

PRODUCT INFORMATION

ZOVIRAX™ INTRAVENOUS INFUSION

APPROVED NAME: Aciclovir

COMPOSITION: Aciclovir 250 mg and 500 mg. Excipient: sodium hydroxide.

DESCRIPTION: Aciclovir is a synthetic acyclic purine nucleoside analogue. Its chemical name is 9-[(2-hydroxyethoxy)methyl]guanine sodium. It is a white crystalline powder. In solution it has a pH of 11.

MICROBIOLOGY:

Aciclovir is an antiviral agent which is active *in vitro* against *Herpes simplex* (HSV) types I and II and *Varicella zoster virus* (VZV). However, the relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established. Aciclovir needs to be phosphorylated to the active compound, aciclovir triphosphate in order to become active against the virus. Such conversion is very limited in normal cells and in addition cellular DNA polymerase is not very sensitive to the active compound. However, in infected cells HSV or VZV coded thymidine kinase facilitates the conversion of aciclovir to aciclovir monophosphate which is then converted to aciclovir triphosphate by cellular enzymes. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes specified DNA polymerase, preventing further viral DNA synthesis.

Animal studies indicate that at high doses aciclovir is cytotoxic.

PHARMACOKINETICS:

In adults the terminal plasma half-life of aciclovir after administration of Zovirax Intravenous Infusion is about 2.9 hours. Approximately 60% of the drug is excreted unchanged by the kidney by glomerular filtration and tubular excretion. When aciclovir is given one hour after 1 gram of probenecid the terminal half-life and the area under the plasma concentration time curve are extended by 18% and 40% respectively. 9-carboxymethoxymethylguanine is the major metabolite of aciclovir and accounts for 10-15% of the dose excreted in the urine.

Mean steady state peak plasma concentrations (C^{SS}_{max}) following a one hour infusion of 5 mg/kg or 10 mg/kg were 9.8 ± 2.6 S.D. and 20.7 ± 10.2 S.D. $\mu\text{g/mL}$ respectively. The trough plasma concentrations (C^{SS}_{min}) were 0.7 ± 0.3 S.D. and 2.0 ± 0.1 S.D. $\mu\text{g/mL}$ 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 children aged 0-3 months the terminal plasma half-life is approximately 4 hours. However, experience is insufficient at present to recommend therapy for this age group.

In patients with chronic renal failure the mean terminal half-life was found to be 19.5 ± 5.9 S.D. hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

Plasma protein binding is low (9 to 33%).

INDICATIONS:

Zovirax Intravenous Infusion is indicated for the purpose of:

1. Promoting resolution of acute clinical manifestations of mucocutaneous *Herpes simplex* virus in immunocompromised patients.
2. Treatment of severe first episode primary or non-primary genital herpes in immune competent patients.
3. Treatment of acute manifestations of *Varicella zoster* virus infection in immunocompromised patients.
4. Treatment of Herpes zoster (shingles) in immune competent patients who show very severe acute local or systemic manifestations of the disease.

Benefits can be expected in patients with rash duration shorter than 72 hours. The use of the intravenous infusion may be warranted in only a small subgroup of immune competent patients.

5. Treatment of *Herpes simplex* encephalitis.

CONTRAINDICATIONS:

Zovirax Intravenous Infusion is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

PRECAUTIONS:

Zovirax powder is intended for intravenous infusion only and should not be used by any other route. Reconstituted Zovirax Intravenous Infusion has a pH of approximately 11.0 and should not be administered by mouth.

Zovirax infusion must be given over a period of at least one hour in order to avoid renal tubular damage. It should not be administered as a bolus injection. Although the aqueous solubility of aciclovir sodium (for infusion) exceeds 100 mg/mL, precipitation of aciclovir crystals in renal tubules, and the consequent renal tubular damage, can occur if the maximum solubility of free aciclovir (2.5 mg/mL at 37°C in water) is exceeded. Zovirax infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first few hours following infusion, particular attention should be given to establish sufficient urine flow during that period. Concomitant use of other nephrotoxic drugs, pre-existing renal disease and dehydration increase the risk of further renal impairment by aciclovir.

As aciclovir has been associated with reversible encephalopathic changes, it should be used with caution in patients with underlying neurological abnormalities, significant hypoxia or serious renal, hepatic or electrolyte abnormalities. It should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitantly interferon or intrathecal methotrexate.

The dose of Zovirax Intravenous Infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body (see DOSAGE AND ADMINISTRATION).

In patients receiving Zovirax Intravenous Infusion at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.

Resistant strains have been isolated *in vitro* and in animals following treatment with aciclovir. HSV strains resistant *in vitro* to aciclovir have also been isolated from immunocompromised patients receiving aciclovir for *Herpes simplex* infections. Therefore the potential for the development of resistant HSV strains in patients treated with aciclovir should be borne in mind. The relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established.

Use in Pregnancy: (Category B3)

Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450 mg/kg/day po), rabbit (50 mg/kg/day sc and iv) or rat (50 mg/kg/day, sc) when dosed throughout the period of major organogenesis. This exposure in the rat resulted in plasma levels similar to the mean steady-state peak concentration in humans after 1 hour infusions of 10 mg/kg every 8 hours. In additional studies in which rats were given 3 sc doses of 100 mg/kg aciclovir on gestation day 10, foetal abnormalities, such as head and tail anomalies, were reported (exposure was 5 fold human levels after 10 mg/kg infusions).

There have been no adequate and well controlled studies concerning the safety of aciclovir in pregnant women. It should not be used during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the foetus. If suppressive therapy is used in the perinatal period it should not be assumed that viral shedding has ceased, or that the risk to foetus/neonate has decreased. Pregnancy should be managed according to considerations normally applicable to patients with genital herpes.

Use in Lactation:

Limited human data show that aciclovir is excreted into human milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

Mutagenicity:

Aciclovir was clastogenic in Chinese hamster cells *in vivo*, at exposure levels also causing nephrotoxicity (500 & 100 mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100 mg/kg) of aciclovir in rats. No activity was found in a dominant lethal study in mice or in 4 microbial assays. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells, negative at 2 other loci in mouse lymphoma cells, and 3 loci in a Chinese hamster ovary cell line).

The results of these mutagenicity tests *in vitro* and *in vivo* suggest that aciclovir is unlikely to pose a genetic threat to man at therapeutic dose levels.

Carcinogenicity:

Aciclovir was positive in one of two mouse cell transformation systems *in vitro*. Inoculation of the transformed cells into immune-suppressed mice resulted in tumours. These data are suggestive of an oncogenic potential. However, the validity of this type of study is unclear.

Lifetime oral dosing studies in mice and rats gave no evidence for tumorigenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

Effects on Fertility:

There is no experience of the effect of ZOVIRAX on human fertility. The results of studies in animals indicate that aciclovir should have no effect on fertility in man at therapeutic doses.

Drug Interactions:

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism or affect renal physiology may increase aciclovir plasma concentrations. Probenecid increases the half-life and the AUC of aciclovir by this mechanism, and reduces aciclovir renal clearance, while cimetidine increases the AUC of aciclovir. However, no dosage adjustment is necessary.

In patients receiving intravenous Zovirax, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. 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.

Care is also required (with monitoring for changes in renal function) if administering intravenous Zovirax with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

In patients over 60 years of age concurrent use of diuretics increases plasma levels of aciclovir very significantly. It is not known whether a similar effect occurs in young adults. In patients receiving RETROVIR (zidovudine) no significant overall increase in toxicity was associated with the addition of ZOVIRAX. No data are available on interactions between aciclovir and other antiretroviral therapies.

Effects on Ability to Drive and Use Machines

Zovirax I.V. for Infusion is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant. There have been no studies to investigate the effect of Zovirax on driving performance or the ability to operate machinery.

ADVERSE REACTIONS:

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

Uncommon: Decreases in haematological indices (anaemia, thrombocytopenia, leukopenia)

Immune system disorders

Very rare: Anaphylaxis

Psychiatric and nervous system disorders

Common: Lethargy, obtundation, tremors, confusion, hallucinations, agitation, somnolence, psychosis, convulsions and coma

Very rare: Headache, dizziness, ataxia, dysarthria, encephalopathy.

The above reversible events are usually seen in medically complicated cases.

Vascular disorders

Common: Phlebitis

Respiratory, thoracic and mediastinal disorders

Very rare: Dyspnoea

Gastrointestinal disorders

Common: Nausea, vomiting

Very rare: Diarrhoea, abdominal pain

Hepato-biliary disorders

Common: Reversible increases in liver-related enzymes

Very rare: Reversible increases in bilirubin, jaundice, hepatitis

Skin and subcutaneous tissue disorders

Common: Pruritus, urticaria, rashes (including photosensitivity)

Very rare: Angioedema

Renal and urinary disorders

Common: Increases in blood urea and creatinine

Rapid increases in blood urea and creatinine levels are believed to be related to the peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one-hour period.

Very rare: Renal impairment, acute renal failure

Adequate hydration should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

General disorders and administration site conditions

Very rare: Fatigue, fever, local inflammatory reactions

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when Zovirax I.V. for Infusion has been inadvertently infused into extracellular tissues.

DOSAGE AND ADMINISTRATION: (See INDICATIONS)

Indication	Immune status	Dosage
<i>Herpes simplex</i> infection	Normal or immuno-compromised	5 mg/kg every 8 hours
Very severe <i>Herpes zoster</i> infection (shingles)	Normal	5 mg/kg every 8 hours
<i>Varicella zoster</i> infection	Immunocompromised	10 mg/kg every 8 hours
<i>Herpes simplex</i> encephalitis	Normal or immuno-compromised	10 mg/kg every 8 hours

Each dose should be administered by slow intravenous infusion **over a one-hour period**.

In patients with **renal impairment**, Zovirax should be administered with caution since the drug is excreted by the kidneys. The following modifications in dosage are suggested:

Creatinine Clearance	Dosage
25-50 mL/min	The recommended dose (5 or 10 mg/kg) every 12 hours
10-25 mL/min	The recommended dose (5 or 10 mg/kg) every 24 hours
0 (anuric) - 10 mL/min	The recommended dose should be halved (2.5 or 5 mg/kg) every 24 hours and after dialysis

DOSAGE IN CHILDREN:

The dose of Zovirax Intravenous Infusion in children aged 1-12 years should be calculated on the basis of body surface area.

Children in this age group with *Herpes simplex* infections (except *Herpes simplex* encephalitis) or *Varicella zoster* infections should be given Zovirax Intravenous in doses of 250 mg per square metre of body surface area (equivalent to 5 mg/kg in adults).

Immunocompromised children in this age group with *Varicella zoster* virus infection or with *Herpes simplex* encephalitis should be given Zovirax Intravenous in doses of 500 mg per square metre of body surface area (equivalent to 10 mg/kg in adults).

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

DOSAGE IN THE ELDERLY:

No data are available on this age group. However, as creatinine clearance is often low in the elderly, special attention should be given to dosage reduction.

DURATION OF TREATMENT:

It is recommended that Zovirax Intravenous Infusion be administered for five to seven days in the treatment of most infections and for at least ten days in the treatment of *Herpes simplex* encephalitis.

RECONSTITUTION:

Each 250 mg vial of Zovirax Intravenous Infusion should be reconstituted by the addition of 10 mL of either Water for Injections BP or Sodium Chloride Intravenous Infusion BP (0.9% w/v). This provides a solution containing 25 mg aciclovir per mL.

Each 500 mg vial of Zovirax Intravenous Infusion should be reconstituted by the addition of 20 mL of either Water for Injections BP or Sodium Chloride Intravenous Infusion BP (0.9% w/v). This provides a solution containing 25 mg aciclovir per mL.

ADMINISTRATION:

Zovirax Intravenous Infusion after reconstitution may be injected directly into a vein over one hour by a controlled-rate infusion pump or be further diluted for administration by infusion.

For intravenous injection by a controlled-rate infusion pump a solution containing 25 mg aciclovir per mL is used.

For intravenous infusion each vial of Zovirax Intravenous Infusion should be reconstituted and then, wholly or in part according to the dosage required, added to and mixed with at least 50 mL-100 mL infusion solution. A maximum of 250 mg of aciclovir may be added to 50 mL infusion solution and a maximum of 500 mg of aciclovir may be added to 100 mL of infusion solution. After addition of Zovirax Intravenous Infusion to an infusion solution the mixture should be shaken to ensure thorough mixing. Zovirax Intravenous Infusion when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Zovirax Intravenous Infusion is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (below 25°C) when diluted to a concentration not greater than 0.5% w/v aciclovir.

Sodium Chloride Intravenous Infusion BP (0.45% and 0.9% w/v)
Sodium Chloride (0.18% w/v) and Glucose (4% w/v)
Intravenous Infusion BP
Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v)
Intravenous Infusion BP
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution)

Zovirax Intravenous Infusion contains no preservative. Reconstitution and dilution should therefore be carried out immediately before use and any unused solution should be discarded. Should visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

THE SOLUTION SHOULD NOT BE REFRIGERATED as this causes precipitation of crystals. These crystals usually do not redissolve when solution temperature is brought to room temperature.

OVERDOSAGE:

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 overdosage. Adequate hydration is essential to reduce the possibility of crystal formation in the urine. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

PRESENTATION:

Each vial of Zovirax Intravenous Infusion contains the equivalent of 250 mg or 500 mg aciclovir as the sterile freeze-dried sodium salt. When reconstituted as directed, the solution will have a pH of approximately 11.

STORAGE AND CONDITIONS AND SHELF LIFE:

Store below 25°C. Unopened vials of Zovirax Lyophilized powder for Intravenous Infusion have a shelf-life of 5 years.

DISTRIBUTED BY:

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