Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax 800 mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg aciclovir

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Dispersible Tablets

White, biconvex, elongated, film-coated tablet, impressed with “GX CG1” on one face and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zovirax Dispersible tablets are indicated for the treatment of Varicella infections (chicken-pox) and Herpes zoster (shingles). 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 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 immune-compromised 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 an infection. Treatment yields better results if initiated as soon as possible after onset of the rash.

Dosage for Infants and Children:-

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

Dosing may be more accurately calculated as 20 mg Zovirax/kg bodyweight (not to exceed 800 mg) four times daily. Treatment should continue for five days.

No specific data are available on the treatment of Herpes zoster infections in immune-competent 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 treatment of Varicella and Herpes zoster infections, and in the management of severely immunocompromised patients it is recommended to adjust the dosage to 800 mg twice daily, at approximately twelve-hourly intervals, for patients with severe renal impairment (creatinine clearance less than 10 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 10 to 25 mL/minute).

Administration: Zovirax Dispersible Tablets may be swallowed whole with a little water, or dispersed in a minimum of 50 mL of water.

4.3 Contraindications

Zovirax Dispersible Tablets are contraindicated in patients known to be hypersensitive to aciclovir and valciclovir 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 acyclovir 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@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 1 and 2, 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 aciclovir for HSV-1, HSV-2, 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 immune-compromised 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 acyclovir 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.

All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

5.2 Pharmacokinetic properties

Absorption
Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C^{ss}max) following doses of 200 mg administered four-hourly were 3.1 micromolar (0.7 micrograms/mL) and equivalent trough plasma levels (C^{ss}min) were 1.8 micromolar (0.4 micrograms/mL). Corresponding C^{ss}max levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 micromolar (1.2 micrograms/mL) and 8 micromolar (1.8 micrograms/mL) respectively, and equivalent C^{ss}min levels were 2.7 micromolar (0.6 micrograms/mL) and 4 micromolar (0.9 micrograms/mL).

Elimination
In adults the terminal plasma half-life of aciclovir after administration of intravenous aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of acyclovir is substantially greater than creatinine clearance, indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug.

9-Carboxymethoxy- methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10-15% of the administered dose recovered from the urine. When aciclovir is given one hour after 1 gram of probenecid the terminal half-life and the area under the plasma concentration-time curve is extended by 18% and 40% respectively.

In adults, mean C^{ss}max levels following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 micromolar (5.1 micrograms/mL), 43.6 micromolar (9.8 micrograms/mL) and 92 micromolar (20.7 micrograms/mL), respectively. The corresponding C^{ss}min levels 7 hours later were 2.2 micromolar (0.5 micrograms/mL), 3.1 micromolar (0.7 micrograms/mL) and 10.2 micromolar (2.3 micrograms/mL), respectively.

In children over 1 year of age similar mean C^{ss}max and C^{ss}min levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg. In neonates and young infants (0-3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}max was found to be 61.2 micromolar (13.8 micrograms/mL) and the C^{ss}min to be 10.1 micromolar (2.3 micrograms/mL). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 micrograms/mL) and Cmin of 14.1 micromolar (3.2 micrograms/mL).

The terminal plasma half-life in these patients was 3.8 hours. 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.

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.

Distribution
Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.

Studies have shown no apparent changes in the pharmacokinetic behaviour of aciclovir or zidovudine when both are administered simultaneously to HIV infected patients.

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 1 g 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 acyclovir 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

Tablet Core
Microcrystalline cellulose
Aluminium magnesium silicate
Sodium starch glycollate
Povidone K30
Magnesium stearate

Film-coat
White colour concentrate Y-1-7000:
Hypromellose
Titanium Dioxide (E171)
Macrogol 400

Polish
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

Zovirax Dispersible tablets are stored in PVC/Aluminium/Paper child resistant foil blister packs with one table per blister. Each pack contains 35 tablets on 7 blister strips.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1077/084/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 1994

Date of last renewal: 09 September 2009

10 DATE OF REVISION OF THE TEXT

September 2017