

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZOVIRAX ORAL FORMULATIONS

ZOVIRAX TABLETS / ZOVIRAX SUSPENSION

1. GENERIC NAME

Aciclovir Tablets IP
Aciclovir Oral Suspension IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets:

Each uncoated tablet contains:
Aciclovir IP ... 200 mg / 400 mg / 800 mg

List of Excipients

Microcrystalline Cellulose, Sodium Starch Glycolate, Starch Maize, Magnesium Stearate, Purified water.

Suspension:

Each 5 ml (one teaspoonful)
Contains:
Aciclovir IP ... 400 mg
in a flavoured syrup base.
Colour: Carmoisine

List of Excipients

Sorbitol Solution 70%, Glycerin, Methylparaben, Propylparaben, Cellulose Dispersible, Flavour Raspberry, Carmoisine Supra, Purified water.

3. DOSAGE FORM AND STRENGTH

Tablets
Oral suspension

For information on strength(s) refer 2. *Qualitative and Quantitative Composition* above.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZOVIRAX oral formulations are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes, including initial and recurrent genital herpes.

ZOVIRAX oral formulations are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immune-competent patients.

ZOVIRAX oral formulations are indicated for the prophylaxis of herpes simplex infections in immune-compromised patients.

ZOVIRAX oral formulations 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).

ZOVIRAX oral formulations are indicated for the management of certain severely immunocompromised patients, namely those with advanced HIV disease (CD4+ counts <200/mm³, including patients with AIDS or severe ARC) or following bone marrow transplantation. Studies have shown that oral aciclovir given in conjunction with antiretroviral therapy (mainly oral zidovudine) reduced mortality in patients with advanced HIV disease and that oral aciclovir preceded by one month's treatment with intravenous *ZOVIRAX* reduced mortality in bone marrow transplant recipients. In addition, oral aciclovir provided effective prophylaxis for herpes virus disease.

4.2 Posology and Method of Administration

Treatment of herpes simplex

Adults

For 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 five days but in severe initial infections may have to be extended.

In severely immune-compromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg 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.

Infants and Children

For treatment of herpes simplex infections, and for prophylaxis of herpes simplex infections in the immune-compromised, children aged two years and over should be given adult dosages and infants

and children below the age of two years should be given half the adult dose. Do not dilute the oral suspension formulation.

Elderly

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

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

Renal Impairment

Caution is advised when administering *ZOVIRAX* oral formulations to patients with impaired renal function. Adequate hydration should be maintained.

In the treatment and 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 intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 mL/minute) 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, 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* taken 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 infections 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.

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*).

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 IV 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, 200 mg *ZOVIRAX* should be taken four times daily at approximately six-hourly intervals.

In severely immune-compromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg or, alternatively, intravenous dosing could be considered.

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

Infants and children

For prophylaxis of herpes simplex infections in the immune-compromised, children aged two years and over should be given adult dosages and infants and children below the age of two years should be given half the adult dose. Do not dilute the oral suspension formulation.

Elderly

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

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 IV 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 varicella and herpes zoster

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.

Infants and Children

For treatment of varicella infections in children:

6 years and over:	800 mg <i>ZOVIRAX</i> four times daily
2 - < 6 years:	400 mg <i>ZOVIRAX</i> four times daily
Under 2 years:	200 mg <i>ZOVIRAX</i> four times daily

Dosing may be more accurately calculated as 20 mg aciclovir/kg body weight (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.

Elderly

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

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 varicella and 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 8 hours, for patients with moderate renal impairment (creatinine clearance in the range 10 to 25 mL/min).

Management of CMV infection in severely immunocompromised patients

Adults

For management of severely immunocompromised patients, 800 mg *ZOVIRAX* should be taken four times daily at approximately six-hourly intervals.

In the management of bone marrow recipients this would normally be preceded by up to one month's therapy with IV aciclovir.

The duration of treatment studied in bone marrow transplant patients was 6 months (from 1 to 7 months post-transplant). In patients with advanced HIV disease, study treatment was 12 months, but it is likely that these patients would continue to benefit from a longer duration of treatment.

Children

Limited data suggest that for management of severely immunocompromised children, over two years of age, the adult dose may be given.

Elderly

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

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 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/min) and to 800 mg three times daily, at intervals of approximately 8 hours, for patients with moderate renal impairment (creatinine clearance in the range 10 to 25 mL/min).

4.3 Contraindications

ZOVIRAX oral formulations are contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

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 4.3 Contraindications and 4.8 Undesirable Effects*).

Use in patients with renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced 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 reduction 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*).

Hydration status:

Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

4.5 Drug Interactions

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 Use in Special Populations

Pregnancy

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

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 aciclovir 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 aciclovir 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 aciclovir 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 ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 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 4.4 *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.

General disorders and administration site conditions

Common: Fatigue, fever.

4.9 Overdose

Symptoms and signs

Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g 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 IV 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.

Treatment

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

ATC Code

Pharmacotherapeutic group: Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors.

ATC code: J05AB01

5.1 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.

5.2 Pharmacodynamic Properties

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.

5.3 Pharmacokinetic Properties

Absorption

Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. Under fasting conditions, mean peak concentrations (C_{\max}) of 0.4 microgram/ml are achieved at approximately 1.6 hours after a 200 mg dose administered as oral suspension or capsule. Mean peak plasma concentrations (C_{ssmax}) increase to 0.7 microgram/ml (3.1 micromoles) at steady state following doses of 200 mg administered every four hours. A less than proportional increase is observed for C_{ssmax} levels following doses of 400 mg and 800 mg administered four-hourly, with values reaching 1.2 and 1.8 microgram/ml (5.3 and 8 micromoles), respectively.

Distribution

The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (V_d/F) ranged from 2.3 to 17.8 L/kg. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels at steady-state.

Metabolism

Aciclovir is predominantly excreted unchanged by the kidney. The only known urinary metabolite is 9-[(carboxymethoxy) methyl]guanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination

Mean systemic exposure ($AUC_{0-\infty}$) to aciclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. In adults the terminal plasma half-life after oral administration has been shown to vary between 2.8 and 4.1 hours. Renal clearance of aciclovir ($CL_r = 14.3$ L/h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

Special Patient Populations

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.

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.

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

5.4 Clinical Studies

There is no information on the effect of aciclovir oral formulations 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

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.

7. DESCRIPTION

Tablets
Oral suspension

Tablets:

Each uncoated tablet contains:
Aciclovir IP ... 200 mg / 400 mg / 800 mg

List of Excipients

Microcrystalline Cellulose, Sodium Starch Glycolate, Starch Maize, Magnesium Stearate, Purified water.

Suspension:

Each 5 ml (one teaspoonful)

Contains:

Aciclovir IP ... 400 mg

in a flavoured syrup base.

Colour: Carmoisine

List of Excipients

Sorbitol Solution 70%, Glycerin, Methylparaben, Propylparaben, Cellulose Dispersible, Flavour Raspberry, Carmoisine Supra, Purified water.

8. PHARMACEUTICAL PARTICULARS**8.1 Incompatibilities**

There are relevant data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Tablets: Aluminium blister foil strips.

Suspension: Glass bottle with measuring spoon.

Oral Suspensions containing 400 mg per 5 mL

All presentations may not be marketed in India.

8.4 Storage and Handling Information

Tablets: Store in dry place protected from light at temperatures not exceeding 25°C.

Suspension: Store in a well closed container at temperature not exceeding 30°C. Protect from light. Do not freeze.

Shake well before use.

Keep out of reach of children

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *ZOVIRAX TABLETS/SUSPENSION*. Patients (and/or

patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging

For further information please contact:

GlaxoSmithKline Pharmaceuticals Limited.

Registered Office:

Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging

12. DATE OF REVISION

18-JUL-2025

Trade marks are owned by or licensed to the GSK group of companies.

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