AUSTRALIAN PRODUCT INFORMATION

ACICLOVIR VIATRIS

(Aciclovir (as sodium dihydrate)) powder for injection

1 NAME OF THE MEDICINE

Aciclovir sodium dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACICLOVIR VIATRIS 250 mg Powder for Injection contains aciclovir sodium dihydrate 314.4 mg, as the active ingredient equivalent to 250 mg aciclovir per vial.

ACICLOVIR VIATRIS 500 mg Powder for Injection contains aciclovir sodium dihydrate 628.8 mg, as the active ingredient equivalent to 500 mg aciclovir per vial.

Excipients with known effect: none

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ACICLOVIR VIATRIS 250 mg Powder for Injection is white to off-white lyophilized powder or cake.

ACICLOVIR VIATRIS 500 mg Powder for Injection is white to off-white lyophilized powder or cake.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ACICLOVIR VIATRIS (aciclovir sodium dihydrate) 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Rapid or bolus intravenous and intramuscular or subcutaneous injection of aciclovir must be avoided (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Method of Administration below).

Dosage

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

In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained. Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

Dosage Adjustment

Renal Impairment

In patients with renal impairment, Aciclovir Intravenous Infusion should be administered with caution since the drug is excreted by the kidneys. 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
25-50 mL/minute	5 mg/kg, every 8 hours 10 mg/kg, every 8 hours	5 mg/kg, every 12 hours 10 mg/kg, every 12 hours
10-25 mL/minute	5 mg/kg, every 8 hours 10 mg/kg, every 8 hours	5 mg/kg, every 24 hours 10 mg/kg, every 24 hours
0-10 mL/minute	5 mg/kg, every 8 hours 10 mg/kg, every 8 hours	2.5 mg/kg, every 24 hours and after dialysis 5 mg/kg, every 24 hours and after dialysis

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 Sodium infusion in doses of 250 mg per square metre of body surface area (equivalent to 5 mg/kg in adults) every 8 hours if renal function is not impaired.

Immunocompromised children in this age group with *Varicella zoster* virus infections or with *Herpes simplex* encephalitis should be given Aciclovir Sodium infusion in doses of 500 mg per square metre of body surface area (equivalent to 10 mg/kg in adults) every 8 hours if renal function is not impaired.

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. However, as creatinine clearance is often low in the elderly special attention should be given to using a reduced dose in these patients. It is recommended that the state of hydration and the creatinine clearance should be evaluated before the administration of high dosages of aciclovir, especially in elderly people, who may have reduced renal function despite a normal serum creatinine concentration.

Adequate hydration should be maintained.

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.

Method of Administration

Every dose should be administered by slow intravenous infusion over a period of at least one hour to avoid renal tubular damage (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The preparation of the infusion fluid must be performed in two steps, reconstitution and dilution. Every vial of 250 mg should be reconstituted by adding either 10 mL of Water for Injections or 10 mL of 0.9% w/v Sodium Chloride IV infusion. Every vial of 500 mg should be reconstituted by adding either 20 mL of Water for Injections or 20 mL 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 25 mg/mL of aciclovir is obtained.

ACICLOVIR VIATRIS powder for injection can be reconstituted for direct intravenous injection over an hour by means of a controlled rate infusion pump or can be further diluted for administration by infusion. **The product should not be administered as a bolus injection.**

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

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 5 mg/mL.

The product is preservative-free. Reconstitution and dilution should be carried out immediately before use. Once reconstituted, the IV solution may only be used in one patient and on one occasion only. Any unused IV solutions must be disposed. Solutions that crystallise or become opaque before or during infusion cannot be used and should be disposed. The IV solution should not be refrigerated as this causes precipitation and crystallisation that is difficult to re-disperse.

4.3 CONTRAINDICATIONS

Aciclovir IV infusion powder for reconstitution is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir or any component of aciclovir intravenous infusion preparation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Infusion Time and Patient Hydration

The peak plasma levels of aciclovir and the state of hydration of the patient are believed to be related to rapid increases in blood urea and creatinine levels. To avoid this effect and precipitation of aciclovir in the kidney, slow infusion of aciclovir must be given over a period of at least one hour. 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 37ºC 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.

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 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Thrombotic Thrombocytopenic Purpura/Haemolytic Uraemic Syndrome

Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, which has resulted in death, has occurred in immunocompromised patients receiving aciclovir therapy.

Resistant HSV Strains

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.

Prolonged or repeated courses of aciclovir in severely immunocompromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment.

Use in Renal Impairment

Aciclovir is eliminated by renal clearance, therefore in patients with impaired renal function the dosage must be adjusted in order to avoid accumulation of aciclovir in the body (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). 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.

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.

Concomitant use of other nephrotoxic drugs, pre-existing renal disease and dehydration increase the risk of further renal impairment by aciclovir. Care is required if administering intravenous aciclovir with other nephrotoxic drugs.

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

Use in the Elderly

Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment must be considered in this group of patients (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Elderly patients 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.

Paediatric Use

Adjustment of dosage is required for administration to children (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 active 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. 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. ciclosporin, tacrolimus). There are reports of additive nephrotoxicity when both aciclovir and ciclosporin are administered concomitantly.

Lithium: If lithium is administered concurrently with high dose intravenous aciclovir, the lithium serum concentration should be closely monitored because of the risk of lithium toxicity.

Theophylline: An experimental study on five male subjects indicated that concomitant therapy with aciclovir increases AUC of totally administered theophylline by approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

When aciclovir is administered concomitantly with theophylline, close monitoring of theophylline concentrations and possible theophylline dose reduction is recommended. A study has shown that when theophylline was given as single 320 mg doses before and with the sixth dose of aciclovir 800 mg five times daily for 2 days, the AUC of theophylline was increased by 45% (from 189.9 to 274.9 micrograms.h/mL) and the total body clearance was reduced by 30%.

Diuretics: 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.

Zidovudine: In most patients receiving zidovudine no significant overall increase in toxicity was associated with the addition of aciclovir. There is one published report of profound lethargy associated with concomitant use of aciclovir and zidovudine. 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. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. In a reproductive toxicity study in mice administered aciclovir at doses up to 450 mg/kg/day orally, no effects on fertility were observed.

Use in Pregnancy - Category B3

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.

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, fetal abnormalities, such as head and tail anomalies, were reported (exposure was 5 fold human levels after 10 mg/kg infusions). The clinical relevance of these findings is uncertain.

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.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an 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.

Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

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 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of the medicinal product on the ability to drive or use machines has not been systematically evaluated. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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).
Very rare: neutropenia

Immune system disorders

Very rare: anaphylaxis.

Psychiatric and nervous system disorders

Very rare: headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, encephalopathy, hallucinations, psychotic symptoms, convulsions, somnolence, coma[$], lethargy, paraesthesia and reversible psychiatric effect.

[$]The events are usually reversible and usually reported in patients with renal impairment or with other predisposing factors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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*
Very rare: renal impairment, acute renal failure[+] and renal pain[§]

*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, when administered intravenously 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.

[§]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[¥].

[¥]Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when Aciclovir Infusion has been inadvertently infused into extracellular tissues. In case of high doses thirst has been reported in patients who had been treated previously with aciclovir.

The following lists the incidence of effects is based on clinical studies in patients who received aciclovir:

Body as a whole: local inflammation at injection site (approximately 9%), fever (≤1%), headache (≤1%).

Cardiovascular: injection site phlebitis (approximately 9%), hypotension (≤1%).

Gastrointestinal: nausea and vomiting (approximately 7%), anorexia (≤1%).

Genitourinary: abnormal urinalysis (characterised by an increase in formed elements in urine sediment) (≤1%), anuria (≤1%), dysuria (≤1%), haematuria (≤1%).

Haematological: anaemia (≤1%), neutropenia (≤1%), thrombocytopenia (≤1%).

Metabolic and nutritional: elevation of transaminases (1 to 2%), rapid increases in serum urea nitrogen and creatinine (5 to 10%)*, oedema, (≤1%), thirst (≤1%).

Nervous: encephalopathic changes characterised by one or more of the following: lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, and coma (approximately 1%), dizziness (≤1%).

Skin and appendages: hives (approximately 2%), itching (approximately 2%), rashes (approximately 2%), diaphoresis (≤1%).

**These increases 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.*

Other less frequent adverse effects reported in patients receiving therapy with aciclovir include:

Skin and subcutaneous disorders: diaphoresis, leukocytoclastic vasculitis, erythema multiforme

Renal and urinary disorders: haematuria

Vascular disorders: hypotension

Blood and lymphatic system disorders: haemolysis

In immunocompromised patients also: thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (sometimes fatal).

Hepatobiliary disorders: hyperbilirubinaemia.

Other reactions have been reported with a frequency of less than 1% in patients receiving aciclovir, but a causal relationship between aciclovir and the reaction could not be determined. These include:

Body as a whole: Chest pain, chills, ischaemia of digits.

Cardiovascular: Purpura fulminans.

Haematological: Haemoglobinemia, leukocytosis, neutrophilia, thrombocytosis.

Metabolic and nutritional: Hypokalemia.

Respiratory: Pulmonary oedema with cardiac tamponade.

Urogenital: Pressure on urination.

The following adverse reactions have been reported during clinical practice with aciclovir:

Body as a whole: Pain.

Haematological: Disseminated intravascular coagulation has also been noted.

Neurological: Delirium, psychosis.

Skin: Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Urogenital: Renal failure.

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

There is little experience concerning overdosage with aciclovir. Effects from overdosage may be expected to be similar in nature but more severe effects to those described under Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Overdosage has been reported following administration of bolus injections, or inappropriately high doses and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations of serum urea and creatinine, and subsequent renal failure. Neurological effects including lethargy, confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage.

Precipitation of aciclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In the even of overdosage, adequate hydration is essential to reduce the possibility of crystal formation in the urine. It is recommended that urine output is maintained at greater than 500 mL per gram of drug infused to prevent precipitation of aciclovir in the renal tubules. Patients should be observed closely for signs of toxicity.

Aciclovir can be removed from the circulation by haemodialysis: a 6 hour haemodialysis results in a 60% decrease in plasma aciclovir concentration.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Aciclovir sodium is a synthetic acyclic purine nucleoside analogue.

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.

Animal studies indicate that at high doses aciclovir is cytotoxic.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Mean steady state peak plasma concentrations (C_{SS}max) following a one hour infusion of 5 mg/kg or 10 mg/kg of aciclovir were about 9.8 ± 2.6 S.D and 20.7 ± 10.2 S.D mg/mL, respectively. The trough plasma concentrations (C_{SS}min) were about 0.7 ± 0.3 S.D and 2.0 ± 0.1 S.D. mg/mL, respectively. In children over 1 year of age similar mean peak (C_{SS}max) and trough (C_{SS}max) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg.

Distribution

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

Metabolism

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

Excretion

The terminal plasma half-life of aciclovir in adults with normal renal function after intravenous administration is approximately 2.9 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.

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 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

There are no excipients in this product.

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 can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container. The product should be used immediately after reconstitution or dilution.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Type I Glass Clear vial

ACICLOVIR VIATRIS 250 mg - 10 mL glass vials, available in packs of 5 vials.

ACICLOVIR VIATRIS 500 mg - 20 mL glass vials, available in packs of 5 vials.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 233648 – ACICLOVIR VIATRIS aciclovir (as sodium) 500 mg powder for injection vial

AUST R 233649 - ACICLOVIR VIATRIS aciclovir (as sodium) 250 mg powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

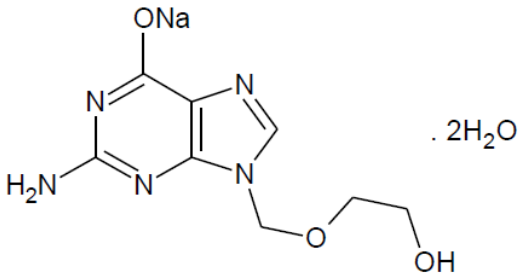
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : 9-[(2-hydroxyethoxy)methyl]guanine monosodium salt, dihydrate

Structural formula :



Molecular formula : $C_8H_{10}N_5NaO_3.2H_2O$ Molecular weight : 283.22

Aciclovir sodium dihydrate is a white to almost white powder, freely soluble in water, slightly soluble in methanol.

CAS Number

69657-51-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

28/05/2021

10 DATE OF REVISION

14/02/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Editorial Changes
4.2	Added precautionary text on rapid or bolus intravenous and intramuscular or subcutaneous injection; precautionary text on obese patients plasma

	concentrations; reiterated dosing interval in children if renal function is not impaired and precautionary text on dosage in the elderly added regarding adequate hydration maintenance. Method of Administration: added information of dilution with Glucose.
4.4	Added precautionary text on peak plasma levels and state of hydration. Added Thrombotic Thrombocytopenic Purpura/Haemolytic Uraemic Syndrome. Use in Renal Impairment: added renal clearance, risk of generally reversible neurological side effects, adequate hydration should be maintained, care with concomitant use of other nephrotoxic drugs. Use in the Elderly: added precautionary text on dose adjustment and neurological side effects.
4.5	Added information on dosage adjustment with concomitant use with probenecid and cimetidine; interactions with lithium and theophylline; active ingredient names amended; reports about interaction with Ciclosporin and Zidovudine.
4.6	Effects on Fertility: added information on animal studies and a study in men. Use in Pregnancy: added clarification on the animal study and information on post-marketing pregnancy registry.
4.7	Added precautionary text on refraining from driving or using machines.
4.8	Updated adverse effects and frequencies: MedDRA System Organ Classes (SOC) updated throughout and effects relocated where required.
4.9	Added precautionary text regarding observation for toxicity signs. Updated treatment regarding precipitation of aciclovir in renal tubules, urine output and haemodialysis.
5.1	Added statement: aciclovir sodium is a synthetic acyclic purine nucleoside analogue.
5.2	Updated data of absorption and excretion.

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