

NEW ZEALAND DATASHEET

Acihexal

Aciclovir, powder for infusion, 250 mg and 500 mg

Presentation

Acihexal is a white crystalline freeze dried powder aseptically filled into 25 ml glass vials.

- Acihexal 250 mg contains sterile aciclovir 250 mg.
- Acihexal 500 mg contains sterile aciclovir 500 mg.

Uses

Actions

Pharmacotherapeutic group

J05AB01 - Direct acting antivirals, nucleosides and nucleotides excluding reverse transcriptase inhibitors, aciclovir.

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 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.

Pharmacodynamic effects

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The antiviral activity of aciclovir is attributed to the phosphorylated cellular metabolite, aciclovir triphosphate. In uninfected cells, the enzyme thymidine kinase does not use aciclovir effectively as a substrate thereby limiting the conversion to aciclovir triphosphate and cellular DNA polymerase is not very sensitive to the active compound hence toxicity to mammalian host cells is low. However, thymidine kinase encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further phosphorylated 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 thymidine kinase; however, strains with altered viral thymidine kinase 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. All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Pharmacokinetics

Absorption

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour IV infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 5.1 mcg/ml, 9.8 mcg/ml, 20.7 mcg/ml and 23.6 mcg/ml, respectively. The corresponding trough levels (C_{ssmin}) 7 hours later were 0.5 mcg/ml, 0.7

mcg/ml, 2.3 mcg/ml and 2.0mcg/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 per square metre body surface area was substituted for 5 mg/kg and a dose of 500 mg per square metre body surface area was substituted for 10 mg/kg.

Distribution

Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low at 9 to 33% and drug interactions involving binding site displacement are not anticipated.

Biotransformation

9-carboxymethoxymethylguanine is the major metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

Elimination

In adults the terminal plasma half-life of aciclovir after intravenous administration is about 2.9 hours. Approximately 60% of the medicine is excreted unchanged by the kidney by glomerular filtration and tubular secretion. When aciclovir is given one hour after 1 g of probenecid the terminal half-life and the area under the plasma concentration time curve are extended by 18% and 40%, respectively.

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.

Special patient considerations

In neonates aged up to 3 months treated with doses of 10 mg/kg IV over a one-hour period every 8 hours the C_{ss}max was 13.8 mcg/ml and the C_{ss}min was 2.3 mcg/ml. The terminal plasma half life in these patients was 3.8 hours. 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.

Indications

Treatment of Herpes simplex infections.

Prophylaxis of Herpes simplex infections in immune-compromised patients.

Treatment of Varicella zoster infections.

Treatment of Herpes simplex infections in the neonate.

Prophylaxis of CMV infection in bone marrow transplant recipients. It has been shown that high dose intravenous aciclovir reduces the incidence and delays the onset of CMV infection. When high dose intravenous aciclovir is followed by 6 months treatment with high dose oral aciclovir (refer to separate prescribing information for oral aciclovir) mortality and the incidence of viraemia are also reduced.

Dosage and administration

Dosage

Adults

Obese patients should be dosed at the recommended adult dose using ideal body weight, rather than actual body weight.

Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given intravenous aciclovir in doses of 5 mg/kg bodyweight every 8 hours.

Immune-compromised patients with Varicella zoster infections or patients with herpes encephalitis should be given intravenous aciclovir in doses of 10 mg/kg bodyweight every 8 hours provided renal function is not impaired.

For prophylaxis of CMV infection in bone marrow transplant recipients aciclovir 500 mg per square metre body surface area should be given intravenously 3 times daily at approximately 8 hourly intervals. The duration of treatment recommended in bone marrow transplant recipients is from 5 days before transplant to up to 30 days after transplant.

Children

The dose of intravenous aciclovir for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given intravenous aciclovir in doses of 250 mg per square metre body surface area every 8 hours.

In immune-compromised children with Varicella zoster infections or children with herpes encephalitis, intravenous aciclovir should be given in doses of 500 mg per square metre body surface area every 8 hours if renal function is not impaired.

Limited data suggest 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 intravenous aciclovir in neonates is calculated on the basis of bodyweight.

Neonates with Herpes simplex infections should be given intravenous aciclovir in doses of 10 mg/kg bodyweight every 8 hours.

Elderly patients

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (refer to Dosage in renal impairment below). Adequate hydration should be maintained.

Dosage in renal impairment

Caution is advised when administering intravenous aciclovir to patients with impaired renal function. The following adjustments in dosage are suggested. Adequate hydration should be maintained.

Creatinine clearance	Dosage
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight or 500 mg per square metre body surface area) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg bodyweight or 500 mg per square metre body surface area) should be given every 24 hours.
0 (anuric) to 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight or 500 mg per square metre body surface area) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight or 500 mg per square metre body surface area) should be halved and administered every 24 hours and after dialysis.

A course of treatment with intravenous aciclovir 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.

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

Administration

The required dose of aciclovir should be administered by slow intravenous infusion over a one hour period.

Acihexal powder for infusion should be reconstituted in 10 ml of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing 25 mg aciclovir per ml. From the calculated dose, determine the appropriate number of vials to be used. To reconstitute each vial, add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.

Reconstituted aciclovir intravenous infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion. Add the required volume of reconstituted solution to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4 ml reconstituted solution (100 mg aciclovir) added to 20 ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 and 1000 mg.

When diluted in accordance with the recommended schedules, aciclovir intravenous infusion is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15°C to 25°C): 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). Aciclovir intravenous infusion when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

Contraindications

Known hypersensitivity to aciclovir, valaciclovir or to any of the inactive ingredients listed in [Further information](#).

Warnings and precautions

This medicine is intended for intravenous infusion only and should not be used by any other route. Reconstituted aciclovir intravenous infusion has a pH of approximately 11.0 and should not be

administered by mouth.

Aciclovir intravenous 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. The 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 medicines, 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 medicines 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.

Use in patients with renal impairment and in elderly patients

Intravenous aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment to avoid accumulation of aciclovir in the body (refer to Dosage and 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 (refer to Adverse effects).

In patients receiving intravenous aciclovir 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.

Pregnancy and lactation

Use in pregnancy

Assigned Category B3 by the Australian Drug Evaluation Committee. This category includes medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Animal studies show that aciclovir readily diffuses across the placenta. Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. 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, foetal abnormalities, e.g. head and tail anomalies, were reported however aciclovir exposure was five times the human levels after 10 mg/kg infusions). The clinical relevance of these findings is uncertain.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown any 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 intravenous aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. 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 or neonate has decreased.

Use in lactation

Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in human 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 0.3mg/kg bodyweight/day. Caution is therefore advised if ZOVIRAX is to be administered to a nursing woman.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect. Aciclovir powder for infusion is generally used in a hospital setting and information on ability to drive and operate machinery is not usually relevant. There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery.

Other

Preclinical safety data

Animal studies indicate that at high doses aciclovir is cytotoxic.

Mutagenesis

Aciclovir was clastogenic in Chinese hamster cells *in vivo* at exposure levels also causing nephrotoxicity (500 and 1000 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 gave no evidence for 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 intravenous aciclovir on human fertility. The results of studies in animals indicate that aciclovir should have no effect on fertility in humans at therapeutic doses.

Adverse 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 in 10 or more, common between 1 in 100 and 1 in 10, uncommon between 1 in 1000 and 1 in 100, rare between 1 in 10,000 and 1 in 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.

Very rare - headache, dizziness, 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 (refer to Warnings and precautions).

Vascular disorders

Common - phlebitis.

Respiratory, thoracic and mediastinal disorders

Very rare - dyspnoea.

Gastrointestinal disorders

Common - nausea, vomiting.

Very rare - diarrhoea, abdominal pain.

Hepatobiliary 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 aciclovir 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, renal pain. 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. Renal pain may be associated with renal failure.

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 aciclovir has been inadvertently infused into extracellular tissues.

Interactions

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism or affect renal physiology may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

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

Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with medicines 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 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.

Aciclovir should also be used with caution in patients who have manifested neurological reactions to cytotoxic medicines or are receiving concomitantly interferon or intrathecal methotrexate.

Overdosage

Signs and symptoms

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.

Management

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.

Pharmaceutical precautions

Instructions for use/handling

Acihexal powder for infusion contains no antimicrobial preservative. Reconstitution or dilution should therefore be carried out either under full aseptic conditions or immediately before use and any unused solution discarded.

Acihexal powder for infusion should be reconstituted using 10 ml of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing aciclovir 25 mg/ml (refer to [Dosage and Administration](#)).

Incompatibilities

None known.

Special precautions for storage

Store at or below 25°C. Protect from light and moisture. Store the reconstituted medicine between 15 to 25°C and use within 12 hours. Reconstituted or diluted solutions should not be refrigerated.

Medicine classification

Prescription Medicine.

Package quantities

Packs of 5 vials. Not all pack sizes and/or strengths may be currently marketed.

Further information

List of excipients

Sodium hydroxide.

Name and address

Novartis New Zealand Limited
Private Bag 65904 Mairangi Bay
AUCKLAND 0754

Telephone: (09) 361 8100

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