

NEW ZEALAND DATA SHEET

1 ACICLOVIR-BAXTER (25mg/mL, solution for infusion)

ACICLOVIR-BAXTER 25mg/mL solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

ACICLOVIR-BAXTER solution for infusion contains aciclovir sodium equivalent to 25mg/mL of aciclovir in Water for Injections.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

ACICLOVIR-BAXTER solution for infusion is a clear colourless or almost colourless sterile solution.

ACICLOVIR-BAXTER solution for infusion has a pH of approximately 11.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACICLOVIR-BAXTER solution for intravenous infusion is indicated for:

- 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 (see prescribing information for oral aciclovir) mortality and the incidence of viraemia are also reduced.

4.2 Dose and method of administration

Dosage

Dosage in adults

Patients with herpes simplex (except herpes encephalitis) or varicella zoster infections should be given **ACICLOVIR-BAXTER** in doses of 5mg/kg bodyweight every 8 hours.

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

For prophylaxis of CMV infection in bone marrow transplant recipients 500mg/m² **ACICLOVIR-BAXTER** 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 up to 30 days after transplant.

Dosage in children

The dose of **ACICLOVIR-BAXTER** for children aged between 3 months and 12 years is calculated on the basis of body surface area.

NEW ZEALAND DATA SHEET

Children with herpes simplex (except herpes encephalitis) or varicella zoster infections should be given **ACICLOVIR-BAXTER** in doses of 250mg/m² body surface area every 8 hours.

In immune-compromised children with varicella zoster infections or children with herpes encephalitis, **ACICLOVIR-BAXTER** should be given in doses of 500mg/m² 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.

Dosage in neonates

The dosage of **ACICLOVIR-BAXTER** in neonates is calculated on the basis of bodyweight.

Neonates with herpes simplex infections should be given **ACICLOVIR-BAXTER** in doses of 10mg/kg bodyweight every 8 hours.

Dosage in the elderly

In the elderly total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Dosage in renal impairment

Caution is advised when administering **ACICLOVIR-BAXTER** to patients with impaired renal function. The following adjustments in dosage are suggested.

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

A course of treatment with **ACICLOVIR-BAXTER** 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 **ACICLOVIR-BAXTER** is determined by the duration of the period at risk.

Administration

The required dose of **ACICLOVIR-BAXTER** should be administered by slow intravenous infusion over a one-hour period.

ACICLOVIR-BAXTER may be administered by a controlled-rate infusion pump.

NEW ZEALAND DATA SHEET

Alternatively, **ACICLOVIR-BAXTER** may be further diluted to give an aciclovir concentration of not greater than 5mg/mL (0.5%w/v) for administration by infusion. Add the required volume of **ACICLOVIR-BAXTER** 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 4mL **ACICLOVIR-BAXTER** (100mg aciclovir) is added to 20mL of infusion fluid.

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

When diluted in accordance with the recommended schedules, **ACICLOVIR-BAXTER** is compatible with the following infusion fluids and is 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-BAXTER 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, 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.

4.3 Contraindications

ACICLOVIR-BAXTER is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

4.4 Special warnings and precautions for use

The dose of **ACICLOVIR-BAXTER** must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body (see section 4.2).

In patients receiving **ACICLOVIR-BAXTER** 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.

ACICLOVIR-BAXTER has a pH of approximately 11 and should not be administered by mouth.

4.5 Interaction with other medicines and other forms of interaction

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 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.

NEW ZEALAND DATA SHEET

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 co-administered.

Care is also required (with monitoring for changes in renal function) if administering intravenous acyclovir with medicines which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation

Fertility

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. Two generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

There is no experience of the effect of **ACICLOVIR-BAXTER** on human fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

Pregnancy (Category B3)

Limited data are available on the use of aciclovir during pregnancy.

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

Breast-feeding

Following oral administration of 200mg 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 aciclovir is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Gastrointestinal

Nausea and vomiting have been reported.

Haematological

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

Hypersensitivity and skin

Rashes including photosensitivity, urticaria, pruritus, fevers and rarely dyspnoea, angioedema and anaphylaxis. Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when aciclovir intravenous infusions have been inadvertently infused into extravascular tissues.

Kidney

Rapid increases in blood urea and creatinine levels may occasionally occur in patients given aciclovir intravenous infusions. This is believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect, the medicine should not be given as an intravenous bolus injection but by slow infusion over a one-hour period.

NEW ZEALAND DATA SHEET

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

Liver

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

Neurological

Reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with aciclovir intravenous infusion therapy, usually in medically complicated cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphv.otago.ac.nz/reporting/>

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. 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.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antiinfectives for systemic use, Antivirals for systemic use, Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors.

ATC code

J05AB01.

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.

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted 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.

NEW ZEALAND DATA SHEET

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 TK; however, strains with altered viral TK 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.

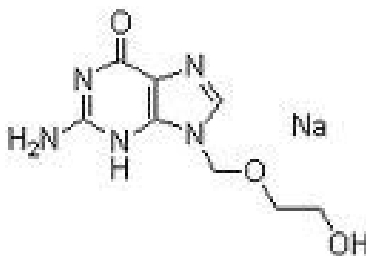
Further information

Aciclovir sodium is a synthetic acyclic purine nucleoside analogue.

Its chemical name is 9- [(2-hydroxyethoxy)-methyl] guanine sodium.

It is a white crystalline powder with a molecular weight (MW) of 247.2.

The chemical structure of aciclovir sodium (CAS 69657-51-8) is:



Each mL of **ACICLOVIR-BAXTER** contains 2.67mg of sodium.

5.2 Pharmacokinetic properties

In adults, the terminal plasma half-life of aciclovir is about 2.9 hours. Most of the medicine is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug. 9-carboxymethoxy- methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10 - 15% of the dose excreted in the urine. When aciclovir is given one hour after 1 gram of probenecid the terminal half-life and the area under the plasma concentration time curve is extended by 18% and 40% respectively.

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5mg/kg, 5mg/kg, 10mg/kg and 15mg/kg were 22.7microM (5.1mcg/mL), 43.6microM (9.8mcg/mL), 92microM (20.7mcg/mL) and 105microM (23.6mcg/mL), respectively. The corresponding trough levels (C_{ssmin}) 7 hours later were 2.2microM (0.5mcg/mL), 3.1microM (0.7mcg/mL), 10.2microM (2.3mcg/mL) and 8.8microM (2.0mcg/mL), respectively. In children over 1 year of age similar mean peak (C_{ssmax}) and trough (C_{ssmin}) levels were observed when a dose of 250mg/m² was substituted for 5mg/kg and a dose of 500mg/m² was substituted for 10mg/kg. In neonates (0 - 3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours the C_{ssmax} was found to be 61.2microM (13.8mcg/mL) and the C_{ssmin} to be 10.1microM (2.3mcg/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.

NEW ZEALAND DATA SHEET

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.

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

5.3 Preclinical safety data

Genotoxicity

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir is unlikely to pose a genetic risk to man.

Carcinogenicity

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Reproductive and developmental toxicity

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium hydroxide - q.s. to pH
Nitrogen
Sodium hydroxide
Water for injection.

6.2 Incompatibilities

See section 4.2.

6.3 Shelf life

24 months from date of manufacture.

6.4 Special precautions for storage

Store below 25 °C. Do not refrigerate. Protect from light.

6.5 Nature and contents of container

ACICLOVIR-BAXTER is available in vials containing either 10mL or 20mL of product.

Package quantities

ACICLOVIR-BAXTER is available as:

- 250mg/10mL in packs of 5 vials
- 500mg/20mL in packs of 5 vials

NEW ZEALAND DATA SHEET

6.6 Special precautions for disposal and other handling

Instructions for use/handling

ACICLOVIR-BAXTER 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.

ACICLOVIR-BAXTER should not be refrigerated as this causes precipitation of crystals. These crystals usually do not redissolve when solution temperature is brought back to room temperature.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

ACICLOVIR-BAXTER is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
20 November 2014.

10 DATE OF REVISION OF THE TEXT

11 September 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
ALL	Consistent use of capitals, trade name, units, references to other sections, spacing, headings.
2	Amount of aciclovir salt moved from section 3 to 2.
3	Pack size information moved to section 6.5.
5.3	Paragraphs rearranged.
6.5	Repeated information on pH removed.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.