Acyclovenir

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acyclovenir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg Aciclovir in each vial
Excipients with known effect:
Sodium hydroxide
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Solution for Infusion

PRESENTATION
A sterile, white to off-white, freeze dried powder in vials containing 250mg acyclovir as the sodium salt.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acyclovenir is indicated for:

- the treatment of Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.
- the prophylaxis of Herpes simplex infections in immunocompromised patients.
- the treatment of Varicella zoster infections.
- the treatment of herpes encephalitis.
- the treatment of Herpes simplex infections in the neonate and infant up to 3 months of age.

4.2 Posology and method of administration

Route of administration: Slow intravenous infusion over 1 hour.
A course of treatment with Acyclovenir usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts 10 days. Treatment for neonatal herpes infections usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for disseminated or central nervous system disease.
The duration of prophylactic administration of Acyclovenir is determined by the duration of the period at risk.

Dosage in adults:
Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Acyclovenir in doses of 5 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).
Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Acyclovenir in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).
In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

Dosage in infants and children:
The dose of Acyclovenir for infants and children aged between 3 months and 12 years is calculated on the basis of body surface area.
Infants and children 3 months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Acyclovenir in doses of 250 mg per square metre of body surface area every 8 hours if renal function is not impaired.
In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, Acyclovenir should be given in doses of 500 mg per square metre body surface area every 8 hours if renal function is not impaired.
The dosage of Acyclovenir in neonates and infants up to 3 months of age is calculated on the basis of body weight.
The recommended regimen for infants treated for known or suspected neonatal herpes is aciclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.
Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).

Dosage in the elderly:
The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly (see *Dosage in renal impairment* below).
Adequate hydration should be maintained.

Dosage in renal impairment:
Caution is advised when administering Acyclovenir to patients with impaired renal function. Adequate hydration should be maintained.
Dosage adjustment for patients with renal impairment is based on creatinine clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m^2 for infants and children less than 13 years of age.
The following adjustments in dosage are suggested:

Dosage adjustments in adults and adolescents:

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 the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.

Dosage adjustments in infants and children:

Creatinine Clearance	Dosage
25 to 50 ml/min/1.73m^2	The dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min/1.73m^2	The dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be given every 24 hours.
0(anuric) to 10 ml/min/1.73m^2	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m^2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis

4.3 Contraindications

Hypersensitivity to aciclovir or valaciclovir, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Adequate hydration should be maintained in patients given i.v. or high oral doses of aciclovir.
Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided.
The risk of renal impairment is increased by use with other nephrotoxic drugs. Care is required if administering i.v. aciclovir with other nephrotoxic drugs.

Use in patients with renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see section 4.2 Posology and method of administration). Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment must be considered in this group of patients. Both elderly patients and 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 (see section 4.8 Undesirable effects). 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 (see section 5.1).
In patients receiving Acyclovenir 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 Acyclovenir has a pH of approximately 11.0 and should not be administered by mouth.

Product contains sodium –

To be taken into consideration by patients on a controlled sodium diet.
Acyclovenir contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.
Other warnings and precautions
The labels shall contain the following statements:
For intravenous infusion only
Keep out of the reach and sight of children
Store below 25°C
Prepare immediately prior to use
Discard unused solution
Excipients
This medicinal product contains 45 mg sodium hydroxide per vial.
To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs 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 Acyclovir BioAvenir, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma concentrations 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.
If lithium is administered concurrently with high dose aciclovir IV, the lithium serum concentration should be closely monitored because of the risk of lithium toxicity
Care is also required (with monitoring for changes in renal function) if administering intravenous Acyclovenir with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).
An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered **theophylline** with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

4.6 Fertility, Pregnancy and Lactation

Fertility:

There is no information on 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 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.
See clinical studies in section 5.2

Pregnancy:

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of the drug. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared to with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.
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 tests in-rats, fetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.
Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard. Findings from reproduction toxicology studies are included in Section 5.3.

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 concentrations. These concentrations would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg bodyweight/day. Caution is therefore advised if Acyclovenir is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Aciclovir i.v. for infusion is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant. There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery.

4.8 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 ≥ 1/10, common ≥ 1/100 and < 1/10, uncommon ≥ 1/1,000 and < 1/100, rare ≥ 1/10,000 and < 1/1,000, very rare < 1/10,000.

Blood and lymphatic system disorders:
Uncommon: Decreases in hematological indices (anemia, thrombocytopenia, leucopenia).

Immune system disorders:
Very rare: anaphylaxis.

Psychiatric and nervous system disorders:
Very rare: headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.
The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see 4.4 Special Warnings and Precautions for Use).

Vascular disorders:
Common: phlebitis.

Respiratory, thoracic and mediastinal disorders:
Very rare: dyspnoea.

Gastrointestinal disorders:
Common: nausea, vomiting.
Very rare: diarrhoea, abdominal pain.

Hepato-biliary disorders:
Common: reversible increases in liver-related enzymes.
Very rare: reversible increases in bilirubin, jaundice, hepatitis.

Skin and subcutaneous tissue disorders:
Common: pruritus, urticaria, rashes (including photosensitivity).
Very rare: angioedema.

Renal and urinary disorders:
Common: increases in blood urea and creatinine.
Rapid increases in blood urea and creatinine concentrations are believed to be related to the peak plasma concentrations 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.
Very rare: renal impairment, acute renal failure and renal pain.
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 and crystalluria.

General disorders and administration site conditions:
Very rare: fatigue, fever, local inflammatory reactions
Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when the drug has been inadvertently infused into extracellular tissues.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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.
Patients should be observed closely for signs of toxicity.
Hemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors ATC code: J05AB01.
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 acyclovir 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.

5.2 Pharmacokinetic properties
Absorption
Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. Under fasting conditions, mean peak concentrations (Cmax) of 0.4 microgram/ml are achieved at approximately 1.6 hours after a 200 mg dose administered as oral suspension or capsule. Mean peak plasma concentrations (C^{ss}max) increase to 0.7 microgram/ml (3.1 micromoles) at steady state following doses of 200 mg administered every four hours. A less than proportional increase is observed for C^{ss}max concentrations following doses of 400 mg and 800 mg administered four-hourly, with values reaching 1.2 and 1.8 microgram/ml (5.3 and 8 micromoles), respectively.

Distribution
The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2.3 to 17.8 L/kg. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid concentrations are approximately 50% of corresponding plasma concentrations at steady-state.

Metabolism
Aciclovir is predominantly excreted unchanged by the kidney. The only significant urinary metabolite is 9-[(carboxymethoxy) methyl]guanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination
In adults mean systemic exposure (AUC0-∞) to aciclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. At this dose, the mean terminal plasma half-life after oral administration has been shown to vary between 2.8 and 4.1 hours.
In adults the terminal plasma half life of aciclovir after administration of Acyclovenir is about 2.9 hours.
Renal clearance of aciclovir (CLr= 14.3 L/h) is substantially greater than creatinine clearance indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug.
The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients
In adults, mean steady state peak plasma concentrations (C^{ss}max) following a one-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 concentrations (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 through (C^{ss}min) concentrations 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 neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one 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).
A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml). The terminal plasma half life in these patients was 3.8 hours.

Special Patient Populations
Elderly
In the elderly patients with normal renal function total clearance falls with increasing age due to decreases in creatinine clearance. However, the possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly.
Renal impairment
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 concentrations dropped approximately 60% during dialysis.

Weight
In a clinical study in which morbidly obese female patients (n=7) were dosed with intravenous 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.

5.3 Preclinical safety data
Mutagenicity: 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.

Teratogenicity:
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.

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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium hydroxide

6.2 Incompatibilities
The reconstituted concentrate and diluted solution for infusion must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.
See section 6.6 -
When diluted in accordance with the recommended schedules, Acyclovenir for Infusion is known to be compatible with the infusion fluids (see section 6.6) and stable for up to 12 hours at room temperature (15°C to 25°C)
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.
Reconstituted or diluted solution should not be refrigerated.

6.5 Nature and contents of container
Type II glass vial, stoppered with a rubber stopper and capped with an aluminum capsule in extractable plastic cover (type flip-off).

Pack Sizes: 250 mg / Vial: Carton box containing 5 or 50 vials

6.6 Special precautions for disposal and other handling
Administration:
The required dose of Acyclovenir for Infusion should be administered by slow intravenous infusion over a one-hour period.
Acyclovenir for Infusion 250mg vial should be reconstituted using 10ml of either Water for Injections BP or Sodium Chloride Injection BP (0.9% w/v) to provide a solution containing 25 mg aciclovir per ml.
To reconstitute each vial, add 10ml of infusion fluid and shake gently until the contents of the vial have dissolved completely.
After reconstitution Acyclovenir 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 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, intravenous Acyclovenir for 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).

Acyclovir BioAvenir for 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.
Reconstituted or diluted solution should not be refrigerated.
Should any visible turbidity or crystallization appear in the solution before or during infusion, the preparation should be discarded.

7. MANUFACTURER
Laboratory Reig Jofre, S.A., Barcelona, Spain.

8. LICENSE HOLDER AND IMPORTER
BioAvenir Ltd., 1 David Hamelech St., Herzelia Pituach, 4666101, Israel.

9. LICENSE NUMBER
143-05-31907-00

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