IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/067/002
Case No: 2028983

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Zovirax 200 mg Dispersible Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/05/2007** until **17/05/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax 200 mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg aciclovir.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Dispersible, film-coated tablet. (Dispersible tablet)
Product imported from Germany:
White, round tablets branded with 'GX CF3' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zovirax Tablets 200mg are indicated for the treatment of Herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital Herpes.
Zovirax Tablets 200mg are indicated for the suppression (prevention of recurrences) of recurrent Herpes simplex infections in immunocompetent patients.
Zovirax Tablets 200mg are indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.
Zovirax Tablets 200mg are 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, 200mg 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 400mg 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, 200mg Zovirax should be taken four times daily at approximately six-hourly intervals.
Many patients may be conveniently managed on a regimen of 400mg Zovirax taken twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200mg 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 800mg 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, 200mg 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 400mg 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, 800mg 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 in 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 and children below the age of two years should be given *half* the adult dose.

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
Treatment should continue for five days.
Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg) 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: In the elderly, total aciclovir body clearance declines along 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 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 safe 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).
Administration: Zovirax Tablets 200mg may be dispersed in a minimum of 50ml of water or swallowed whole with a little water.

4.3 Contraindications

Zovirax Tablets 200mg are contra-indicated in patients known to be hypersensitive to aciclovir or valaciclovir.

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 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 aciclovirfive 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 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥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

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 aciclovir 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.
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

a) General characteristics of the active substances.

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C^{ss}max) following doses of 200mg aciclovir administered four-hourly were 3.1 microMol (0.7 micrograms/ml) and equivalent trough plasma levels (C^{ss}min) were 1.8 microMol (0.4 micrograms/ml). Corresponding C^{ss}max levels following doses of 400mg and 800mg administered four-hourly were 5.3 microMol (1.2 micrograms/ml) and 8 microMol (1.8 micrograms/ml) respectively, and equivalent C^{ss}min levels were 2.7 microMol (0.6 micrograms/ml) and 4 microMol (0.9 micrograms/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-Carboxymethoxymethylguanine 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 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 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7 µMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding C^{ss}min levels 7 hours later were 2.2 microMol (0.5 micrograms/ml) 3.1 microMol (0.7 micrograms/ml) and 10.2 microMol (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 5mg/kg and a dose of 500mg/m^2 was substituted for 10mg/kg.
In neonates and young infants (0-3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}max was found to be 61.2 microMol (13.8 micrograms/ml) and the C^{ss}min to be 10.1 microMol (2.3 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.
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.

b) Characteristics in patients

(see sections 4.2, 4.4, 4.8 & 5.1)

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

Core

Microcrystalline cellulose
Aluminium magnesium silicate
Sodium starch glycolate
Povidone K30
Magnesium stearate
Hypromellose
Titanium dioxide (E171)
Macrogol 400
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.
Store in the original package. Keep blister in the outer carton.

6.5 Nature and contents of container

PVC/PVDC/aluminium foil blister pack of 25 film-coated tablets.

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 Parallel Product Authorisation Holder

B&S Healthcare
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United Kingdom

8 Parallel Product Authorisation Number

PPA 1328/67/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18th May 2007.

10 DATE OF REVISION OF THE TEXT

March 2007