PRODUCT INFORMATION

ACICLOVIR SANDOZ® IV INFUSION

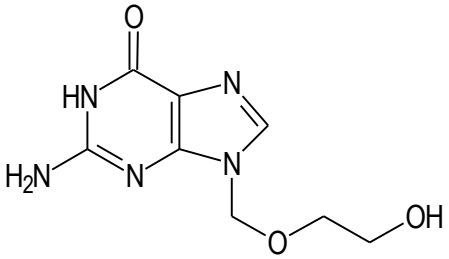
NAME OF THE MEDICINE

Active: Aciclovir

Excipient: A small residual of sodium hydroxide, used to form the aciclovir sodium salt, will be present in the vials.

Chemical name: 9-[(2-hydroxyethoxy)methyl]guanine.

The structural formula of aciclovir is:



Molecular formula: $C_8H_{11}N_5O_3$

Molecular weight: 225.2

CAS Number: 59277-89-3

DESCRIPTION

Aciclovir Sandoz IV Infusion 250mg Powder for Injection contains aciclovir sodium 274.4mg equivalent to 250mg aciclovir per vial.

Aciclovir Sandoz IV Infusion 500mg Powder for Injection contains aciclovir sodium 548.8mg equivalent to 500mg aciclovir per vial.

Physical characteristics
Aciclovir is a white or almost white, crystalline powder, slightly soluble in water, freely soluble in dimethyl sulphoxide, very slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids and alkali hydroxides. Soluble in 1 in 10 of water.

PHARMACOLOGY

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); the latter being considerably less sensitive. However, the relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has not been adequately established. Development of resistance by HSV to aciclovir has been documented. 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.

Pharmacokinetics

The terminal plasma half-life of aciclovir in adults with normal renal function is approximately 3 hours. Approximately 60% of the medicine 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 - 15% of the dose excreted in the urine following I.V. administration.

Mean steady state peak plasma concentrations (C_{ss}max) following a one hour infusion of 5mg/kg or 10mg/kg of aciclovir were about 9.8 and 20.7mg/mL, respectively. The trough plasma concentrations (C_{ss}min) were about 0.7 and 2.0mg/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 250mg/m^2 was substituted for 5mg/kg and a dose of 500mg/m^2 was substituted for 10mg/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 following intravenous administration was found to be approximately 20 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

Aciclovir Sandoz I.V. infusion is indicated for:

- Promoting resolution of acute clinical manifestations of mucocutaneous *Herpes simplex* virus infections in immunocompromised patients
- Treatment of severe first episode primary or non-primary genital herpes in immune competent patients
- Treatment of acute manifestations of *Varicella zoster* virus infection in immunocompromised patients

- 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 with shingles).
- Treatment of *Herpes simplex* encephalitis.

CONTRAINDICATIONS

Aciclovir IV infusion powder for reconstitution is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

PRECAUTIONS

Aciclovir intravenous infusion is intended for intravenous use only and should not be administered by any other route. Extravascular infusion can cause a severe local inflammation, possibly with tissue necrosis, because the infusion fluid has a pH of 10 – 11. The product should not be administered orally. Contact with the eyes and the unprotected skin must be avoided.

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 who are receiving concomitantly interferon or intrathecal methotrexate. Animal studies indicate that at high doses aciclovir is cytotoxic.

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. 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. The relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established.

Impaired renal function:

Warnings: In patients with impaired renal function the dosage must be adjusted in order to avoid accumulation of aciclovir in the body. For patients who are treated with high doses of aciclovir intravenous infusion, e.g. because of herpes encephalitis, special attention must be paid to the renal function, particularly in patients who are dehydrated or who have impaired renal function.
Aciclovir is eliminated by renal clearance. Therefore the dose must be reduced in patients with renal impairment. 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 ADVERSE EFFECTS).

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 100mg/mL, precipitation of aciclovir crystals in renal tubules, and the consequent renal tubular damage, can occur if the maximum solubility of free aciclovir (2.5mg/mL at 37°C in water) is exceeded.

Aciclovir intravenous 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 infusion.

Use in Pregnancy (Category B3)
Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450mg/kg/day po), rabbit (50mg/kg/day sc and iv) or rat (50mg/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 10mg/kg every 8 hours. In additional studies in which rats were given 3 sc doses of 100mg/kg aciclovir on gestation day 10, fetal abnormalities, such as head and tail anomalies, were reported (exposure was 5 fold human levels after 10mg/kg infusions).

There have been no adequate and well-controlled studies concerning the safety of aciclovir in pregnant women. Aciclovir should not be used during pregnancy unless the potential benefit to the patient justifies the potential risk 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 fetus/neonate has decreased. Pregnancy should be managed according to considerations normally applicable to patients with genital herpes.

Australian categorisation definition of **Category B3:** Drugs 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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation
Limited human data show that aciclovir does pass into breast milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

Paediatric Use
Adjustment of dosage is required for administration to children (see DOSAGE AND ADMINISTRATION).

Patients with Impaired Renal Function
Both in adults as well as in children the daily dose must be reduced by increasing the dosing intervals (see DOSAGE AND ADMINISTRATION). Furthermore, a new dose must be administered to patients who are undergoing haemodialysis after every haemodialysis.

Mutagenicity
Aciclovir was clastogenic in Chinese hamster cells *in vivo*, at exposure levels also causing nephrotoxicity (500 & 100mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100mg/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 result of these mutagenicity tests *in vitro* and *in vivo* suggests 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 of tumourogenicity 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 aciclovir on human fertility. The results of studies in animals indicate that aciclovir should have no effect on fertility in man at therapeutic doses.

INTERACTIONS WITH OTHER MEDICINES

Aciclovir is eliminated primarily unchanged in the urine via renal tubular secretion. Any medicines administered concurrently that compete with this mechanism or affect renal physiology may increase aciclovir plasma concentration. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance.

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 drugs or are receiving concomitantly interferon or intrathecal methotrexate (See **PRECAUTIONS**).

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 greater than or equal to 1/10, common greater than or equal to 1/100 and < 1/10, uncommon greater than or equal to 1/1,000 and < 1/100, rare greater than or equal to 1/10,000 and < 1/1,000, very rare < 1/10,000.

Blood and lymphatic system disorders
Uncommon: decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

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.

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 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.

Renal pain may be associated with renal failure.

Liver
Very rare: hepatitis and jaundice.

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 Infusion has been inadvertently infused into extracellular tissues.

Others:
Uncommon: diaphoresis, haematuria, hypotension and headache.

DOSAGE AND ADMINISTRATION (see INDICATIONS)

Indication	**Immune Status**	**Dosage**
Herpes simplex infection	Normal or Immunocompromised	5mg/kg every 8 hours
Very severe *Herpes zoster* infection (shingles)	Normal	5mg/kg every 8 hours
Varicella zoster infection	Immunocompromised	10mg/kg every 8 hours
Herpes simplex encephalitis	Normal or Immunocompromised	10mg/kg every 8 hours

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

Patients with Impaired Renal Function
Both in adults as well as in children the daily dose must be reduced by increasing the dosing intervals (see table below).

Creatinine clearance	Original Dosing schedule	Adjusted dosing schedule
25 - 50mL/minute	5mg/kg, every 8 hours 10mg/kg, every 8 hours	5mg/kg, every 12 hours 10mg/kg, every 12 hours
10 - 25mL/minute	5mg/kg, every 8 hours 10mg/kg, every 8 hours	5mg/kg, every 24 hours 10mg/kg, every 24 hours
0 - 10mL/minute	5mg/kg, every 8 hours 10mg/kg, every 8 hours	2.5mg/kg, every 24 hours 5mg/kg, every 24 hours

Dosage in Children
The dosage of aciclovir intravenous infusion in children aged 1-12 years should be calculated on the basis of the body surface area.

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

Immunocompromised children in this age group with *Varicella zoster* virus infections or with *Herpes simplex* encephalitis should be given Aciclovir Sandoz infusion in doses of 500mg per square metre of body surface area (equivalent to 10mg/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 in this group. As creatinine clearance is often low in the elderly, consideration should be given to using a reduced dose in these patients. In the case of impaired renal function the dose must be reduced in accordance with the above table.

Duration of Therapy
The duration of the treatment for patients with *Herpes simplex* encephalitis is at least 10 days. The duration of treatment in patients with *Herpes simplex* infections or patients with *Herpes zoster* infection is usually 5 to 7 days.

Administration
Every dose should be administered by slow intravenous infusion over a one hour period.
The preparation of the infusion fluid must be performed in two steps, reconstitution and dilution. Every vial of 250mg should be reconstituted by adding either 10mL of Water for Injections or 10mL of 0.9% w/v Sodium Chloride IV infusion. Every vial of 500mg should be reconstituted by adding either 20mL of Water for Injections or 20mL of 0.9% w/v Sodium Chloride IV infusion. The solvent should be at room temperature (15°C to 25°C). In this way an IV stock solution containing 25mg/mL of aciclovir is obtained.

Aciclovir Sandoz IV Infusion (powder for injection) can be reconstituted for direct intravenous injection over an hour by means of an infusion pump or can be further diluted for administration by infusion. **The product should not be administered as a bolus injection.**

The preparation of the solution for intravenous infusion is performed by diluting the aciclovir 25mg/mL stock solution with one of the following infusion fluids:
Sodium chloride 0.9% w/v
Sodium chloride 0.45% w/v and glucose 2.5% w/v
Sodium chloride 0.18% w/v and glucose 4% w/v
Glucose 5% w/v
Ringer lactate (Hartmann's solution)

The final aciclovir concentration in the infusion fluid should not exceed 5mg/mL.

The product is preservative-free. Reconstitution and dilution should be carried out immediately before use. For use in one patient and on one occasion only. Unused IV solutions must be destroyed as should solutions which preceding or during infusion opacificate or crystallise. The IV solution should not be refrigerated as this causes precipitation and crystallisation that is difficult to re-disperse.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on the management of overdose.

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 medicine.

PRESENTATION AND STORAGE CONDITIONS

Colourless 20mL glass vials, closed with a bromobutyl rubber stopper. Stoppers fixed into position with aluminium flip cap.

Store the dry powder below 25°C in original product packaging. The product should be used immediately after reconstitution or dilution.

POISONS SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
19 Harris Street
Pyrmont NSW 2009
Australia
Tel: 1800 634 500

DATE OF FIRST INCUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 30/08/2000

Date of last amendment: 27 June 2012