to creatinine clearance (see Renal impairment below). For maximum clinical benefit, the treatment should be started within 48 hours. A strict monitoring of the evolution of lesions is advised.

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

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

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

**Prophylaxis of cytomegalovirus (CMV) infection and disease in adults and adolescents (≥12 years)**
The dosage of Valaciclovir is 2000 mg four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see Renal impairment below).

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

**Special populations**

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

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

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

In patients on intermittent haemodialysis, the Valaciclovir dose should be administered after the haemodialysis has been performed. The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after renal transplantation or engraftment. The Valaciclovir dosage should be adjusted accordingly.
Hepatic impairment
Studies with a 1000 mg dose of valaciclovir in adult patients show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in adult patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dose adjustment; however, clinical experience is limited. For higher doses (4000 mg or more per day), see section 4.4.

Table 1: DOSAGE ADJUSTMENT FOR RENAL IMPAIRMENT

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

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

4.3 Contraindications
Hypersensitivity to valaciclovir, aciclovir or any of the excipients (see section 6.1).
4.4 Special warnings and precautions for use

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

Use in patients with renal impairment and in elderly patients
Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side-effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

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

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

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

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

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

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

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

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).
4.5 Interaction with other medicinal products and other forms of interaction
The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Valaciclovir should be borne in mind when considering the patient’s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.
4.8 Undesirable effects

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

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

The following frequency categories are used for classification of adverse effects:
- Very common ($\geq 1/10$)
- Common ($\geq 1/100, <1/10$)
- Uncommon ($\geq 1/1,000, \leq 1/100$)
- Rare ($\geq 1/10,000, <1/1,000$)
- Very rare ($\leq 1/10,000$)

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

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

**Clinical Trial Data**

**Nervous system disorders**
- Very common: Headache

**Gastrointestinal disorders**
- Common: Nausea

**Post Marketing Data**

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

**Immune system disorders**
- Rare: Anaphylaxis

**Psychiatric and nervous system disorders**
- Common: Dizziness
- Uncommon: Confusion, hallucinations, decreased consciousness, tremor, agitation
- Rare: Ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms.

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8g daily) of Valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

**Respiratory, thoracic and mediastinal disorders**
- Uncommon: Dyspnoea

**Gastrointestinal disorders**
- Common: Vomiting, diarrhoea.
- Uncommon: Abdominal discomfort

**Hepato-biliary disorders**
- Uncommon: Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).
Skin and subcutaneous tissue disorders
Common: Rashes including photosensitivity, pruritus.
Uncommon: Urticaria
Rare: Angioedema

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

Renal pain may be associated with renal failure.

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors
ATC code: J05A B11

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

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

Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

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

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

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

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

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

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

Herpes Simplex Virus Infection
Valaciclovir for ocular HSV infections should be given according to applicable treatment guidelines.

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

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

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

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

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

<table>
<thead>
<tr>
<th>Aciclovir PK Parameter</th>
<th>250 mg (N=15)</th>
<th>500 mg (N=15)</th>
<th>1000 mg (N=15)</th>
<th>2000 mg (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax micrograms/mL</td>
<td>2.20 ± 0.38</td>
<td>3.37 ± 0.95</td>
<td>5.20 ± 1.92</td>
<td>8.30 ± 1.43</td>
</tr>
<tr>
<td>Tmax hours (h)</td>
<td>0.75 (0.75–1.5)</td>
<td>1.0 (0.75–2.5)</td>
<td>2.0 (0.75–3.0)</td>
<td>2.0 (1.5–3.0)</td>
</tr>
<tr>
<td>AUC h.micrograms/mL</td>
<td>5.50 ± 0.82</td>
<td>11.1 ± 1.75</td>
<td>18.9 ± 4.51</td>
<td>29.5 ± 6.36</td>
</tr>
</tbody>
</table>

Cmax = peak concentration; Tmax = time to peak concentration; AUC = area under the concentration-time curve. Values for Cmax and AUC denote mean ± standard deviation. Values for Tmax denote median and range.

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

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

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

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

Special Populations
Renal impairment
The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).
Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, at severe renal impairment compared with normal renal function.

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

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

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

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

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

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

### PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**
- Microcrystalline cellulose,
- Crospovidone,
- Povidone,
- Talc,
- Magnesium stearate.

**Tablet coating:**
- Polyvinyl alcohol,
- Titanium dioxide (E-171),
- Macrogol,
- Talc

#### 6.2 Incompatibilities
Not Applicable

#### 6.3 Shelf life
2 Years

#### 6.4 Special precautions for storage
The medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
Aclar/PVC/aluminium foil blister packs containing 4, 6, 10, 20, 21, 24, 30, 42, 50, 60, 80, 90 and 112 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY
Arrow Generics Limited
Unit 2, Eastman Way, Stevenage
Hertfordshire, SG1 4SZ
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 18909/0329

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
22/07/2010

10 DATE OF REVISION OF THE TEXT
22/07/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valaciclovir 500mg 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 get 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 is and what it is 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 VALACICLOVR IS AND WHAT IT IS USED FOR

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

Valaciclovir Tablets can be used to:
• Treat shingles (in adults).
• Treat HSV infections of the skin and genital herpes (in adults and adolescents over 12 years old). It is also used to help prevent those infections from returning.
• Treat cold sores (in adults and adolescents over 12 years old).
• Prevent infection with CMV after organ transplant (in adults and adolescents over 12 years old).
• Infections in the eye.

2. BEFORE YOU TAKE VALACICLOVR TABLETS

Do not take Valaciclovir Tablets:
• If you are allergic (hypersensitive) to valaciclovir or aciclovir.
• If you are allergic to any of the other ingredients of Valaciclovir Tablets (see section 6. Further information).

Do not take Valaciclovir Tablets if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Valaciclovir Tablets.

Take special care with Valaciclovir Tablets
Check with your doctor or pharmacist before taking Valaciclovir Tablets if:
• you have kidney problems.
• you have liver problems.
• you are over 65 years of age.
• your immune system is weak.

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

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

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

Tell your doctor or pharmacist if you are taking any other medicines that affect the kidneys. These include: aminoglycosides, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, furosemide, glyburide, irbesartan, indinavir, irinotecan, methotrexate, netilmicin, quinapril, ramipril, telmisartan, ticagrelor, trastuzumab, vancomycin, zidovudine.

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

Pregnancy and breastfeeding
Valaciclovir Tablets are not usually recommended for use during pregnancy. If you are pregnant, or think you could be, or if you are planning to become pregnant, do not take Valaciclovir Tablets without checking with your doctor. Your doctor will weigh up the benefit to you against the risk to your baby of taking Valaciclovir Tablets while you’re pregnant or breastfeeding.

Driving and using machines
Valaciclovir Tablets can cause side effects that affect your ability to drive. Do not drive or use machines unless you are sure you’re not affected.

3. HOW TO TAKE VALACICLOVR 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 dose that you should take will depend on why your doctor has prescribed Valaciclovir Tablets for you. Your doctor will discuss this with you.

Treatment of shingles
• The usual dose is 1000 mg (one 1000 mg tablet or two 500 mg tablets) three times a day.
• You should take Valaciclovir Tablets for seven days.

Treatment of cold sores
• The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) twice a day.
• The second dose should be taken 12 hours (or sooner than 6 hours) after the first dose.
• You should take Valaciclovir Tablets for one day (two doses) only.

Treatment of HSV infections of the skin and genital herpes
• The usual dose is 500 mg (one 500 mg tablet or two 250 mg tablets) twice a day.
• For the first infection you should take Valaciclovir Tablets for five days or for up to ten days if your doctor tells you to. For recurrent infections the duration of treatment is normally 3-5 days.

Helping to prevent HSV infections from returning after you have had them
• The usual dose is one 500 mg tablet once a day.
• Some people with frequent recurrences may benefit from taking one 250 mg tablet twice a day.
• You should take Valaciclovir Tablets until your doctor tells you to stop.

To stop you becoming infected with CMV (Cytomegalovirus)
• The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) four times a day.
• You should take each dose about 6 hours apart.
• You will usually start taking Valaciclovir Tablets as soon as possible after your surgery.
• You should take Valaciclovir Tablets for around 30 days after your surgery, until your doctor tells you to stop.

Your doctor may adjust the dose of Valaciclovir Tablets if:
• You are over 65 years of age.
• You have a weak immune system.
• You have kidney problems.

Talk to your doctor before taking Valaciclovir Tablets if any of the above apply to you.

Taking this medicine
• Take this medicine by mouth.
• Swallow the tablets whole with a drink of water.
• Take Valaciclovir Tablets at the same time each day.
• Take Valaciclovir Tablets according to the instructions from your doctor or pharmacist.
People over 65 years of age or with kidney problems

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

If you take more Valaciclovir Tablets than you should

Valaciclovir Tablets are not usually harmful, unless you take too many over several days. If you take too many tablets you may feel sick, vomit, or be confused, agitated or unusually sleepy. Talk to your doctor or pharmacist if you take too many Valaciclovir Tablets. Remember to take the pack and any remaining tablets with you.

If you forget to take Valaciclovir Tablets

• If you forget to take Valaciclovir Tablets take the missed dose as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose.
• Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

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

Conditions you need to look out for

• Severe allergic reactions (anaphylaxis). These are rare in people taking Valaciclovir Tablets. Rapid development of symptoms including:
  o Hives, itchy skin rash.
  o Swelling of the face, lips, tongue and throat, causing difficulty in breathing (angioedema).
  o Sore throat and fever. If you have an allergic reaction, stop taking Valaciclovir Tablets and see a doctor straight away.

Very Common (affects more than 1 in 10 people):
• Headache
• Common (affects up to 1 in 10 people)
• Feeling sick.
• Dizziness.
• Vomiting.
• Diarrhoea.
• Skin reaction after exposure to sunlight (photosensitivity).
• Rash.

Uncommon (affects up to 1 in 100 people):
• Feeling confused.
• Severe or hearing things that aren’t there (hallucinations).
• Feeling very sleepy.
• Tremors.
• Feeling agitated.

Rare (affects up to 1 in 1,000 people)
• Unsteadiness when walking and lack of coordination (ataxia).
• Slow, slurred speech (dysarthria).
• Fits (convulsions).
• Altered brain function (encephalopathy).
• Unconsciousness (coma).
• Confused or disturbed thoughts.

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

Other rare side effects:
• Kidney problems where you pass little or no urine.

If any of the side effects get 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 the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Valaciclovir Tablets after the expiry date which is stated on the carton after “Exp”. The expiry date refers to the last day of the month.

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

6. FURTHER INFORMATION

What Valaciclovir Tablets contain:

The active substance is valaciclovir.

Each tablet contains valaciclovir hydrochloride monohydrate equivalent to 500 mg of valaciclovir. The other ingredients are microcrystalline cellulose, crospovidone, povidone, talc, magnesium stearate.

The tablet coating contains polyvinyl alcohol, titanium dioxide (E-171), macrogol and talc.

What Valaciclovir Tablets look like and contents of the pack

Valaciclovir 500 mg Film-coated Tablets are white to off-white, capsule shaped coated tablets with 'VA 500' on one side and 'S' on the other side.

Valaciclovir 500 mg Film-coated Tablets are available in foil packs containing 4, 8, 10, 20, 21, 24, 30, 42, 50, 58, 60, 80, 90 and 112 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K.

Manufacturer:

Arrow Pharm (Malta) Limited, 62 Hal Far Industrial Estate, Birzebbugia, B66 3003, Malta.

This leaflet was last approved in 07/2010.
Valaciclovir belongs to a group of medicines called antivirals. It works by killing or stopping the growth of viruses called herpes simplex 1 (HSV), varicella zoster (VZV) and cytomegalovirus (CMV).

Valaciclovir Tablets can be used to:
- Treat shingles (in adults).
- Treat HSV infections of the skin and genital herpes (in adults and adolescents over 12 years old). It is also used to help prevent these infections from recurring.
- Treat cold sores (in adults and adolescents over 12 years old).
- Prevent infection with CMV after organ transplants (in adults and adolescents over 12 years old).
- Infections in the eye.

Do not take Valaciclovir Tablets:
- If you are allergic (hypersensitive) to valaciclovir or aciclovir.
- If you are allergic to any of the other ingredients of Valaciclovir Tablets (see section 6, further information).

Do not take Valaciclovir Tablets if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Valaciclovir Tablets.

Take special care with Valaciclovir Tablets:
Check with your doctor or pharmacist before taking Valaciclovir Tablets if:
- you have kidney problems.
- you have liver problems.
- you are over 65 years of age.
- your immune system is weak.

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

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

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

Tell your doctor or pharmacist if you are taking any other medicines that affect the kidneys. These include: aminoglycosides, organoplumbum compounds, iodinated contrast media, methotrexate, pentamidine, foscamet, diltiazem, tacrolimus, cinacalcet and probenecid.

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

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

Driving and using machines
Valaciclovir Tablets can cause side effects that affect your ability to drive. Do not drive or use machines unless you are sure you're not affected.

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

Treatment of shingles:
The usual dose is 1000 mg (one 1000 mg tablet or two 500 mg tablets) three times a day.
You should take Valaciclovir Tablets for seven days.

Treatment of cold sores:
The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) twice a day.
The second dose should be taken 12 hours (no sooner than 5 hours) after the first dose.
You should take Valaciclovir Tablets for one day (two doses) only.

Treatment of HSV infections of the skin and genital herpes:
The usual dose is 500 mg (one 500 mg tablet or two 250 mg tablets) twice a day.
For the first infection you should take Valaciclovir Tablets for five days or for up to ten days if your doctor tells you to. For recrurant infection the duration of treatment is normally 3-6 days.

Helping to prevent HSV infections from returning after you have had them:
The usual dose is one 500 mg tablet once a day.
Some people with frequent recurrences may benefit from taking one 250 mg tablet twice a day.
You should take Valaciclovir Tablets until your doctor tells you to stop.
To stop you being infected with CMV (Cytomegalovirus):
The usual dose is 2000 mg (two 1000 mg tablets or four 500 mg tablets) four times a day.
You should take each dose about 6 hours apart.
You will usually start taking Valaciclovir Tablets as soon as possible after your surgery.
You should take Valaciclovir Tablets for around 90 days after your surgery, until your doctor tells you to stop.
Your doctor may adjust the dose of Valaciclovir Tablets if:
- You are over 65 years of age.
- You have a weak immune system.
- You have kidney problems.
Talk to your doctor before taking Valaciclovir Tablets if any of the above apply to you.

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

People over 65 years of age or with kidney problems
It is very important while you are taking Valaciclovir Tablets that you drink water regularly during the day. This will help to reduce side effects that can affect the kidney or nervous system. Your doctor will closely monitor you for signs of these. Nervous system side effects might include feeling confused or agitated, or feeling unusually sleepy or drowsy.

If you take more Valaciclovir Tablets than you should
Valaciclovir Tablets are not usually harmful, unless you take too many over several days. If you take too many tablets you may feel sick, vomit, be confused, agitated or unusually sleepy. Talk to your doctor or pharmacist if you take too many Valaciclovir Tablets. Remember to take the pack and any remaining tablets with you.

If you forget to take Valaciclovir Tablets
- If you forget to take Valaciclovir Tablets take the missed dose as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS
Like all medicines, valaciclovir can cause side effects in some people. The following side effects may happen with this medicine:

Conditions you need to look out for
- Severe allergic reactions (anaphylaxis). These are rare in people taking Valaciclovir Tablets. Rapid development of symptoms including:
  - Difficulty breathing
  - Swelling of the lips, face, neck or throat causing difficulty in breathing (angioedema)
  - Skin rash or swelling of legs
  - Rash or swelling of the skin
- Feeling generally unwell (feeling generally unwell).
- Feeling more unwell.
- Feeling dizzy or unsteady.

Other side effects:
- Nausea or vomiting (commonly)
- Abdominal pain or discomfort
- Headache or the head feeling heavy (commonly)
- Dizziness or feeling faint (commonly)
- Blurred vision.
- Feeling tired or weak (commonly)
- Liver problems (rarely)

Rare side effects:
- Severe allergic reactions (anaphylaxis).
- Increased sensitivity to sunlight (photosensitivity).
- Headache.
- Nausea or vomiting.
- Abdominal pain or discomfort.
- Dizziness or feeling faint.
- Blurred vision.
- Feeling tired or weak.
- Liver problems.

5. HOW TO STORE VALACICLOVIR TABLETS
Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Valaciclovir Tablets after the expiry date which is stated on the carton after “Exp”. The expiry date refers to the last day of the month.

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

6. FURTHER INFORMATION
What Valaciclovir Tablets contain:
The active substance is valaciclovir.

Each tablet contains valaciclovir hydrochloride monohydrate equivalent to 1000 mg of valaciclovir. The other ingredients are microcrystalline cellulose, croscarmellose sodium, talc, magnesium stearate.

The tablet coating contains polyvinyl alcohol, titanium dioxide (E-171), macrogol and talc.

What Valaciclovir Tablets look like and contents of the pack
Valaciclovir 1000 mg Film-coated Tablets are white capsule shaped coated tablets with "VA 1000" on one side and "1" on the other side.

Valaciclovir 1000 mg Film-coated Tablets are available in foil packs containing 4, 6, 10, 20, 21, 24, 30, 42, 50, 60, 80, 90 and 120 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Arrow Genomics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, UK.

Manufacturer:
Arrow Pharm (Malta) Limited, 62 Hal Far Industrial Estate, Brzezbuga, SBK 3000, Malta.

This leaflet was last approved in: 07/2010.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Valaciclovir 500mg and 1000mg Film-coated Tablets, in the treatment of varicella zoster virus (VZV), herpes simplex virus (HSV) and cytomegalovirus (CMV) infections, could be approved.

These applications were submitted via the Decentralised Procedure (UK/H/2217/001-2/DC), with the UK as RMS and the following CMSs: UK/H/2217/001/DC: Cyprus, Czech Republic, Denmark, Spain, France, Ireland, Italy, Malta, Norway, Poland, Portugal, Sweden, Slovenia, Slovakia and the Netherlands UK/H/2217/002/DC: Portugal and Spain

These applications were submitted under Article 10.1 (for Valaciclovir 500mg Film-coated Tablets) and Article 10.3 (for Valaciclovir 1000mg Film-coated Tablets), claiming to be either a generic medicinal product or a hybrid medicinal product of Valtrex Tablets 500mg (PL 00003/0352), which was first licensed to The Wellcome Foundation Ltd, UK, on 20th January 1995.

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue. Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase. Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal product/hybrid of an originator product that has been licensed for over 10 years. No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal product/hybrid of an originator product that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture and assembly of these products.

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for not submitting a risk management plan for these products.

All Concerned Member States agreed to grant respective licences for the above products at the end of procedure (Day 210 – 22nd July 2010). Marketing Authorisation licences were granted in the UK on 29th July 2010 (PL 18909/0328-9).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Valaciclovir 500mg and 1000mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Valaciclovir hydrochloride monohydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>J05A B11 Nucleosides and nucleotides excluding reverse transcriptase inhibitors,</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated Tablets</td>
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<td>Name and address of the authorisation holder</td>
<td>Arrow Generics Limited</td>
</tr>
<tr>
<td></td>
<td>Unit 2 Eastman Way</td>
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<tr>
<td></td>
<td>Stevenage</td>
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<td></td>
<td>Hertfordshire</td>
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<td>SG1 4SZ</td>
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<td></td>
<td>United Kingdom</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE
INN: Valaciclovir hydrochloride monohydrate
Chemical Name: 2-[(2-amino-1,6-dihydro-6-oxo-9h-purin-9-yl)methoxy]ethyl-l-valinate hydrochloride
Or
2-[(2-amino-6-oxo-1,6-dihydro-9h-purin-9-yl)methoxy]ethyl-l-valinate hydrochloride

Structure:

*Asymmetric centre

Molecular Formula: $\text{C}_{13}\text{H}_{20}\text{N}_{6}\text{O}_{4}\text{HCl.H}_{2}\text{O}$
Molecular Weight: 378.8
Appearance: A white or almost white powder, freely soluble in water, practically insoluble in anhydrous ethanol and 1-octanol

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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, crospovidone, povidone, magnesium stearate, talc, Opadry II 85F18378 White and water purified.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry II 85F18378 White, which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Valtrex 500mg Tablets, which was first granted in the UK to The Wellcome Foundation Ltd, on 20th January 1995.

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and dissolution profiles have been provided for the proposed and originator products.

Manufacture
A description and flow-chart of the manufacturing method 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 batches of the product. The results are satisfactory.

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

Container-Closure System
The finished product is packed in aclar/ polyvinylchloride /aluminium foil blister packs with pack sizes of 4, 6, 10, 20, 21, 24, 30, 42, 50, 60, 80, 90, and 112 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

The marketing authorisation holder has stated that not all packs are intended to be marketed. However, they have committed to submitting mock-ups of any pack size to the relevant regulatory authorities before marketing.
Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set for these products, with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labels are pharmaceutically acceptable.

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Famiclovir Film-coated Tablets. The package leaflet of the reference 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 it contains. Therefore, the bridging report is acceptable.

Marketing Authorisation Application Forms (MAA)
The MAA forms are pharmaceutically satisfactory.

Expert report
The Pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
These applications claim to be generic medicinal products of Valtrex 500mg Film-coated Tablets, which has been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:
Study 1
This is a randomized, single dose, open-label, two-treatment, two-period, two-sequence, crossover study comparing the pharmacokinetics of the test product Valaciclovir 500mg Film-coated Tablets (Arrow Generic Limited, UK) versus the reference product Valtrex 500mg Film-coated Tablets (GlaxoSmithKline, UK) in healthy subjects under fasting conditions.

All subjects were given the single-dose of treatment after a fast of at least 10 hours. Blood samples were taken pre and up to 16 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results for the active metabolite aciclovir are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LSMeans*</th>
<th>Ratio T/R (%)</th>
<th>90% Confidence Limits (%)</th>
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<tr>
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<td>Test (T)</td>
<td>Reference (R)</td>
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</table>

*Units are ng/ml for C<sub>max</sub> and ng.h/ml for AUC<sub>T</sub> and AUC<sub>∞</sub>*

The 90% confidence intervals for C<sub>max</sub> and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Valaciclovir 500mg Film-coated Tablets) and the reference formulation (Valtrex 500mg Film-coated Tablets) for the active metabolite aciclovir.

Study 2
This is an open-label, randomised, two-treatment, two-sequence, two period, crossover, single-dose study comparing the pharmacokinetics of the test product Valaciclovir 1000mg Film-coated Tablets (Arrow Generics Limited, UK) versus the reference product Zelitrex 1000mg Film-coated Tablets (GlaxoSmithKline S.P.A, Italy) in healthy subjects under fasting conditions.

All subjects were given the single-dose of treatment after a fast of at least 10 hours. Blood samples were taken pre and up to 16 hours post dose. The two treatment arms were separated by a 7-day washout period.

The results for the active metabolite aciclovir are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>90% Confidence Limits (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
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*Units are µg/ml for C<sub>max</sub> and µg.h/ml for AUC<sub>T</sub> and AUC<sub>∞</sub>*

The 90% confidence intervals for C<sub>max</sub> and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Valaciclovir 1000mg Film-coated Tablets) and the reference formulation (Zelitrex® 1000mg Film-coated Tablet) for the active metabolite aciclovir.
Pharmacodynamics
The pharmacodynamic characteristics of valaciclovir hydrochloride monohydrate have been well-studied in the past. There are no particular concerns for these generic medicinal products. No new data have been submitted and none are required.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Module 1 – Administrative information
Marketing Authorisation Application forms (MAA)
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SmPC)
The SmPCs are medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packaging is medically satisfactory.

Conclusion
There are no objections to the approval of these products from a clinical point of view.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Valaciclovir 500mg and 1000mg Film-coated Tablets 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 these type.

EFFICACY
Bioequivalence have been demonstrated between the applicant’s Valaciclovir 500mg Film-coated Tablets and Valtrex 500mg Film-coated Tablets and also between Valaciclovir 1000mg Film-coated Tablets and Zelitrex® 1000mg Film-coated Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.
RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with valaciclovir hydrochloride monohydrate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
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