

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Aciclovir Intravenous Infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Aciclovir Intravenous Infusion contains the equivalent of 25 mg/mL of aciclovir; the aciclovir is present as aciclovir sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for Infusion

DBL™ Aciclovir Intravenous Infusion is a clear colourless or almost colourless sterile solution.

DBL™ Aciclovir Intravenous Infusion has a pH of approximately 11.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DBL™ Aciclovir Intravenous Infusion is indicated for the treatment of Herpes simplex infections.

DBL™ Aciclovir Intravenous Infusion is indicated for the prophylaxis of Herpes simplex infections in immune-compromised patients.

DBL™ Aciclovir Intravenous Infusion is indicated in the treatment of Varicella zoster infections.

DBL™ Aciclovir Intravenous Infusion is indicated for the treatment of Herpes simplex infections in the neonate.

DBL™ Aciclovir Intravenous Infusion formulations are 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 DBL™ Aciclovir Intravenous Infusion in doses of 5 mg/kg bodyweight every 8 hours.

Immune-compromised patients with Varicella zoster infections or patients with herpes encephalitis should be given DBL™ Aciclovir Intravenous Infusion 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<sup>2</sup> aciclovir 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 DBL™ Aciclovir Intravenous Infusion 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 DBL™ Aciclovir Intravenous Infusion in doses of 250 mg per square metre body surface area every 8 hours.

In immune-compromised children with Varicella zoster infections or children with herpes encephalitis, DBL™ Aciclovir Intravenous Infusion should be given in doses of 500 mg per square metre 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 DBL™ Aciclovir Intravenous Infusion in neonates is calculated on the basis of bodyweight.

Neonates with Herpes simplex infections should be given DBL™ Aciclovir Intravenous Infusion 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.

### ***Dosage in Renal Impairment***

Caution is advised when administering DBL™ Aciclovir Intravenous Infusion to patients with impaired renal function. The following adjustments in dosage are suggested.

<b>Creatinine Clearance</b>	<b>Dosage</b>
25-50 mL/min	The dose recommended above (5 or 10 mg/kg bodyweight or 500 mg/m <sup>2</sup> ) should be given every 12 hours.
10-25 mL/min	The dose recommended above (5 or 10 mg/kg bodyweight or 500 mg/m <sup>2</sup> ) 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 <sup>2</sup> ) 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 <sup>2</sup> ) should be halved and administered every 24 hours and after dialysis.

A course of treatment with DBL™ Aciclovir Intravenous Infusion 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 DBL™ Aciclovir Intravenous Infusion is determined by the duration of the period at risk.

### **Method of Administration**

The required dose of DBL™ Aciclovir Intravenous Infusion should be administered by slow intravenous infusion over a one-hour period.

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.

After reconstitution DBL™ Aciclovir Intravenous Infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution 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 reconstituted solution 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 reconstituted solution (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 reconstituted solution) but a second bag must be used for doses between 500 and 1000 mg.

When diluted in accordance with the recommended schedules, DBL™ Aciclovir Intravenous Infusion 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).

DBL™ Aciclovir Intravenous Infusion 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**

DBL™ Aciclovir Intravenous Infusion is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

### **4.4 Special warnings and precautions for use**

The dose of DBL™ Aciclovir Intravenous Infusion 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 DBL™ 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.

Reconstituted DBL™ Aciclovir Intravenous Infusion has a pH of approximately 11.0 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.

In patients receiving intravenous aciclovir, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the

potential for increased plasma levels of one or both medicines or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the medicines are coadministered.

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

## **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 DBL™ Aciclovir Intravenous Infusion on human fertility. Aciclovir Tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

### **Pregnancy**

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.

### **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**

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 DBL™ Aciclovir Intravenous Infusion has been inadvertently infused into extravascular tissues.

*Kidney:* Rapid increases in blood urea and creatinine levels may occasionally occur in patients given Aciclovir Intravenous Infusion. 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.

Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with DBL™ Aciclovir Intravenous Infusion 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.

*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 DBL™ 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 continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.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 0800 POISON (0800 764766).

## **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

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 2.5 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<sup>2</sup> was substituted for 5 mg/kg and a dose of 500 mg/m<sup>2</sup> was substituted for 10 mg/kg. 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.

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**

- Sodium hydroxide
- Water for injection

### **6.2 Incompatibilities**

See section 4.2.

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Store below 25°C. Do not refrigerate.



## 6.5 Nature and contents of container

<b>Strength</b>	<b>Pack Size</b>
aciclovir 250 mg/10 mL	5s
aciclovir 500 mg/20 mL	5s

## 6.6 Special cautions for disposal and other handling

DBL™ 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.

## 7. MEDICINE SCHEDULE

Prescription Medicine.

## 8. SPONSOR

Pfizer New Zealand Limited

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## 9. DATE OF FIRST APPROVAL

25 Sep 1997

## 10. DATE OF REVISION OF THE TEXT

1 February 2019

### Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
All	Reformat to MedSafe Data Sheet guidance

