ACIVIR I.V. Injection (Aciclovir)

Composition

ACIVIR I.V.
Each ml contains:
Aciclovir BP ..... 25 mg
Water for Injection IP .....q.s.

Dosage Form

Injection for I.V. use

Pharmacology

Pharmacodynamics

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 and *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.

Pharmacokinetics

In adults, the terminal plasma half-life of aciclovir after administration of aciclovir I.V. is about 3 hours. Most of the drug is excreted unchanged by the kidneys. 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-carboxymethox- -methylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

When aciclovir is given 1 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 adults, mean steady-state peak plasma concentrations (C_{ss}max) following a 1-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 micromolar (5.1 microgram/mL), 43.6 micromolar (9.8 microgram/mL) and 92 micromolar (20.7 microgram/mL), respectively. The corresponding trough levels (C_{ss}min), 7 hours later, were 2.2 micromolar (0.5 microgram/mL), 3.1 micromolar (0.7

microgram/mL) and 10.2 micromolar (2.3 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/m2 was substituted for 5 mg/kg and a dose of 500 mg/m2 was substituted for 10 mg/kg. In neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a 1-hour period every 8 hours, the C_{ss}max was found to be 61.2 micromolar (13.8 microgram/mL) and the C_{ss}min to be 10.1 micromolar (2.3 microgram/mL).

The terminal plasma half-life in these patients was approximately 4 hours. In the elderly, total body clearance falls with increasing age and is 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 increased, extending to a mean terminal half-life of approximately 20 hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

In a clinical study in which morbidly obese female patients (n=7) were dosed with I.V. aciclovir based on their actual body weight, plasma concentrations were found to be approximately twice that of normal weight patients (n=5), consistent with the difference in body weight between the two groups. Cerebrospinal fluid levels were 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.

Indications

ACIVIR I.V. is indicated for the following:

- Treatment of severe initial genital herpes in the immunocompromised and the non-immunocompromised patients.
- Prophylaxis and treatment of *Herpes simplex* infections in immunocompromised patients.
- Treatment of Shingles (Varicella zoster virus) in immunocompetent patients in whom a serious course of illness can be anticipated.
- Treatment of initial and recurrent *Varicella zoster* infections in immunocompromised patients.
- Treatment of herpes encephalitis.
- Treatment of *Herpes simplex* infections in neonates and infants up to 3 months of age.

Dosage and Administration

Dosage

Treatment should be started as early as possible during the course of an active infection.

A course of treatment with **ACIVIR I.V.** usually lasts between 5 and 7 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 **ACIVIR I.V.** is determined by the duration of the period at risk.

Adults

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections (with normal immune response) should be given **ACIVIR I.V.** in doses of 5 mg/kg body weight every 8 hours.

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given **ACIVIR I.V.** in doses of 10 mg/kg body weight every 8 hours, provided renal function is not impaired (see dosage in *Renal Impairment*).

Paediatric
The dose of **ACIVIR I.V.** 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* (with normal immune response) should be given ACIVIR I.V. in doses of 250 mg per square meter of body surface area every 8 hours.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, **ACIVIR I.V.** should be given in doses of 500 mg per square meter body surface area 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.

The dosage of **ACIVIR I.V.** in neonates and infants up to 3 months of age is calculated on the basis of body weight.

Neonates and infants up to 3 months of age with *Herpes simplex* infections should be given **ACIVIR I.V.** in doses of 10 mg/kg body weight every 8 hours. Treatment for neonatal herpes simplex infections usually lasts 10 days.

Geriatric
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 (see **Renal Impairment**). 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 patients, who may have reduced renal function despite a normal serum creatinine concentration.

Renal Impairment
Caution is advised when administering **ACIVIR I.V.** to patients with impaired renal function since the drug is excreted through the kidneys.

The following adjustments in dosage are suggested:

Creatinine Clearance	Dosage
25 to 50 mL/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours
10 to 25 mL/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 24 hours

0 (anuric) to 10 mL/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD), the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis, half the dose recommended above should be administered immediately after dialysis and thereafter every 24 hours.

Method of Administration

ACIVIR I.V. should be administered by slow I.V. infusion over a 1-hour period and adequate hydration should be established.

Dilution should be carried out immediately before use under full aseptic conditions and any unused solution should be discarded.

Refrigeration is not recommended as precipitation may occur.

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, but a second bag must be used for doses between 500 mg and 1000 mg. Aciclovir I.V. should not be diluted to a concentration greater than 5 mg/mL (0.5% w/v) for administration by infusion. After addition of aciclovir I.V. to an infusion solution, the mixture should be shaken to ensure thorough mixing.

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 of solution added to 20 mL of infusion fluid.

When diluted in accordance with the recommended schedules, aciclovir I.V. is known to be compatible with the following infusion fluids:
Sodium chloride I.V. infusion 0.9% w/v
Sodium chloride (0.18% w/v) and Glucose (4% w/v) I.V. infusion
Sodium chloride (0.9% w/v) and Glucose (5% w/v) I.V. infusion
Sodium chloride (0.45% w/v) and Glucose (2.5% w/v) I.V. infusion
Compound sodium lactate I.V. infusion (Hartmann's solution)
Aciclovir I.V., when diluted in accordance with the above schedule, will give an aciclovir concentration not greater than 0.5% w/v.
Should any visible turbidity or crystallization appear in the solution before or during infusion, the preparation should be discarded.

Contraindications

ACIVIR I.V. is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

Warnings and Precautions

General

Solutions of aciclovir are alkaline (pH of approximately 11) and intended for I.V. infusion only and should not be used by any other route.

The dose of aciclovir I.V. must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body. Infusions of aciclovir must be given over a period of at least 1 hour in order to avoid renal tubular damage (see dosage in renal impairment).

Although the aqueous solubility of aciclovir 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 infusions 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 aciclovir I.V. 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.

Contact with the eyes or unprotected skin should be avoided.

Drug interactions

There have been rare reports of probenecid, cimetidine, theophylline and mycophenolate mofetil linked to increases in the acyclovir mean half-life and area under the plasma concentration-time curve. In these cases an adjustment of the acyclovir dosage is not thought to be necessary given the large therapeutic range of acyclovir.

According to one case report, co-administration of intravenous acyclovir and lithium caused a four-fold increase in lithium serum concentrations. Lithium concentrations should be closely monitored and a reduced lithium dose may be needed.

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 %.

Care is also required (with monitoring changes in renal function) if administering **ACIVIR I.V.** with other drugs that affect other aspects or renal physiology (e.g cyclosporine, tacrolimus) as they may influence the nephrotoxic effect of aciclovir.

Pregnancy

No adequate data is available regarding the effect of aciclovir during human pregnancy. Aciclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Limited human data show that aciclovir is excreted in human breast milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

Undesirable Effects

Renal

Rapid increases in blood urea and creatinine levels may occasionally occur in patients given aciclovir I.V. These are usually reversible but progression to acute renal failure can occur in rare cases. The rapid increases in blood urea and creatinine levels are believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect, the drug should not be given as an I.V. bolus injection but by slow infusion over a 1-hour period. Adequate hydration of the patient should be maintained. The risk of renal damage is increased by concomitant use of other nephrotoxic drugs and pre-existing renal disease.

Renal impairment developing during treatment with aciclovir I.V. 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.

Skin

Local necrosis and inflammation have occurred when aciclovir I.V. has been inadvertently infused into extravascular tissues. Severe local inflammatory reactions or phlebitis have occurred at the injection site sometimes, leading to breakdown of the skin. These local effects occur more frequently following inadvertent infusion of aciclovir into extravascular tissues.

Rashes and hives may occur.

Neurological

Reversible neurological reactions such as confusion, lethargy, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with aciclovir I.V. therapy. Reversible psychiatric effects and headaches have been reported less frequently.

Therefore, aciclovir should be used with caution in patients with underlying neurological abnormalities. It should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitant interferon or intrathecal methotrexate.

Haematological

Increases in liver-related enzymes and fever have been reported in patients receiving aciclovir I.V. Haemotological disorders, including anaemia, thrombocytopenia and leucopoenia, have been rarely reported.

Other

Aciclovir should be used with caution in patients with significant hypoxia or serious hepatic or electrolyte abnormalities.

Other less frequent adverse effects reported in patients receiving therapy with aciclovir I.V. include, diaphoresis, haematuria, hypotension, nausea and vomiting.

In case of high doses, abdominal pain and thirst have been reported in patients who had been treated previously with aciclovir.

Overdosage

There is little experience concerning overdosage with aciclovir; however, single doses of aciclovir I.V. up to 80 mg/kg bodyweight have been inadvertently administered without adverse effects. Effects of overdosage may be expected to be similar in nature to those described under adverse reactions. Adequate hydration is essential to reduce the possibility of crystal formation in the urine. Aciclovir can be removed from the circulation by haemodialysis.

Incompatibility

Aciclovir sodium is reported to be incompatible with solutions of amifostine, amsacrine, aztreonam, diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, fludarabine phosphate, foscarnet sodium, idarubicin hydrochloride, meropenem, morphine sulphate, ondansetron hydrochloride, pethidine hydrochloride, piperacillin sodium-tazobactam sodium, sargramostim and vinorelbine tartrate.
Do not use bacteriostatic water for injection containing parabens or benzyl alcohol. Biologic or colloidal fluids (e.g., blood products, protein-containing solutions) are incompatible with aciclovir sodium.

Storage and Handling Instructions

Do not store above 25°C. Do not refrigerate.

Packaging Information

ACIVIR I.V.: Snapoules of 10 mL

Last reviewed: September 2013
Last updated: September 2013