

DATA SHEET

Lovir Intravenous Infusion

Aciclovir BP 250mg Intravenous Infusion

Presentation

Vial containing freeze dried powder for injection. Synthetic acyclic purine nucleoside analogue. It is a white crystalline powder. In solution it has a pH of approximately 11.

Uses

Actions

Microbiology

Aciclovir is an antiviral agent which is active *in vitro* against *Herpes simplex* virus (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 aciclovir 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 1g 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% to 15% of the dose excreted in the urine.

Mean steady state peak plasma concentrations ($C_{ss,max}$) following a one hour infusion of 5mg/kg or 10mg/kg were 9.8 ± 2.6 SD and 20.7 ± 10.2 SD microgram/mL respectively. The trough plasma concentrations ($C_{ss,min}$) were 0.7 ± 0.3 SD and 2 ± 0.1 SD microgram/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 5mg/kg. In children aged 0 to 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 ± 5.9SD 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

For the purpose of promoting resolution of acute clinical manifestations of mucocutaneous *Herpes simplex* virus infections in normal and immunocompromised patients.

Treatment of acute manifestations of *Varicella zoster* virus infection in normal and immunocompromised patients.

Treatment of *Herpes simplex* infections in the neonate.

Prophylaxis of CMV infection in bone marrow transplant recipients.

Dosage and Administration

Each dose should be administered by slow intravenous infusion over a one hour period. See Table 1.

Table 1: Lovir Intravenous Infusion

Dosage recommendations: every 8 hours

Indication	Immune status	Dose
<i>Herpes simplex</i> infection	Normal or immunocompromised	5mg/kg bodyweight
Very severe <i>Herpes zoster</i> infection (shingles)	Normal	5mg/kg bodyweight
<i>Varicella zoster</i> infection	Immunocompromised	10mg/kg bodyweight
<i>Herpes simplex</i> encephalitis	Normal or immunocompromised	10mg/kg bodyweight

For prophylaxis of CMV infection in bone marrow transplant recipients 500mg/m² Lovir should be given intravenously three times daily at approximately 8 hourly intervals. The duration of treatment recommended in bone marrow transplant recipients is from 5 days before up to 30 days after treatment.

Impaired renal function

Lovir should be administered with caution since the drug is excreted by the kidneys. Table 2 shows dosage modifications.

Table 2: Lovir Intravenous Infusion in Renal Impairment

Dosage recommendations based on creatinine clearance

Creatinine clearance	Dosage
25 to 50mL/minute	Recommended dose (5 or 10mg/kg bodyweight or 500mg/m ²) every 12 hours
10 to 25mL/minute	Recommended dose (5 or 10mg/kg bodyweight or 500mg/m ²) every 24 hours
0 (anuric) to 10mL/minute	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be halved and administered every 24 hours and after dialysis.

A course of treatment with Lovir usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for *Herpes* encephalitis and neonatal *Herpes simplex* infections usually lasts 10 days.

Children

The dose of Lovir Intravenous Infusion in children aged 3 months to 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 250mg/m² body surface area (equivalent to 5mg/kg adults) every 8 hours. Immunocompromised children in this age group with *Varicella zoster* virus infection or with *Herpes simplex* encephalitis should be given 500mg/m² body surface area (equivalent to 10mg/kg in adults) every 8 hours.

Limited data suggests that for the prophylaxis of CMV infection in children over 2 years of age, who have undergone bone marrow transplantation, the adult dose may be given.

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

Neonates

The dosage of Lovir Intravenous Injection for neonates is calculated on the basis of bodyweight. Neonates with *Herpes simplex* infections should be given Lovir in doses of 10mg/kg bodyweight every 8 hours.

Use 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 Lovir 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.

Administration

Lovir 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 aciclovir 25mg/mL is used.

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

Lovir 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).

Contraindications

Known hypersensitivity to aciclovir.

Warnings and Precautions

Lovir powder is intended for intravenous infusion only and should not be used by any other route.

Lovir 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 100mg/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. Lovir 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.

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.

Carcinogenesis, mutagenesis, impairment of fertility

Mutagenesis. Aciclovir was clastogenic in Chinese hamster cells *in vivo* at exposure levels also causing nephrotoxicity (500 and 1,00 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 four microbial assays. Positive results were obtained in two of seven genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells, negative at two other loci in mouse lymphoma cells and three 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 humans at therapeutic dose levels.

Carcinogenesis. 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 give no evidence of tumorigenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

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

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 orally), rabbit (50 mg/kg/day subcutaneously)

and intravenously) or rat (50 mg/kg/day subcutaneously) 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 one hour infusions of 10 mg/kg every eight hours. In additional studies in which rats were given three subcutaneous doses of aciclovir 100 mg/kg on gestation day 10, fetal abnormalities, e.g. head and tail anomalies, were reported (exposure was five times the human levels after 10mg/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 fetus. If suppressive therapy is used in the perinatal period it should not be assumed that viral shedding has ceased, or that the risk to fetus/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 breastfeeding mothers if the benefits to the mother outweigh the potential risks to the infant.

Adverse Effects

Local

Local inflammation or phlebitis at injection site.

Systemic

Renal. Rapid increases in blood urea and creatinine levels may occur occasionally in patients given aciclovir intravenous infusion. These are usually reversible but progression to acute renal failure can occur in rare cases. The risk of renal damage is increased by bolus injection, dehydration, concomitant use of other nephrotoxic drugs and pre-existing renal disease.

Dermatological. Rashes and hives may occur.

Neurological. Approximately 1% of patients receiving aciclovir have manifested encephalopathic changes characterised by one or more of the following: lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, and coma.

Other. Less frequent adverse effects include nausea, vomiting, diaphoresis, haematuria, hypotension and headache. Events reported in patients receiving intravenous aciclovir include increases in liver related enzymes and decreases in haematological indices.

Interactions

Probenecid increases the aciclovir mean half-life and area under the plasma concentration curve. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of aciclovir. 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 aciclovir. No data are available on interactions between aciclovir and other antiretroviral therapies.

Overdosage

There is little experience concerning overdosage with aciclovir. Adverse effects from overdosage may be expected to follow the pattern listed under Adverse Reactions. Adequate hydration is essential to reduce the possibility of crystal formation in the urine. Aciclovir can be removed from circulation by haemodialysis.

Pharmaceutical Precautions

Lovir 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.

Reconstitution

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

Medicine Classification

Prescription only medicine

Package Quantities

Vial (sterile, preservative free, freeze dried sodium salt) = aciclovir 250mg, 5's.

Further Information

Aciclovir is anhydrous 2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6*H*-purin-6-one. Its molecular structure is C₁₈H₁₁N₅O and molecular weight is 225.2. There are no other ingredients in Lovir Intravenous Infusion powder.

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