SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zovinex 250mg Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains: Acyclovir Sodium (Sterile)
Equivalent to Acyclovir USP 250mg (Sodium content 24.5 mg)
For I.V. Infusion only.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dry Injection (Powder For Solution For Infusion)

White to off-white crystalline powder filled in clear colourless glass vials sealed with flip-off seal.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.

Aciclovir for infusion is indicated for the prophylaxis of *Herpes simplex* infections in immunocompromised patients.

Aciclovir for infusion is indicated for the treatment of *Varicella zoster* infections.

Aciclovir for infusion is indicated for the treatment of herpes encephalitis.

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in the neonate and infant up to three months of age.

4.2. Posology and method of administration

Route of administration: Slow intravenous infusion over one hour.

A course of treatment with aciclovir for infusion usually lasts five days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts ten days. Treatment for neonatal herpes 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 aciclovir for infusion is determined by the duration of the period at risk.

Posology

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 5mg/kg bodyweight every eight 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 aciclovir for infusion in doses of 10mg/kg bodyweight every eight 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 children:

The dose of aciclovir for infusion for children aged between three months and 12 years is calculated on the basis of body surface area.

Children three months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 250 mg per square metre of body surface area every eight hours if renal function is not impaired.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, aciclovir for infusion should be given in doses of 500 mg per square metre body surface area every eight hours if renal function is not impaired.

The dosage of aciclovir for infusion in neonates and infants up to three months of age is calculated on the basis of bodyweight.

The recommended regimen for infants treated for known or suspected neonatal herpes is aciclovir 20 mg/kg body weight IV every eight 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. 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.

Adequate hydration should be maintained.

Dosage in renal impairment:

Caution is advised when administering aciclovir for infusion 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 bodyweight) should be given every 12 hours.
10 to 25 ml/min:	The dose recommended above (5 or 10 mg/kg bodyweight) 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 bodyweight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight) 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.

Method of Administration

The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period.

After reconstitution aciclovir for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

For instructions on reconstitution and dilution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to acyclovir and valaciclovir, or to any of the excipients.

4.4. Special warnings and precautions for use

Use in patients with renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction 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).

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.

In patients receiving aciclovir 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 aciclovir for infusion has a pH of approximately 11.0 and should not be administered by mouth.

Aciclovir for infusion 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.

This vial contains approximately 26mg of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

4.5. Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified.

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 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).

4.6. Fertility, pregnancy and lactation

Pregnancy

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

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.

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.

Breast-feeding

Following oral administration of 200mg 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 levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg bodyweight/day. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

4.7. Effects on ability to drive and use machines

Aciclovir 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. However, aciclovir can cause reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis and coma, which can all affect the ability to drive and use 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 haematological indices (anaemia, thrombocytopenia, leucopenia).

Immune system disorders

Very rare: Anaphylaxis.
Psychiatric and nervous system disorders
Very rare: Headache, dizziness, confusion, hallucinations, agitation, tremor, ataxia, dysarthria, somnolence, psychotic symptoms, encephalopathy, convulsions and coma.
The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see section 4.4).
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, hepatitis and jaundice.
Skin and subcutaneous tissue disorders
Common: Rashes including photosensitivity, urticaria, pruritus
Very rare: Angioedema.
Renal and urinary disorders
Common: Increases in blood urea and creatinine
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 intravenous bolus injection but by slow infusion over a one hour period.
Very rare: Renal impairment, acute renal failure, renal pain
Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with aciclovir 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.
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 formulations of aciclovir for intravenous use have been inadvertently infused into extravascular tissues.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose

Symptoms and Signs

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.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: J05A B01, Direct Acting Antiviral

Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including *Herpes simplex* virus (HSV) 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.

5.2. Pharmacokinetic properties

In adults, the terminal plasma half-life of aciclovir after administration of aciclovir for infusion is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. 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-carboxymethoxymethylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

When aciclovir is given one hour after 1g 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 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 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 one 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 neonates (0 to three 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 eight 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. 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 was found to be 19.5 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 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.

Cerebrospinal fluid levels are 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.

5.3. Preclinical safety data

The results of a wide range of mutagenicity test *in vitro* and *in vivo* indicate that aciclovir is unlikely to pose a genetic risk to man.

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

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.

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.

There is no experience of the effect of aciclovir for infusion on human fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

There is no excipients used in the formulation.

Diluent: Sterile Water For Injection

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months from the date of manufacturing.

6.4. Special precautions for storage

Store at a temperature below 30°C. Protect from light & moisture Keep medicine out of reach of children.

6.5. Nature and contents of container

250 mg sterile powder for injection filled in 10ml clear colorless glass vial duly labeled sealed with a flip-off seal, along with one plastic ampoule of 10ml WFI in a tray, packed in a printed mono carton with insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

Novo Medi Sciences Pvt. Ltd.
40-B1, Shankar Smruti, Sir Bhalchandra, Road,
Dadar (E), Mumbai 400014, INDIA

Manufacturer

EAST AFRICAN (INDIA) OVERSEAS
Plot no. 1, Pharmacity, Selaqui
Dehradun – 248011, Uttarakhand (India)

8. Marketing authorization number(s)

H2024/CTD10778/24009

9. Date of First Authorization

9th February 2024

10. Date of revision of text

November 2024