

HIKMA ACYCLOVIR® I.V. for Infusion Acyclovir (as sodium)

ACTION

Acyclovir 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, acyclovir 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 acyclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir 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 acyclovir in severely immunocompromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued acyclovir 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 acyclovir 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 acyclovir therapy is not clear. All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

INDICATIONS

Hikma Acyclovir I.V. for Infusion is indicated for the treatment of Herpes simplex infections.
Hikma Acyclovir I.V. for Infusion is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.
Hikma Acyclovir I.V. for Infusion is indicated in treatment of Varicella zoster infections.
Hikma Acyclovir I.V. for Infusion is indicated for the treatment of Herpes simplex infections in the neonate.
Hikma Acyclovir I.V. for Infusion formulations are indicated for prophylaxis of CMV infection in bone marrow transplant recipients. It has been shown that high dose intravenous Hikma Acyclovir reduces the incidence and delays the onset of CMV infection. When high dose intravenous Hikma Acyclovir is followed by 6 months treatment with high dose oral Hikma Acyclovir, mortality and the incidence of viraemia are also reduced.

DOSE AND ADMINISTRATION

Dosage in Adults

Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given Hikma Acyclovir I.V. for Infusion in doses of 5mg/kg bodyweight every 8 hours.
Immunocompromised patients with Varicella zoster infections or patients with herpes encephalitis should be given Hikma Acyclovir I.V. for Infusion in doses of 10mg/kg bodyweight every 8 hours provided renal function is not impaired.
For prophylaxis of CMV infection in bone marrow transplant recipients 500mg/m² Hikma Acyclovir 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 Hikma Acyclovir I.V. for 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 Hikma Acyclovir I.V. for Infusion in doses of 250mg per square meter body surface area every 8 hours. In immunocompromised children with Varicella zoster infections or children with herpes encephalitis, Hikma Acyclovir I.V. for Infusion should be given in doses of 500mg 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 Hikma Acyclovir I.V. for Infusion in neonates is calculated on the basis of bodyweight. Neonates with Herpes simplex infections should be given Hikma Acyclovir I.V. for Infusion in doses of 10 mg/kg bodyweight every 8 hours.

Dosage in the Elderly

In the elderly, total acyclovir 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 Hikma Acyclovir I.V. for Infusion to patients with impaired renal function.

The following adjustments in dosage are suggested:

Cratinine Clearance

25-50 ml/min

Dosage

The dose recommended above (5 or 10 mg/kg bodyweight

or 500mg/m²) should be given every 12 hours

10-25 ml/min

The dose recommended above (5 or 10 mg/kg bodyweight

or 500mg/m²) should be given every 24 hours.

0 (anuria) to 10 ml/min

In patients receiving continuous ambulatory peritoneal dialysis

(CAPD) the dose recommended above (5 or 10 mg/kg bodyweight or 500mg/m²) should be halved and administered every 24 hours.

In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight or 500mg/m²) should be halved and administered every 24 hours and after dialysis.

A course of treatment with Hikma Acyclovir I.V. for 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 Hikma Acyclovir I.V. for Infusion is determined by the duration of the period at risk.

Reconstitution

Hikma Acyclovir I.V. for Infusion should be reconstituted with 10 ml of either Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v) to provide a solution containing 25 mg acyclovir per ml.

From the calculated dose, determine the appropriate number and strength 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.

Administration

The required dose of Hikma Acyclovir I.V. for Infusion should be administered by slow intravenous infusion over a one-hour period.

After reconstitution, Hikma Acyclovir I.V. for Infusion may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an acyclovir concentration of not greater than 5mg/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 4ml reconstituted solution (100 mg acyclovir) 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 acyclovir concentration substantially below 0.5% w/v. Thus one 100 ml infusion bag may be used for any dose between 250mg and 500mg acyclovir, 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, Hikma Acyclovir I.V. for Infusion is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (18°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;
- Goniosol® Sodium Lactate Intravenous Infusion BP (Hartmann's Solution).

Hikma Acyclovir I.V. for Infusion when diluted in accordance with the above schedule will give an acyclovir 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 crystallization appear in the solution before or during infusion, the preparation should be discarded.

CONTRA-INDICATIONS

Acyclovir sodium I.V. for Infusion is contra-indicated in patients known to be previously hypersensitive to acyclovir or valacyclovir.

PRECAUTIONS/Warnings

The dose of Acyclovir sodium I.V. for Infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of acyclovir in the body.
In patients receiving Acyclovir sodium I.V. for 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 Acyclovir sodium I.V. for Infusion has a pH of approximately 11.0 and should not be administered by mouth.

Mutagenicity

The results of a wide range of mutagenicity test in vitro and in vivo indicate that acyclovir does not pose a genetic risk to man.

Carcinogenicity

Acyclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Teratogenicity

Systemic administration of acyclovir 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.

Fertility

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Long-term studies in mice did not reveal any effect of (orally administered) acyclovir on fertility. There is no experience of the effect of Acyclovir sodium I.V. for Infusion on human fertility. 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 acyclovir during pregnancy. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

Lactation

Following oral administration of 200mg five times a day, acyclovir 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 acyclovir dosage of up to 0.3 mg/kg bodyweight/day. Caution is therefore advised. Acyclovir sodium I.V. for Infusion is to be administered to a nursing woman.

Pharmaceutical precautions

Hikma Acyclovir I.V. for Infusion contains no antimicrobial preservative. Reconstitution or dilution should therefore be carried out either under full aseptic conditions or immediately before use and any unused solution discarded.

Reconstituted or diluted solutions should not be refrigerated.

When reconstituted as directed, Acyclovir sodium I.V. for Infusion has a pH of approximately 11.

Drug interactions

No clinically significant interactions have been identified.
Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increase the AUC of acyclovir by this mechanism, and reduce acyclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of acyclovir.

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

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

SIDE EFFECTS

Gastrointestinal: Nausea and vomiting have been reported.

Haematological: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia), hypersensitivity and skin flashes 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 Acyclovir sodium I.V. for Infusion has been inadvertently infused into extravascular tissues.

Ginary: Rapid increases in blood urea and creatinine levels may occasionally occur in patients given Acyclovir sodium I.V. for Infusion. This is 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 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 Acyclovir sodium I.V. for Infusion 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.

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 Acyclovir sodium I.V. for Infusion therapy, usually in medically complicated cases.

OVERDOSAGE

Overdose of intravenous acyclovir 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 overdose. Haemodialysis significantly enhances the removal of acyclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

STORAGE

Store below 30 °C.

PRESENTATIONS

Vials
Hikma Acyclovir 250 mg; Sterile, freeze-dried (lyophilized) acyclovir sodium equivalent to 250 mg acyclovir
Etiopient: Sodium Hydroxide

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription exactly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not use a medicament unless you are sure of the period of treatment prescribed to you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by Hikma Italy, SpA, Italy
For Hikma Pharmaceuticals, Amman-Jordan

Keep medication out of the reach of children
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