AUSTRALIAN PRODUCT INFORMATION – ACICLOVIR INTRAVENOUS INFUSION (ACICLOVIR)

1. NAME OF THE MEDICINE

Aciclovir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aciclovir Intravenous Infusion contains aciclovir. The solutions are available as either 250 mg in 10 mL or 500 mg in 20 mL.

It does not contain preservatives.

3. PHARMACEUTICAL FORM

Solution for injection.

Aciclovir Intravenous Infusion is an isotonic, sterile, clear, colourless to pale yellow solution in a ready-to use, single dose presentation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir Intravenous Infusion is indicated for the purpose of:

- 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 immunocompetent patients.
- Treatment of acute manifestations of *Varicella zoster* virus infection in immunocompromised patients.
- Treatment of *Herpes zoster* (shingles) in immunocompetent 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 immunocompetent patients with shingles.
- Treatment of *Herpes simplex* encephalitis.

4.2 Dose and method of administration

Dosage

Indications	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**.

Dosage adjustment

Impaired renal function:

Aciclovir Intravenous Infusion should be administered with caution since the drug is excreted by the kidneys. The following modifications in dosage are suggested:

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

Children:

The dose of Aciclovir 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 Aciclovir Intravenous Infusion doses of 250mg/m^2 body surface area (equivalent of 5mg/kg in adults).

Immunocompromised children in this age group with *Varicella zoster* virus infection or with *Herpes simplex* encephalitis should be given Aciclovir Intravenous Infusion in doses of 500mg/m^2 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.

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 Aciclovir 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.

Method of administration

Aciclovir Intravenous Infusion 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 25mg aciclovir per mL is used.

For intravenous infusion the dosage required should be added to and mixed with at least 50mL to 100mL of infusion solution (listed below). A maximum of 250mg of aciclovir may be added to 50mL of infusion solution and a maximum of 500mg of aciclovir may be added to 100mL of infusion solution. After addition of Aciclovir Intravenous Infusion the mixture should be shaken to ensure thorough mixing. Aciclovir Intravenous Infusion when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Aciclovir Intravenous Infusion is known to be compatible with the following infusion fluids and stable for up to 24 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 Dextrose (4% w/v) Intravenous Infusion BP, Sodium Chloride (0.45% w/v) and Dextrose (2.5% w/v) Intravenous Infusion BP, Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution).

Aciclovir Intravenous Infusion contains no preservative. 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.

4.3 Contraindications

Hypersensitivity to aciclovir or valaciclovir.

4.4 Special warnings and precautions for use

Aciclovir Intravenous Infusion is intended for intravenous infusion only and should not be used by any other route. 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 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 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 the 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 renal impairment

The dose of aciclovir intravenous infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body.

In patients receiving aciclovir 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.

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

Paediatric use

No data available

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

Aciclovir is eliminated primarily unchanged in the urine via renal tubular secretion. Any drugs 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 drugs that 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 aciclovir with drugs that 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 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 Section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

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.

Use in pregnancy – Pregnancy Category B3

Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450mg/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 1 hour infusions of 10 mg/kg every 8 hours. In additional studies in which rats were given 3 subcutaneously 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 10 mg/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 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 the fetus/neonate has decreased. Pregnancy should be managed according to consideration normally applicable to patients with genital herpes.

Use in lactation

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

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable 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. The risk of renal damage is increased by bolus injection, dehydration, concomitant use of other nephrotoxic drugs and pre-existing renal disease. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one hour period.

Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with aciclovir intravenous infusion usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure can occur in rare cases.

Hypersensitivity and Skin: Rashes including photosensitivity, urticaria, pruritis, fevers and rarely dyspnoea, angioedema and anaphylaxis.

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when aciclovir intravenous infusion has been inadvertently infused into extravascular tissues.

Neurological: Approximately 1% of patients receiving aciclovir have manifested reversible neurological reactions characterised by one or more of the following: lethargy, obtundation, tremors, confusion, hallucinations, agitation, somnolence, psychosis, convulsions and coma.

Haematological: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Gastrointestinal: Nausea and vomiting.

Liver: Reversible increases in bilirubin and liver-related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Others: Less frequent adverse effects include diaphoresis, haematuria, hypotension and headache.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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 drug.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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 kinases 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.

Clinical trials

No data available

5.2 Pharmacokinetic properties

In adults the terminal plasma half-life of aciclovir after intravenous administration 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-carboxy-methoxymethylguanine 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 5mg/kg or 10mg/kg were 9.8 ± 2.6 SD and 20.7 ± 10.2 SD µg/mL respectively. The trough plasma concentrations (C_{ss}min) were 0.7 ± 0.3 SD and 2.0 ± 0.1 SD µg/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 was found to be 19.5 ± 5.9 SD 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%).

5.3 Preclinical safety data

Genotoxicity

Mutagenicity:

Aciclovir was clastogenic in Chinese hamster cells *in vivo*, at high exposure levels also causing nephrotoxicity (500 and 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 tumourogenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (for isotonicity)

Water for Injections

Sodium hydroxide

Hydrochloric acid

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date (month/year) is stated on the package after the word expiry.

The product will be suitable for use for up to nine months after the foil sachet has been opened.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate.

6.5 Nature and contents of container

AUST R 66116 Aciclovir Intravenous Infusion 250mg in 10mL (sterile) ampoule (5)

AUST R 66117 Aciclovir Intravenous Infusion 500mg in 20mL (sterile) ampoule (6)

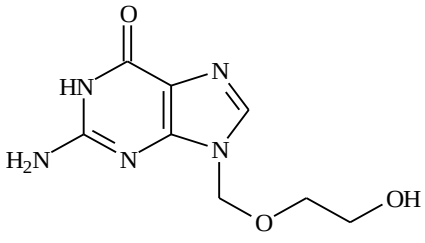
6.6 Special precautions for disposal

6.7 Physicochemical properties

Aciclovir is a synthetic acyclic purine nucleoside analogue. Its chemical name is 2-amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6H-purin-6-one. It is a white or almost white crystalline powder.

The structural formula is represented below.

Chemical structure



Molecular Formula: $C_8H_{11}N_5O_3$

Molecular Weight: 225.2

CAS number

59277-89-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Australia S4.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

3 September 1998.

10. DATE OF REVISION

30 September 2019

Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form.
2; 3; 4; 5; 6; & 8	Editorial
3	Dose form added
6.1	Excipients added
8	Sponsor details updated