Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valtrex 1000 mg Film-Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000mg Valaciclovir as Valaciclovir hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Biconvex, elongated white film-coated tablets imprinted ‘Valtrex’ and ‘1000’ with a partial scorebar on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Valtrex is indicated for the treatment of herpes zoster (shingles). Valtrex reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and postherpetic neuralgia, thus accelerating resolution of pain.

4.2 Posology and method of administration

Dosage in Adults

Treatment of herpes zoster:
1000 mg of Valtrex to be taken three times daily for seven days.

Dosage in Children
No data are available.

Dosage in the Elderly
Dosage modification is not required unless renal function is significantly impaired. Adequate hydration should be maintained.

Dosage in Renal Impairment
The dosage of Valtrex should be modified as follows in patients with significantly impaired renal function:

Renal Function (CLcr ml/min)	Valtrex Dose
15 to 30	1000mg twice a day.
<15	1000mg once a day.

In patients on haemodialysis the Valtrex dosage recommended for patients with a creatinine clearance of less than 15 ml/min should be used, but this should be administered after the haemodialysis has been performed.

Dosage in Hepatic Impairment
Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis, (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment; however, clinical experience is limited.
Dosage in Special Patient Groups
No dosage recommendations.
Monitoring Advice
No special monitoring necessary.

4.3 Contraindications

Valtrex is contraindicated in patients known to be hypersensitive to valaciclovir, aciclovir or any component of their formulations.

4.4 Special warnings and precautions for use

Use in renal impairment:
The valaciclovir dose should be adjusted in patients with significant renal impairment (see section 4.2, Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified.
Cimetidine and probenecid increase the area under the plasma concentration time curve of aciclovir by reducing its renal clearance: however no dosage adjustment is necessary because of the wide therapeutic index of aciclovir. Other drugs which affect renal physiology could affect plasma levels of aciclovir.

4.6 Pregnancy and lactation

Teratogenicity:
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 were observed at subcutaneous doses that produced plasma levels of 100 micrograms/ml and maternal toxicity.

Fertility:
Valaciclovir did not affect fertility in male or females rats dosed by the oral route.

Pregnancy:
There are no data on the use of valtrex in pregnancy. Valtrex should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

In prospective studies there has not been an increase incidence of birth defects in approximately 300 women exposed to systemic aciclovir (most at oral doses of up to 1000mg per day), during the first trimester of pregnancy, as compared with the incidence in the general population. The reported defects show no uniqueness or pattern to suggest a common aetiology.

The daily aciclovir AUC (area under plasma concentration-time curve) following valtrex 1000mg and 800 mg would be approximately 2 to 9 times greater than that expected with oral zovirax 1000 mg daily.

The principle metabolite of valaciclovir is aciclovir which is excreted in breast milk.

Lactation: Aciclovir, the principle metabolite of valaciclovir is excreted in 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 (median 1.4) times the corresponding maternal aciclovir serum concentrations. The aciclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2). The median aciclovir concentration in breast milk was 2.24 µg/ml (9.95 µM). 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 materal serum, breast milk, or infant urine.
* Caution is advised if valtrax is to be administered to a nursing woman. However, Zovirax is used to treat neonatal herpes simplex at intravenous doses of 30 mg/kg/day.

4.7 Effects on ability to drive and use machines

The clinical Status of the patient and the adverse event profile of Valtrex should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect Valtrex on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Adverse reactions are listed below by MedDRA body system organ class and by frequency.

The frequency categories used are:

Very common	≥ 1 in 10,
Common	≥ 1 in 100 and < in 10,
Uncommon	≥ 1 in1,000 and < 1 in 100,
Rare	≥ 1 in 10,000 and < 1 in 1,000,
Very rare	<1 in 10,000.

Clinical trial data have been used to assign frequency categories to adverse reactions if, in the trials, there was evidence for an association with valaciclovir (i.e. there was a statistically significant difference between the incidence in patients taking valaciclovir and placebo). For all other adverse events, spontaneous post-marketing data has been used as a basis for allocating frequency.

<u>Clinical Trial Data</u>
Nervous system disorders
Common: *headache
Gastrointestinal disorders
Common: *Nausea

<u>Post Marketing Data</u>
Blood and lymphatic system disorders
Very rare: * Leukopenia,
*Thrombocytopenia
*Leukopenia is mainly reported in immunocompromised patients

Immune system disorders
Very rare: *Anaphylaxis.

Psychiatric and nervous system disorders
Rare: *Dizziness, *confusion, *hallucinations, *decreased consciousness.

Very rare: *agitations,*Tremor, *ataxia, *dysarthria,* psychotic symptoms, *convulsions, *encephalopathy, *coma.

The above events are reversible and usually seen in patients with renal impairment or with other predisposing factors.

In organ transplant patients receiving high doses (8 g daily) of Valtrex for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.
Respiratory, thoracic and mediastinal disorders

Uncommon: *Dyspnoea.

Gastrointestinal disorders

Rare: *Abdominal discomfort, *vomiting, *diarrhoea.

Hepato-biliary disorders

Very rare: *Reversible increases in liver function tests.

*These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders

Uncommon: *Rashes including photosensitivity

Rare: *Pruritus.

Very rare: *Urticaria, *angioedema.

Renal and urinary disorders

Rare: *Renal impairment.

Very rare: *Acute renal failure.

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

4.9 Overdose

Symptoms and Signs
There are at present no data available on overdosage with Valtrex.
Doses of up to 2000mg given four times daily for extended periods of time (> 12 months) were well tolerated by patients in clinical trials for indications other than herpes zoster.
A dose equivalent to the aciclovir exposure from approximately 15 g Valtrex has been inadvertently administered as a single intravenous dose of aciclovir (up to 80 mg/kg) without adverse effects.
Management
In the event of a symptomatic Valtrex overdose occurring, aciclovir is removable by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mode of action:
Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme 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.

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

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

5.2 Pharmacokinetic properties

General Characteristics
After oral administration, valaciclovir is well absorbed and rapidly, and almost completely, converted to aciclovir and valine. This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from human liver.

Mean peak aciclovir concentrations are 25 µM (5.7 µg/ml) following a single dose of 1000 mg valaciclovir, and occur at a median time of 1.75 hours post dose. The bioavailability of aciclovir from valaciclovir is 54% and is unaffected by food.

Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occur at a median time of 30 to 60 following a 1000mg dose, and are below measurable concentrations 3 hours after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. Binding of valaciclovir to plasma proteins is very low (15%).

The elimination plasma half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine. Valaciclovir is eliminated principally as aciclovir and the known aciclovir metabolite, 9-carboxymethoxymethylguanine (CMMG) in the urine.

Characteristics in patients:
Herpes zoster and herpes simplex do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of Valtrex.

In patients with HIV infection, the disposition and pharmacokinetic characteristics of aciclovir after oral administration of single or multiple doses of 1000mg or 2000mg Valtrex are unaltered compared with healthy subjects.

5.3 Preclinical safety data

Mutagenicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose
Crospovidone
Povidone K90
Magnesium stearate
Colloidal anhydrous silica

Film Coat YS-1-18043
White Colour Concentrate containing:
Hypromellose
Titanium dioxide
Macrogol 400
Polysorbate 80

Printing Ink:
Blue Printing Ink (ED1112 G4) containing:
Acid brilliant green BS (E 142)
Hyprolose
Shellac
Sodium Propionate

Polish:
Carnauba Wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Tablets are packed into polypropylene containers or blister packs.
Valtrex tablets are available in the following pack sizes: 21, 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
Stonemason Way
Rathfarnham
Dublin 16.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/082/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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