Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax Double Strength 400 mg/5 mL Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oral Suspension containing 400 mg aciclovir per 5 mL.

Excipients with known effect:
Liquid Sorbitol solution non-crystallising (E420) 2.25 g/5 mL
Methyl parahydroxybenzoate (E218) 5 mg/5 mL
Propyl parahydroxybenzoate (E216) 1.0 mg/5 mL
Benzyl alcohol <1.0mg/5mL

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.
Off-white, orange flavoured suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zovirax Double Strength Suspension is indicated for the treatment of Herpes simplex virus infections of the skin and mucous membranes, including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).

Zovirax Double Strength Suspension is indicated for the suppression (prevention of recurrences) of recurrent Herpes simplex infections in immunocompetent patients.

Zovirax Double Strength Suspension is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.

Zovirax Double Strength Suspension is indicated for the treatment of Varicella (chickenpox) and Herpes zoster (shingles) infections. Studies have shown that early treatment of shingles with Zovirax has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zoster-associated pain).

4.2 Posology and method of administration

Dosage for treatment of Herpes Simplex in Adults.

For treatment of Herpes simplex infections, 200 mg Zovirax should be taken five times daily at approximately four-hourly intervals omitting the night time dose. Treatment should continue for 5 days, but in severe initial infections may have to be extended.

In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg Zovirax or, alternatively, intravenous dosing could be considered.

Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.

Dosage for suppression of Herpes simplex in adults.

For suppression of Herpes simplex infections in immunocompetent patients, 200 mg Zovirax should be taken FOUR times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regimen of 400 mg Zovirax taken twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200 mg Zovirax taken thrice daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.

Some patients may experience break-through infections on total daily doses of 800 mg Zovirax.

Therapy should be interrupted periodically at intervals of six to twelve months in order to observe possible changes in the natural history of the disease.

Dosage for prophylaxis of Herpes simplex in adults.

For prophylaxis of Herpes simplex infections in immunocompromised patients, 200 mg Zovirax should be taken FOUR times daily at approximately six-hourly intervals.

In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg or, alternatively, intravenous dosing could be considered.

The duration of prophylactic administration is determined by the duration of the period at risk.

Dosage for treatment of Varicella and Herpes zoster in adults.

For treatment of Varicella and Herpes zoster infections, 800 mg Zovirax should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.

In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

Dosing should begin as early as possible after the start of the infection; treatment yields better results if initiated as soon as possible after onset of the rash.

Dosage for Infants and Children.

For treatment of Herpes simplex infections, and for prophylaxis of Herpes simplex infections in the immunocompromised, children aged two years and over should be given adult dosages. Infants and children below the age of two years should be given halfthe adult dose. **Do not dilute the oral suspension formulation.**

For treatment of varicella infections for infants and children:
6 years and over: 800 mg aciclovir four times daily
2 - < 6 years: 400 mg aciclovir four times daily
Under 2 years: 200 mg aciclovir four times daily

Treatment should continue for five days.

Dosing may be more accurately calculated as 20 mg/kg bodyweight (not to exceed 800 mg) Zovirax four times daily.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children.

Dosage in the elderly: The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Dosage in renal impairment). Adequate hydration should be maintained.

Dosage in renal impairment: Caution is advised when administering aciclovir to patients with impaired renal function. Adequate hydration should be maintained.

In the management of Herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than l0 mL/minute) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of Varicella and Herpes zoster infections it is recommended that the dosage be adjusted to 800 mg twice daily at approximately twelve-hourly intervals for patients with severe renal impairment (creatinine clearance less than l0 mL/minute), and to 800 mg three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range l0-25 mL/minute).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Zovirax Double Strength Suspension is contraindicated in patients known to be hypersensitive to aciclovir and valaciclovir or to any of the excipients as listed in section 6.1.

4.4 Special warnings and precautions for use

Use in patients with renal impairment and in elderly patients: Aciclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment 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).

Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment (see section 5.1).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir or valaciclovir.

Excipients
Zovirax Double Strength Suspension contains Methyl parahydroxybenzoate and Propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

Zovirax Double Strength Suspension contains 2.25g Liquid Sorbitol solution (non-crystallising) (E420) per 5mL (per dose).
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
Zovirax Double Strength Suspension contains less than 1 mg benzyl alcohol per 5 mL of oral solution.
Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. Particular care should be taken with neonates.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment, who are pregnant or breast feeding because of the risk of accumulation and toxicity (metabolic acidosis).

Patients with hereditary fructose intolerance (HFI), should not take/be given this medicinal product

This medicine also contains propyl hydroxybenzoate and butyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interactions

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. **Probenecid** and **cimetidine** increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. Similarly 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 coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

4.6 Fertility, pregnancy and lactation

Fertility
See Clinical Studies in section 5.3

Pregnancy
The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Zovirax. The registry findings have not shown an increase in the number of birth defects amongst Zovirax exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

Breast-feeding
Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if Zovirax is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of Zovirax 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 of Zovirax 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

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.
The following convention has been used for the classification of undesirable effects in terms of frequency: Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10,000 to <1/1000); very rare (<1/10,000).

Blood and lymphatic system disorders
Very rare: Anaemia, leukopenia, thrombocytopenia

Immune system disorders
Rare: Anaphylaxis

Psychiatric and nervous system disorders
Common: Headache, dizziness
Very rare: Agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma

The above events are generally reversible and usually reported in patients with renal impairment, or with other predisposing factors (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, abdominal pains

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes
Very rare: Hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: Pruritus, rashes (including photosensitivity)
Uncommon: Urticaria. Accelerated diffuse hair loss.

Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Rare: Angioedema

Renal and urinary disorders
Rare: Increases in blood urea and creatinine
Very rare: Acute renal failure, renal pain.
Renal pain may be associated with renal failure.

General disorders and administration site conditions
Common: Fatigue, fever

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Symptoms & signs: Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with intravenous overdosage.

Management: 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: group Anti infective, ATC code J05AB01.

Mechanism of Action
Aciclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including herpes simplex virus (HSV) types I and II and varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV and CMV.

The inhibitory activity of acyclovir for HSV I, HSV II, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non-infected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Pharmacodynamic Effects
Prolonged or repeated courses of aciclovir in severely immunocompromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment. Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK, however, strains with altered viral TK or DNA polymerase have also been reported. *In vitro* exposure of HSV isolates to aciclovir can also lead to the emergence of less sensitive strains. The relationship between the *in vitro*-determined sensitivity of HSV isolates and clinical response to aciclovir therapy is not clear.

5.2 Pharmacokinetic properties

Absorption
Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. Under fasting conditions, mean peak concentrations (C_{max}) of 0.4 microgram/mL (1.8 micromoles) are achieved at approximately 1.6 hours after a 200 mg dose administered as oral suspension or capsule. Mean peak plasma concentrations (C_{ssmax}) increase to 0.7 microgram/mL (3.1 micromoles) at steady state following doses of 200 mg administered every four hours. A less than proportional increase is observed for C_{ssmax} levels following doses of 400 mg and 800 mg administered four-hourly, with values reaching 1.2 and 1.8 microgram/mL (5.3 and 8 micromoles), respectively.

Distribution
The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2.3 to 17.8 L/kg. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels at steady-state.

Metabolism
Aciclovir is predominantly excreted unchanged by the kidney. The only known urinary metabolite is 9-[(carboxymethoxy) methyl]guanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination
Mean systemic exposure ($AUC_{0-¥}$) to aciclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. In adults the terminal plasma half-life after oral administration has been shown to vary between 2.8 and 4.1 hours. Renal clearance of aciclovir (CLr= 14.3 L/h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

Special Patient Populations
Elderly
In the elderly total body clearance falls with increasing age associated with decreases in creatinine clearance although there is little change in the terminal plasma half life.

Renal impairment
In patients with chronic renal failure the mean terminal half life was found to be 19.5 hours. The mean aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

5.3 Preclinical safety data

- **Fertility**

There is no information on the effect of aciclovir oral formulations or IV for infusion on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

- **Teratogenicity**

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

NON-CLINICAL INFORMATION

- **Mutagenicity**

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

- **Carcinogenicity**

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

- **Fertility**

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Sorbitol solution non-crystallising [E420]
Glycerol
Dispersible cellulose
Methyl parahydroxybenzoate [E218]
Propyl parahydroxybenzoate [E216]
Orange Flavour (contains benzyl alcohol).
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

100 mL or 50 mL amber glass bottle with white, child resistant cap containing an off white aqueous suspension having a characteristic orange odour. The pack contains a polypropylene double ended 5 mL or 2.5 mL spoon.

6.6 Special precautions for disposal and other handling

Administration: Where a dilution of Zovirax Oral Suspension, 400 mg/5 mL is prescribed, it is recommended that the 200 mg/5 mL suspension is dispensed.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/084/006

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