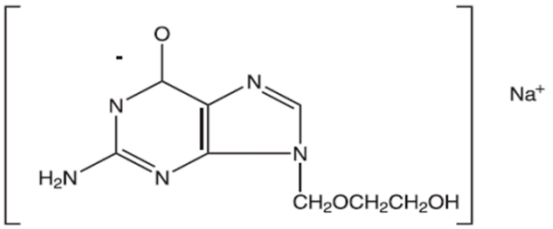
DBL™ Aciclovir Intravenous Infusion

Name of the Medicine

Aciclovir

The chemical structure of aciclovir sodium (CAS 69657-51-8) is shown below.



Description

Aciclovir sodium is a synthetic acyclic purine nucleoside analogue. Its chemical name is 9-[(2-hydroxyethoxy)-methyl] guanine sodium. Aciclovir sodium is a white crystalline powder with a molecular weight (MW) of 247.2.

DBL™ Aciclovir Intravenous Infusion is a clear colourless or almost colourless sterile solution containing the equivalent of 25 mg/mL of aciclovir in Water for Injections BP; the aciclovir is present as aciclovir sodium. Sodium hydroxide (4.65 mg/mL) is included in the formulation. DBL™ Aciclovir Intravenous Infusion has a pH of approximately 11.

Pharmacology

Microbiology

Aciclovir is an antiviral agent which is active *in vitro* against *Herpes simplex* (HSV) types I and II and *Varicella zoster* virus (VZV). However, the relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established. Aciclovir needs to be phosphorylated to the active compound aciclovir triphosphate, in order to become active against the virus. Such conversion is very limited in normal cells and in addition, cellular DNA polymerase is not very sensitive to the active compound. However in infected cells, HSV or VZV coded thymidine 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.

Pharmacokinetics

In adults, the terminal plasma half life of aciclovir after intravenous administration is about 2.9 hours. Approximately 60% of the drug is excreted unchanged by the kidney by glomerular filtration and tubular excretion. When aciclovir is given one hour after 1 gram of probenecid, the terminal half life and the area under the plasma concentration time curve are extended by 18% and 40% respectively. 9-carboxymethoxymethylguanine is the major metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

Mean steady state peak plasma concentrations (C^{SS}_{max}) following a one hour infusion of 5 mg/kg or 10 mg/kg were 9.8 ± 2.6 S.D. and 20.7 ± 10.2 S.D. microgram/mL respectively. The trough plasma concentrations (C^{SS}_{min}) were 0.7.± 0.3 S.D. and 2.0 ± 0.1 S.D. microgram/mL respectively. In children over 1 year of age, similar mean peak (C^{SS}_{max}) and trough (C^{SS}_{min}) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg. In children aged 0 to 3 months, the terminal plasma half life is approximately 4 hours. However, experience is insufficient at present to recommend therapy for this age group.

In patients with chronic renal failure, the mean terminal half-life was found to be 19.5 ± 5.9 S.D. hours. The mean aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

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

Indications

DBL™ Aciclovir Intravenous Infusion is indicated for the purpose of:

1. Promoting resolution of acute clinical manifestations of mucocutaneous *Herpes simplex* virus infections in immunocompromised patients.
2. Treatment of severe first episode primary or non-primary genital herpes in immune competent patients.
3. Treatment of acute manifestations of *Varicella zoster* virus infection in immunocompromised patients.
4. Treatment of shingles *(Varicella zoster* virus infection) 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.
5. Treatment of *Herpes simplex* encephalitis.

Contraindications

DBL™ Aciclovir Intravenous Infusion is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir or any component of the DBL™ Aciclovir Intravenous Infusion preparation.

Precautions

DBL™ Aciclovir Intravenous Infusion is intended for intravenous infusion only and should not be used by any other route.

DBL™ Aciclovir Intravenous Infusion has a pH of approximately 11.0 and should not be administered by mouth.

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

Infusions of aciclovir must be given over a period of at least one hour in order to avoid renal tubular damage. It should not be administered as a bolus injection. Although the aqueous solubility of aciclovir sodium (for infusion) exceeds 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 37°C in water) is exceeded. Aciclovir infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first few hours following infusion particular attention should be given to establish sufficient urine flow during that period. Concomitant use of other nephrotoxic drugs, pre-existing renal disease and dehydration increase the risk of further renal impairment by aciclovir.

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.

As aciclovir has been associated with reversible encephalopathic changes, it should be used with caution in patients with underlying neurological abnormalities, significant hypoxia or serious renal, hepatic or electrolyte abnormalities.

It should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitantly interferon or intrathecal methotrexate (see **Interactions with other**

medicines).

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

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 immune-compromised 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.

Use in renal impairment

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 **Dosage and Administration**).

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 drug. Progression to acute renal failure can occur in rare cases.

Carcinogenicity

Aciclovir was positive in one of two mouse cell transformation systems *in vitro*. Inoculation of the transformed cells into immune-suppressed mice resulted in tumours. These data are suggestive of an oncogenic potential. However, the validity of this type of study is unclear.

Lifetime oral dosing studies in mice and rats gave no evidence for oncogenicity, but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

Mutagenicity

Aciclovir was clastogenic in Chinese hamster cells *in vivo*, at exposure levels also causing nephrotoxicity (500 and 100 mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100 mg/kg) of aciclovir in rats. No activity was found in a dominant lethal study in mice or in 4 microbial assays. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells negative at 2 other loci in mouse lymphoma cells, and 3 loci in a Chinese hamster ovary cell line). The results of these mutagenicity tests *in vitro* and *in vivo* suggest that aciclovir is unlikely to pose a genetic threat to man at therapeutic dose levels.

Effects on fertility

There is no experience of the effect of aciclovir on human fertility. The results of studies in animals indicate that aciclovir should have no effect on fertility in man at therapeutic doses.

Use in pregnancy (Category B3†)

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, foetal abnormalities, such as head and tail anomalies, were reported (exposure was 5 fold human levels after 10 mg/kg infusions).

There have been no adequate and well controlled studies concerning the safety of aciclovir in pregnant women.

Aciclovir should not be used during pregnancy unless the potential benefit to the patient outweighs the

potential risk to the foetus.

If suppressive therapy is used in the perinatal period it should not be assumed that viral shedding has ceased, or that the risk to foetus/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 is excreted in human milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

Interactions with other medicines

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism or affect renal physiology may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance.

In patients receiving intravenous aciclovir, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered.

Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus). There are reports of additive nephrotoxicity when both aciclovir and cyclosporin are administered concomitantly.

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.

Interferon: see **Precautions**.

Methotrexate: see **Precautions.**

Adverse Effects

The following table of incidence of effects is based on clinical studies in patients who received aciclovir.

System	Estimated Overall Incidence >1%	≤1%
Body as a whole	Local inflammation at injection site (approximately 9%)	fever headache
Cardiovascular	Injection site phlebitis (approximately 9%)	hypotension
Gastrointestinal	Nausea and vomiting (approximately 7%)	anorexia
Genitourinary		abnormal urinalysis (characterised by an increase in formed elements in urine sediment) anuria dysuria haematuria

Haematological		anaemia neutropenia thrombocytopenia
Metabolic and nutritional	Elevation of transaminases (1 to 2%) Rapid increases in serum urea nitrogen and creatinine (5 to 10%)*	oedema thirst
Nervous		encephalopathic changes characterised by one or more of the following: lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, and coma (approximately 1%) dizziness
Skin and appendages	Hives (approximately 2%) Itching (approximately 2%) Rashes (approximately 2%)	diaphoresis

**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 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

Abdominal pain, 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

Anaphylaxis, fever, angioedema, pain.

Local necrosis and inflammation may occur due to extravasation at the site of injection.

†Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without the increase in the frequency of malformation or other direct harmful effects in 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 human

Gastrointestinal

Increases in liver related enzymes, nausea. Hepatitis and jaundice have been reported on very rare occasions.

Haematological

Decreases in haematological indices have been reported during clinical practice, leukopenia. Disseminated intravascular coagulation has also been noted.

Metabolic and nutritional

Elevated serum urea nitrogen and creatinine.

Neurological

Agitation, coma, confusion, convulsions, delirium, hallucinations, lethargy, obtundation, psychosis, somnolence and tremor.

Respiratory

Dyspnoea.

Skin

Rash (including photosensitivity), urticaria and pruritus. Stevens-Johnson syndrome and toxic epidermal necrolysis has also been reported.

Urogenital

Renal failure.

Dosage and Administration

Rapid or bolus intravenous and intramuscular or subcutaneous injection of aciclovir must be avoided (see **Precautions and Administration** below**).**

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 patients with renal impairment, aciclovir should be administered with caution since the drug is excreted by the kidneys. The following modifications in dosage are suggested:

Creatinine Clearance	Dosage
25 to 50 mL/min	The recommended dose (5 or 10 mg/kg) every 12 hours
10 to 25 mL/min	The recommended dose (5 or 10 mg/kg) every 24 hours

0 (anuric) to 10 mL/min	The recommended dose should be halved (2.5 or 5 mg/kg) every 24 hours and after dialysis

Dosage in children: The dose of aciclovir intravenous in children aged 1 to 12 years should be calculated on the basis of body surface area.

Children in this age group with *Herpes simplex* infections (except *Herpes simplex* encephalitis) or *Varicella zoster* infections should be given aciclovir intravenous doses of 250 mg per square metre body surface area (equivalent of 5 mg/kg in adults).

Immunocompromised children in this age group with *Varicella zoster* virus infection or with *Herpes simplex* encephalitis should be given aciclovir intravenous in doses of 500 mg per square metre of body surface area (equivalent to 10 mg/kg in adults).

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Dosage in the elderly: No data are available on this age group. However, as creatinine clearance is often low in the elderly, special attention should be given to dosage reduction. 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.

Duration of treatment: It is recommended that aciclovir intravenous be administered for five to seven days in the treatment of most infections and for at least ten days in the treatment of *Herpes simplex* encephalitis.

Administration

Each dose must be administered by slow intravenous infusion over a period of at least one hour to avoid renal tubular damage (see **Precautions**).

DBL™ Aciclovir Intravenous Infusion may be injected directly into a vein over one hour by a controlled rate infusion pump or be diluted for administration by infusion.

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

For intravenous infusion, each vial of DBL™ Aciclovir Intravenous Infusion should be added to and mixed with at least 50 mL to 100 mL infusion solution. A maximum of 250 mg of aciclovir may be added to 50 mL of infusion solution and a maximum of 500 mg of aciclovir may be added to 100 mL of infusion solution. After addition of DBL™ Aciclovir Intravenous Infusion to an infusion solution, the mixture should be shaken to ensure thorough mixing.

DBL™ Aciclovir Intravenous Infusion when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v (5 mg/mL).

DBL™ Aciclovir Intravenous Infusion is known to be compatible with the following infusion fluids and stable for up to 24 hours at room temperature (below 25°C) when diluted to concentrations of aciclovir between 2.5 mg/mL and 10 mg/mL:

Sodium Chloride Intravenous Infusion BP (0.9% w/v)

Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion BP

Sodium Chloride (0.9% w/v) and Glucose (5% w/v) Intravenous Infusion BP

Compound Sodium Lactate Intravenous Infusion BP (Lactated Ringers Solution)

DBL™ Aciclovir Intravenous Infusion is known to be compatible with Glucose Intravenous Infusion BP (5.0% w/v) and stable for up to 24 hours at room temperature (below 25°C) when diluted to concentrations of aciclovir 4.5 mg/mL and 10 mg/mL. When diluted to a concentration of aciclovir 2.5 mg/mL in Glucose Intravenous Infusion BP (5.0% w/v), DBL™ Aciclovir Intravenous Infusion is stable for up to 6 hours. DBL™ Aciclovir Intravenous Infusion should not be diluted to an aciclovir concentration less than 2.5 mg/mL in 5% Glucose Intravenous Infusion.

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.

Overdosage

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 **Adverse 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 in serum urea and creatinine and subsequent renal failure. Lethargy, convulsions and coma have been reported rarely.

Precipitation of aciclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **Precautions**). In the event 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.

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

Presentation and Storage Conditions

DBL™ Aciclovir Intravenous Infusion is available in glass vials in the following presentation:

DBL™ Aciclovir Intravenous Infusion 250 mg/10 mL vials

Store below 25°C. Do not refrigerate.

Name and Address of the Manufacturer

Hospira Australia Pty Ltd.
1 – 5, 7 – 23 and 25 - 39 Lexia Place
Mulgrave, Victoria, 3170 Australia

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