Zovirax Tablets 200 mg
Zovirax Tablets 400 mg

1. Trade Name of the Medicinal Product

Zovirax Tablets 200 mg.
Zovirax Tablets 400 mg.

2. Qualitative and Quantitative Composition

Zovirax Tablets 200 mg - Aciclovir 200 mg
Zovirax Tablets 400 mg - Aciclovir 400 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Zovirax Tablets 200 mg – are white, round, biconvex tablets which are branded "GXCL3" on one side and plain on the other.
Zovirax Tablets 400 mg – are white, shield shaped tablets which are branded "GXCM1" on one side and plain on the other.

4. Clinical Particulars

4.1. Therapeutic Indications

Zovirax Tablets are 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 Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.

Zovirax Tablets are indicated for the prophylaxis of herpes simplex infections in immunocompromised patients.

Zovirax Tablets are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2. Posology and Method of Administration

Route of administration: Oral.

Dosage in adults

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 this 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.

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 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 infection 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.

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 Zovirax or alternatively, intravenous dosing could be considered.

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

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 an infection: Treatment of herpes zoster yields better results if initiated as soon as possible after the onset of the rash. Treatment of chickenpox in immunocompetent patients should begin within 24 hours after onset of the rash.

Dosage in children

Treatment of herpes simplex infections, and 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.

For treatment of neonatal herpes virus infections, intravenous aciclovir is recommended.

Treatment of varicella infection

6 years and over: 800 mg Zovirax four times daily.
2 - 5 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 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 below).

Adequate hydration of elderly patients taking high oral doses of aciclovir 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 safe by intravenous infusion. However for patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800 mg aciclovir twice daily at approximately twelve - hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800 mg aciclovir three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10 – 25 ml/minute).

4.3. Contra-indications

Hypersensitivity to aciclovir or valaciclovir, or to any of the excipients listed in section 6.1.

4.4. Special Warnings and Precautions for Use

Severe cutaneous adverse reactions:
Cases of severe cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme (EM) have been reported in patients treated with aciclovir.
As SCARs can be life-threatening or fatal, if signs and symptoms suggestive of SCARs appear, treatment with aciclovir must be discontinued immediately, and alternative treatment should be given. Patients who have developed SCARs with the use of aciclovir or valaciclovir must not receive aciclovir (see *Contraindications and Adverse Reactions*).

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 4.2 Posology and Method of Administration). 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 4.8 Undesirable 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 (see section 5.1).

Hydration status:
Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.
The risk of renal impairment is increased by use with other nephrotoxic drugs.

The data currently available from clinical studies is not sufficient to conclude that treatment with aciclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.

Zovirax Tablets 200 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5. Interactions with other medicinal products and other forms of interaction

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 immunosuppresant 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.

An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered **theophylline** with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

4.6. Fertility, Pregnancy and Lactation

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. 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.

Caution should however be exercised by balancing the potential benefits of treatment against any possible hazard. Findings from reproduction toxicology studies are included in Section 5.3.

Breast-feeding:
Following oral administration of 200 mg Zovirax 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 aciclovir is to be administered to a nursing woman.

Fertility:

There is no information on the effect of aciclovir 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.

See clinical studies in section 5.2

4.7. Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of the active substance, but the adverse event profile should be borne in mind.

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 ≥1/1,000 and <1/100, rare ≥1/10,000 and <1/1,000, 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 4.4 Special Warnings and Precautions for Use).

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.
Very rare: Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) (see *Special warnings and precautions for use*).

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 and crystalluria.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/
Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9. Overdose

Symptoms and 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: Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors
ATC code: J05AB01.

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).

The inhibitory activity of aciclovir for HSV I, HSV II and VZV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity of mammalian host cells is low; however, TK encoded by HSV and VZV 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 viral 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

Zovirax Tablets 200mg, Zovirax Tablets 400mg:

Acyclovir is incompletely absorbed from the GI tract. Approximately 20% is absorbed shortly after administration. When the dose is increased to 600 mg or more, acyclovir is absorbed relatively less well.
The maximum steady-state plasma concentration ($C_{ss\ max}$) after a 200-mg dose given at four-hour intervals was 3 micromol/L, and the lowest concentration ($C_{ss\ min}$) was 1.6 micromol/L. Corresponding concentrations after a 800-mg dose were 6.9 and 3.5 micromol/L, respectively. Most of it is excreted unchanged via the kidneys.
When a group of neonates were treated with acyclovir 15 mg/kg every eight hours, an approximate dose-dependent increase was observed, with a C_{max} of 83.5 micromol/L (18.8 micrograms/mL) and a C_{min} of 14.1 micromol/L (3.2 micrograms/mL).

As renal excretion of acyclovir exceeds creatinine clearance, elimination is likely to occur by both glomerular filtration and tubular secretion. Acyclovir has a plasma half-life of approximately three hours in patients with normal renal function. Acyclovir's only significant metabolite is 9-carboxymethoxymethylguanine, which makes up 10–15% of the excreted drug in the urine. In chronic renal failure, the mean terminal half-life of the drug is on average 19.5 hours. The mean concentration of acyclovir decreases by approximately 60% during dialysis.

In the elderly, total clearance decreases with age, associated with a decrease in creatinine clearance. However, the terminal half-life does not change much. Administration of acyclovir and zidovudine to HIV patients did not cause any measurable changes in the pharmacokinetics of any of the substances. No mutagenicity was observed in the studies on nine of eleven microbial or mammalian cells. An effect was observed in two studies on mammalian cells, but in this case the concentrations were at least x times higher than the plasma concentrations in humans (x depends on the route of administration: 25-fold after i.v. and 150-fold after oral administration).

Special patient populations

Elderly
In the elderly patients with normal renal function total clearance falls with increasing age due to decreases in creatinine clearance. However, the possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly.

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 concentration dropped approximately 60% during dialysis.

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 found to be carcinogenic in long term studies in the rat and the mouse.

Teratogenicity:- Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits 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.

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 aciclovir on fertility.

Pharmaceutical Particulars

6.1. List of Excipients

Zovirax Tablets 200 mg
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycollate
Povidone K30
Magnesium stearate

Zovirax Tablets 400 mg
Microcrystalline cellulose
Sodium starch glycollate
Povidone K30
Magnesium stearate

6.2. Incompatibilities

There are no special requirements for use on handling of this product.

6.3. Shelf Life

The expiry date of the products is indicated on the packaging materials.

6.4. Special Precautions for Storage

Do not store above 30°C.
Store in the original package.

6.5. Nature and Contents of Container

Zovirax Tablets 200 mg
PVC/PVDC/Aluminium foil blister pack.
Pack size: 25 tablets.
PVC/PVDC/Aluminium/Paper child resistance foil blister pack.
Pack size: 25 tablets.

Zovirax Tablets 400 mg
PVC/Aluminium/Paper child resistance foil blister pack.
Pack size: 25tablets

6.6. Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

GlaxoSmithKline Trading Services Limited, Dublin, Ireland.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

Zovirax Tablets 200 mg – 126-41-30640
Zovirax Tablets 400 mg – 126-40-30639

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