

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. (Short-term: Tablets)

Product imported from Greece, Spain and the UK:

White, biconvex, elongated, film-coated tablets 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 in children:-

For treatment of Varicella infections

6 years and over: 800mg Zovirax four times daily

2-6 years: 400mg Zovirax four times daily

Under 2 years: 200mg 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:-

In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of Zovirax should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

Dosage in renal impairment:-

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).

4.3 Contraindications

Zovirax Dispersible tablets are contraindicated in patients known to be hypersensitive to aciclovir or valciclovir.

4.4 Special warnings and precautions for use

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

Pregnancy:- 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.

Caution should however be exercised by balancing the potential benefits of treatment against any possible hazard.

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.

Lactation:- 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 $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$.

Blood and lymphatic system disorders

Very rare: Anaemia, leucopenia, 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 reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, or with other predisposing factors.

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

General disorders and administration site conditions

Common: Fatigue, fever

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

Mode 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.

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 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.

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

5.2 Pharmacokinetic properties

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C_{ssmax}) following doses of 200 mg administered four-hourly were 3.1 μMol (0.7 $\mu\text{g/ml}$) and equivalent trough plasma levels (C_{ssmin}) were 1.8 μMol (0.4 $\mu\text{g/ml}$). Corresponding C_{ssmax} levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 μMol (1.2 $\mu\text{g/ml}$) and 8 μMol (1.8 $\mu\text{g/ml}$) respectively, and equivalent C_{ssmin} levels were 2.7 μMol (0.6 $\mu\text{g/ml}$) and 4 μMol (0.9 $\mu\text{g/ml}$).

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 aciclovir 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_{ssmax} levels following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 μMol (5.1 $\mu\text{g/ml}$), 43.6 μMol (9.8 $\mu\text{g/ml}$) and 92 μMol (20.7 $\mu\text{g/ml}$), respectively. The corresponding C_{ssmin} levels 7 hours later were 2.2 μMol (0.5 $\mu\text{g/ml}$), 3.1 μMol (0.7 $\mu\text{g/ml}$) and 10.2 μMol (2.3 $\mu\text{g/ml}$), respectively. In children over 1 year of age similar mean C_{ssmax} and C_{ssmin} 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_{ssmax} was found to be 61.2 μMol (13.8 $\mu\text{g/ml}$) and the C_{ssmin} to be 10.1 μMol (2.3 $\mu\text{g/ml}$).

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.

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

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 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.

There is no information on the effect of Zovirax Oral Formulations on human female fertility. In patients with normal sperm count, chronically administered oral aciclovir has been shown to have no clinically significant effect on sperm count, motility or morphology.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Aluminium magnesium silicate
Sodium starch glycolate
Povidone K30
Magnesium stearate

Film-coat

Hypromellose
Titanium dioxide (E171)
Macrogol 400

Polish

Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Keep blister 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 blister packs of PVC, aluminium foil containing 35 tablets contained in an over-labelled outer cardboard carton.

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

Zovirax 800 mg Dispersible Tablets may be swallowed whole with a little water, or dispersed in a minimum of 50 ml of water.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA465/38/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16th March 2007

Date of Last Renewal: 16th March 2012

10 DATE OF REVISION OF THE TEXT

March 2013