

ZoviraxTM Tablets 200 mg
ZoviraxTM Tablets 400 mg
ZoviraxTM Tablets Dispersible 800 mg

1. Trade Name of the Medicinal Product

ZoviraxTM Tablets 200 mg.
ZoviraxTM Tablets 400 mg.
ZoviraxTM Tablets Dispersible 800 mg.

2. Qualitative and Quantitative Composition

Zovirax Tablets 200 mg - Aciclovir 200 mg
Zovirax Tablets 400 mg - Aciclovir 400 mg
Zovirax Tablets Dispersible 800 mg - Aciclovir 800 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.
Zovirax Tablets Dispersible 800 mg - are white film-coated oval biconvex tablets, branded “GXCG1” on one side and plain on the other.

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.
- Zovirax Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immune-competent patients.
- Zovirax Tablets are indicated for the prophylaxis of herpes simplex infections in immune-compromised patients.
- Zovirax Tablets are indicated for the treatment of herpes zoster (shingles) infections. Studies have shown that early treatment of shingles with aciclovir has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zoster associated pain).

- Zovirax Tablets should be considered for the treatment of chickenpox in certain groups at increased risk of severe varicella. These groups are as follows:
 1. Non - pregnant patients over 13 years-of-age who are otherwise healthy.
 2. Children over 12 months of age with a chronic cutaneous or pulmonary condition, or receiving long-term salicylate therapy.
 3. Children receiving short or intermittent courses or aerosolized corticosteroids.

Aciclovir should not be taken if more than 24 hours passed from the onset of a typical chickenpox rash (see *Posology and method of administration - chickenpox*).

4.2. Posology and Method of Administration

Treatment of herpes simplex

▪ Adults

For treatment of herpes simplex infections, 200mg aciclovir should be taken five times daily at approximately 4-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 immune compromised patients (e.g. after bone marrow transplantation) 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.

▪ Children

For treatment of herpes simplex infections, 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.

▪ Elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see *Renal impairment below*).

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

▪ Renal impairment

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

In the treatment 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 i.v. infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 ml/min) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

Suppression of herpes simplex in immune-competent patients

- **Adults**

For suppression of herpes simplex infections in immune-competent patients, 200mg aciclovir should be taken four times daily at approximately 6 hourly intervals.

Many patients may be conveniently managed on a regimen of 400mg aciclovir taken twice daily at approximately 12-hourly intervals.

Dosage titration down to 200 mg aciclovir taken three times 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 aciclovir.

Therapy should be interrupted periodically at intervals of 6-12 months in order to observe possible changes in the natural history of the disease.

- **Children**

No specific data are available on the suppression of herpes simplex infections in immune-competent children.

- **Elderly**

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see *Renal impairment* below).

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

- **Renal impairment**

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

In the prophylaxis 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 i.v. infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 ml/min) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

Prophylaxis of herpes simplex in immune-compromised patients

- **Adults**

For prophylaxis of herpes simplex infections in immune-compromised patients, 200mg aciclovir should be taken four times daily at approximately 6-hourly intervals.

In severely immune-compromised patients (e.g. after bone 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.

- **Children**

For prophylaxis of herpes simplex infections in the immune-compromised, 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.

- **Elderly**

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see *Renal impairment* below).

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

- **Renal impairment**

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

In the prophylaxis 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 i.v. infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 ml/min) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

Treatment of herpes zoster

- **Adults**

For treatment of herpes zoster infections, 800mg aciclovir should be taken five times daily at approximately 4-hourly intervals, omitting the night-time dose.

Treatment should continue for 7 days.

In severely immune-compromised patients (e.g. after bone 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 infection. Treatment yields better results if initiated as soon as possible after onset of the rash.

- **Children**

No specific data are available on the treatment of herpes zoster infections in immune-competent children.

- **Elderly**

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see *Renal impairment* below).

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

- **Renal impairment**

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

In the treatment of herpes zoster infections, 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/min) 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/min).

Treatment of chickenpox

Although Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, for certain groups at increased risk of severe varicella or its complications, oral aciclovir therapy initiated within the first 24 hours after the onset of rash, should be considered.

These groups are as follows:

A) Otherwise healthy, non pregnant individuals 13 years of age or older.

B) Children older than 12 months with a chronic cutaneous or pulmonary disorder and those receiving long-term salicylate therapy, although in the latter instance a reduced risk for Reye Syndrome has not been shown to result from oral aciclovir therapy nor from milder illness with varicella.

C) Children receiving short, intermittent or aerosolized courses of corticosteroids are unlikely to be significantly immunocompromised. Whether such children are at increased risk of complicated or severe varicella is unknown. However, because no data exist to confirm their immunocompetence, such children should also be considered for therapy with oral aciclovir to minimize the likelihood of severe varicella.

If possible, corticosteroids should be discontinued after known exposure to varicella. If a child is immunocompromised because of administration of high-dose corticosteroids as with other immunocompromised children, intravenous aciclovir therapy is indicated.

When given, oral aciclovir should be administered for 5 days, starting within the first 24 hours of rash onset, at a dose of 20mg/kg four times a day, with a maximum dose of 800 mg four times a day. The patient should be maintained in a well-hydrated state by encouraging adequate fluid intake.

Intravenously administered aciclovir therapy continues to be recommended for treatment of primary varicella or recurrent zoster in the immunocompromised child and for virally mediated complications of varicella in the normal host. In this setting oral therapy should not be used as indicated in "The Report of the Committee on Infectious Diseases" American Academy of Pediatrics p.579, 1991.

Oral aciclovir therapy is not recommended in the pregnant adolescent or adult with uncomplicated varicella, because the risk or benefit to the fetus is currently unknown. Intravenous aciclovir should be considered for the pregnant adolescent or adult with serious viral mediated complications of varicella.

Oral aciclovir therapy should not be used prophylactically in the otherwise normal child exposed to varicella in an attempt to prevent infection or illness.

Other considerations:

No recommendations regarding the use of oral aciclovir in infants (0 to 12 months) can be made at this time as insufficient data exist regarding the safety or efficacy of this therapy in children with varicella within the first year of life.

4.3. Contraindications

Zovirax tablets are contra-indicated in patients known to be hypersensitive to aciclovir or valaciclovir, or to any of the excipients.

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 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.

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 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.

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 Breast-feeding

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 1g 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 $\geq 1/10$, 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, 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.

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. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.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.

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).

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 to 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 immuno-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

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 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 400 mg and 800 mg 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 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 the area under the plasma concentration time curve is extended by 18% and 40% respectively.

In adults, mean steady state peak plasma concentrations (C^{SS}_{max}) following a one hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 microMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding trough levels (C^{SS}_{min}) 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 peak (C^{SS}_{max}) and trough (C^{SS}_{min}) levels were observed when a dose of 250 mg/m² was substituted for 5 mg/kg and a dose of 500 mg/m² was substituted for 10 mg/kg. In neonates and young infants (0 to 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 microMol (13.8 micrograms/ml) and C^{SS}_{min} to be 10.1 microMol (2.3 micrograms/ml). The terminal plasma half-life in these patients was 3.8 hours. A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a C_{max} of 83.5 micromolar (18.8 microgram/ml) and C_{min} of 14.1 micromolar (3.2 microgram/ml). 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.

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

Zovirax Tablets Dispersible 800 mg

Microcrystalline cellulose
Aluminium magnesium silicate
Sodium starch glycollate
Povidone (K30)
Magnesium stearate

Film coat

Hypromellose
Titanium dioxide (E171)
Polyethylene glycol 400

Polish

Polyethylene glycol 8000

6.2. Incompatibilities

None known.

6.3. Shelf Life

The expiry date of the products is indicated on the label and packaging.

6.4. Special Precautions for Storage

Do not store above 30°C.

6.5. Nature and Contents of Container

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

Zovirax Tablets 400 mg
PVC/Aluminium foil blister pack.
Pack size: 56, 70 tablets.

Zovirax Tablets Dispersible 800 mg
PVC/Aluminium foil blister pack.
Pack size : 35 tablets.

6.6. Special precautions for disposal
No special requirements.

7. MANUFACTURER
Glaxo Wellcome S.A., Burgos, Spain.

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
Zovirax Tablets Dispersible 800 mg – 126-42-30641

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