1 PRODUCT NAME

ACICLOVIR-BAXTER 25mg/mL solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 the treatment of *Herpes simplex* infections, including in the neonate.
ACICLOVIR-BAXTER solution for intravenous infusion is indicated for the prophylaxis of *Herpes simplex* infections in immune-compromised patients.
ACICLOVIR-BAXTER solution for intravenous infusion is indicated in the treatment of *Varicella zoster* infections.
ACICLOVIR-BAXTER solution for intravenous infusion is indicated for 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 in adults

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given ACICLOVIR-BAXTER in doses of 5 mg/kg bodyweight every 8 hours provided renal function is not impaired.

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

For prophylaxis of CMV infection in bone marrow transplant recipients 500 mg/m^2 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.

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 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.

Children with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given ACICLOVIR-BAXTER in doses of 250mg per square meter body surface area every 8 hours if renal function is not impaired.

In immune-compromised children with *Varicella zoster* infections or children with herpes encephalitis, ACICLOVIR-BAXTER should be given in doses of 500 mg per square meter 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 10 mg/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.

Adequate hydration should be maintained.

Dosage in Renal Impairment
Caution is advised when administering ACICLOVIR-BAXTER to patients with impaired renal function. Adequate hydration should be maintained. The following adjustments in dosage are suggested.

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

Method of Administration
The required dose of ACICLOVIR-BAXTER should be administered by slow intravenous infusion over a one-hour period and adequate hydration should be established.

From the calculated dose, determine the appropriate number of vials to be used. To reconstitute each vial, add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.

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

Alternatively, ACICLOVIR-BAXTER may be further diluted to give an aciclovir concentration of not greater than 5 mg/mL (0.5%w/v) for administration by infusion.

Add the required volume of 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 4 mL ACICLOVIR-BAXTER (100 mg aciclovir) added to 20 mL of infusion fluid.

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

When diluted in accordance with the recommended schedules, ACICLOVIR-BAXTER is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15°C to 25°C).
- Sodium Chloride Intravenous Infusion BP (0.45% and 0.9% w/v);
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP;
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion BP;
- Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution).

ACICLOVIR-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, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.

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

4.3 Contraindications

ACICLOVIR-BAXTER is contraindicated in patients known to be previously hypersensitive to aciclovir, valaciclovir or any of the excipients.

4.4 Special warnings and precautions for use

For intravenous infusion only.

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

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 infustions of aciclovir must ve given over a period of at least one hour.

Resistant HSV strains

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 patients with renal impairment

Aciclovir is eliminated by renal clearance, therefore 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).

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-BAXTER usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the medicine. Progression to acute renal failure, however, can occur in exceptional 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-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.

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). 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.

4.5 Interaction with other medicines and other forms of interaction

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.

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 aciclovir with medicines which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

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: 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 the theophylline was increased by 45% (from 189.9 to 274.9 micrograms.h/ml) and the total body clearance was reduced by 30%.

4.6 Fertility, pregnancy and lactation

Fertility

There is no experience of the effect of aciclovir on human female 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 upon 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. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

Pregnancy - Pregnancy Category B3

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

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. 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, fetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

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

Lactation
Following oral administration of 200 mg 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 0.3 mg/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 machinery
The effect 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 Undesirable effects
The frequency categories associated with adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

The following convention has been used for the classification of undesirable effects in terms of frequency: Very common ≥ 1/10, common ≥ 1/100 and < 1/10, uncommon ≥ 1/1,000 and <1/100, rare ≥1/10,000 and < 1/1,000, very rare < 1/10,000. Not known (cannot be estimated from available data).

MedDRA System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10	Uncommon ≥ 1/1,000 and < 1/100	Rare ≥ 1/10,000 and < 1/1,000	Very rare < 1/10,000
Blood and lymphatic system disorders			decreases in haematological indices (anaemia, thrombocytopenia, leukopenia).		neutropenia
Immune system disorders					anaphylaxis
Psychiatric and nervous system disorders					headache, dizziness agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma[$] Lethargy, paraesthesia, and reversible psychiatric effect

MedDRA System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10	Uncommon ≥ 1/1,000 and < 1/100	Rare ≥ 1/10,000 and < 1/1,000	Very rare < 1/10,000
Vascular disorders		phlebitis			dyspnoea
Respiratory, thoracic and mediastinal disorders		nausea, vomiting			diarrhoea, abdominal pain
Gastrointestinal disorders		reversible increases in liver-related enzymes			reversible increases in bilirubin, jaundice, hepatitis
Hepatobiliary disorders					
Skin and subcutaneous tissue disorders		pruritus, urticaria, rash (including photosensitivity)			angioedema
Renal and urinary disorders		increases in blood urea and creatinine*			renal impairment, acute renal failure+ and renal pain§
General disorders and administration site conditions					fatigue, fever, local inflammatory reactions¥, injection site necrosis, injection site extravasation

$The events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see section 4.4).

*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.

+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.

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

The following lists of 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 (characterized 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 thrombocytopenia purpra/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.

Haemotological: 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.

Haemotological: 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including lethargy, confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage. In the event of overdose, adequate hydration is essential to reduce the possibility of crystal formation in the urine. Patients should be observed closely for signs of toxicity. 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 0800 POISON (0800 764 766) .

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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.

5.2 Pharmacokinetic properties

Absorption

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 22.7 microM (5.1 mcg/mL), 43.6 microM (9.8 mcg/mL), 92 microM (20.7 mcg/mL) and 105 microM (23.6 mcg/mL), respectively. The corresponding trough levels (C_{ssmin}) 7 hours later were 2.2 microM (0.5 mcg/mL), 3.1 microM (0.7 mcg/mL), 10.2 microM (2.3 mcg/mL) and 8.8 microM (2.0 mcg/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 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

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.

Metabolism
9-carboxymethoxy- methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10-15% of the dose excreted in the urine.

Excretion
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. 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 neonates (0-3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C_{ssmax} was found to be 61.2 microM (13.8 mcg/mL) and the C_{ssmin} to be 10.1 microM (2.3 mcg/mL). The terminal plasma half life in these patients was 3.8 hours.

In the elderly total body clearance falls with increasing age, associated with decreases in creatinine clearance, although there is little change in the terminal plasma half life. 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.

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
15 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

6.6 Special cautions for disposal and other 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 to room temperature.

Any unused medicine 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 April 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Precautionary text on obese patients plasma concentrations added. Reiterated dosing interval in adults and children if renal function is not impaired. Precautionary text on Dosage in the elderly and those with renal impairment added regarding adequate hydration maintenance.
4.3	Added contraindication for use in patients with known hypersensitivity to any of the excipients
4.4	Added precautionary text on peak plasma levels and state of hydration; prolonged or repeated courses in severely immunocompromised patients; Use in renal impairment: renal clearance added, risk of generally reversible neurological side effects, care with concomitant use of other nephrotoxic drugs; Use in the elderly: precautionary text added.
4.5	Added interactions with lithium and theophylline; active ingredient name of ciclosporin amended.
4.6	Effects on fertility: Information added on animal studies and a study in men. Use in pregnancy: Added clarification on the animal study. Addition of information on post-marketing pregnancy registry.
4.7	Added precautionary text on refraining from driving or using machines.
4.8	AE table added with frequencies updated: MedDRA System Organ Classes (SOC) updated throughout and effects relocated where required. New adverse effects added: ataxia, dysarthria, diarrhoea, acute renal failure, acute renal failure, renal pain, neutropenia, headache, dizziness, tremor, encephalopathy, phlebitis, abdominal pain, injection site necrosis, injection site extravasation, lethargy, paraesthesia, and reversible psychiatric effect.
4.9	Adverse effect added: lethargy. Precautionary text regarding observation for toxicity signs added.
5.2	Editorial changes, addition of subheadings on Absorption, Distribution, Metabolism and Excretion. Addition of neonate pharmacokinetic data. Addition of elderly clearance data.
10	Date of last approval will be updated
2, 3 , 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2, 6.6, 8	Editorial Changes

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