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DBL ACICLOVIR INTRAVENOUS INFUSION

1. NAME OF THE MEDICINE

Aciclovir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Aciclovir Intravenous Infusion contains 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.

Aciclovir sodium is a white crystalline powder.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

DBL Aciclovir Intravenous Infusion is a clear 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 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.

4.2 Dose and method of administration

Dosage

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).

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 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) every 8 hours if renal function is not impaired.

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) 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 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.

Adequate hydration should be maintained.

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.

Method of administration

Each dose must 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).

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.

Dosage adjustment

Renal impairment

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

4.3 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.

4.4 Special warnings and precautions for use

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.

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 infusions 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 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.

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 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 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 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 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.

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 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.

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

No data available.

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 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. 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 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. 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 the 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.

Interferon: see Section 4.4 Special warnings and precautions for use.

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 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 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

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.

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 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.

4.7 Effects on ability to drive and use machines

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 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 $\geqslant$ 1/10, common $\geqslant$ 1/100 to < 1/10, uncommon $\geqslant$ 1/1,000 to < 1/100, rare $\geqslant$ 1/10,000 to < 1/1,000, very rare < 1/10,000.

MedDRA System Organ Class	**Very common ⩾ 1/10**	**Common ⩾ 1/100 to < 1/10**	**Uncommon ⩾ 1/1,000 to < 1/100**	**Rare ⩾ 1/10,000 to < 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.
Vascular disorders		phlebitis			

MedDRA System Organ Class	**Very common ⩾ 1/10**	**Common ⩾ 1/100 to < 1/10**	**Uncommon ⩾ 1/1,000 to < 1/100**	**Rare ⩾ 1/10,000 to < 1/1,000**	**Very rare < 1/10,000**
Respiratory, thoracic and mediastinal disorders					dyspnoea
Gastrointestinal disorders		nausea, vomiting			diarrhoea, abdominal pain
Hepato-biliary disorders		reversible increases in liver-related enzymes			reversible increases in bilirubin, jaundice, hepatitis
Skin and subcutaneous tissue disorders		pruritus, urticaria, rashes (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. Severe local inflammatory reactions.[¥]

[$] The events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see section 4.4 Special Warnings and Precautions for Use).

** 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 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 for 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 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.

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.

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 in serum urea and creatinine and subsequent renal failure. Neurological effects including lethargy, confusion, hallucinations, agitation, seizure, and coma have been reported rarely 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 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. 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.

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* (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.

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 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.

Distribution

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

Metabolism

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

Excretion

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.

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.

5.3 Preclinical safety data

Genotoxicity

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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

Please see details on carton.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate.

6.5 Nature and contents of container

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

DBL Aciclovir Intravenous Infusion 250 mg/10 mL vials

DBL Aciclovir Intravenous Infusion 500 mg/20 mL vials

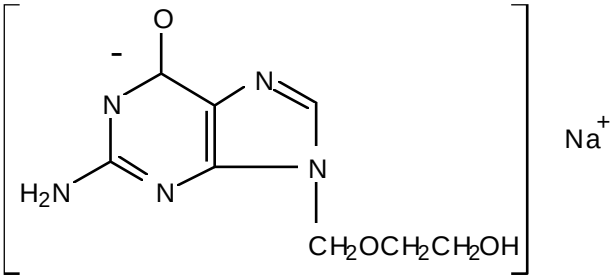
Not all presentations or pack sizes may be marketed

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical structure



Chemical name: 9-[(2-hydroxyethoxy)-methyl] guanine sodium

Molecular weight: 247.2

CAS number

CAS 69657-51-8

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited,

Bangkok

8. MARKETING AUTHORIZATION NUMBER

1C 66/62

9. DATE OF AUTHORIZATION

15 NOVEMBER 2019

10. DATE OF REVISION OF THE TEXT

17 APRIL 2024