Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Zovinex USP 250mg, Powder for solution for infusion

2. Qualitative and quantitative composition

Each vial contains:

Acyclovir Sodium (Sterile) Equivalent to Acyclovir USP 250 mg (Sodium content 24.5 mg)

One ml of reconstituted solution contains 25 mg of Zovinex.

3. Pharmaceutical form

Dry white to off white crystalline sterile powder for solution for infusion.

4. Clinical particulars

4.1 Therapeutic indications

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

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

Zovinex is indicated for the treatment of *Varicella zoster* infections.

Zovinex is indicated for the treatment of *herpes encephalitis*.

Zovinex is indicated for 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 Zovinex 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 Zovinex is determined by the duration of the period at risk.

The required dose of Zovinex for infusion should be administered by slow intravenous infusion over a one-hour period. After reconstitution Zovinex for infusion may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an Zovinex concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion. For instructions on reconstitution and dilution of the product before administration see section 6.6.

Dosage in adults:

Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given Zovinex 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 Zovinex 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 Zovinex 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 Zovinex 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 Zovinex 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, Zovinex 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 Zovinex 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 Zovinex 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. In the elderly, total Zovinex body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance. (see Dosage in renal impairment below)

Adequate hydration should be maintained.

Dosage in renal impairment:

Caution is advised when administering Zovinex 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/1.73m2 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 adjustment 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 Zovinex or valaciclovir.

4.4 Special warnings and precautions for use

Adequate hydration should be maintained in patients given i.v. or high oral doses of Zovinex.

Intravenous doses should be given by infusion over one hour to avoid precipitation of Zovinex 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. Zovinex with other nephrotoxic drugs.

Use in patients with renal impairment and in elderly patients:

Zovinex 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 Zovinex in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued Zovinex treatment (see section 5.1).

In patients receiving Zovinex 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 Zovinex has a pH of approximately 11 and should not be administered by mouth.

This medicinal product contains less than 1 mmol (23 mg) sodium, i.e. essentially “sodium-free”.

Zovinex contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded.

4.5 Interaction with other medicinal products and other forms of interaction

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

In patients receiving intravenous Zovinex caution is required during concurrent administration with drugs which compete with Zovinex for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites. Increases in plasma AUCs of Zovinex 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 Zovinex 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 Zovinex 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 Zovinex increases AUC of totally administered

theophylline with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with Zovinex.

4.6 Pregnancy and Lactation

Fertility:

There is no information on the effect of Zovinex on human female fertility.

In a study of 20 male patients with normal sperm count, oral Zovinex 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 Zovinex pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Zovinex . The registry findings have not shown an increase in the number of birth defects amongst Zovinex 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 Zovinex 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 texicity 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.

Breast-feeding:

Following oral administration of 200 mg five times a day, Zovinex 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 Zovinex dosages of up to 0.3 mg/kg body weight/day. Caution is therefore advised if Zovinex is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Zovinex 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 Zovinex 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 haematological indices (anaemia, thrombocytopenia, leukopenia).

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 levels are believed to be related to the 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 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 Zovinex has been inadvertently infused into extravascular tissue.

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. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons Board- Pharmacovigilance Electronic Reporting System (PvERS); *https://pv.pharmacyboardkenya.org* .

4.9 Overdose

Symptoms and Signs

Overdosage of intravenous Zovinex 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 Zovinex 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.
Zovinex 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 Zovinex 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 Zovinex for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use Zovinex effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts Zovinex to Zovinex monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Zovinex 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

In adults, mean steady state peak plasma concentrations (Cssmax) 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 (Cssmin) 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 (Cssmax) and trough (Cssmin) 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 one-hour period every 8 hours the Cssmax was found to be 61.2 micromolar (13.8 microgram/ml) and the Cssmin 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. 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 Zovinex half-life during haemodialysis was 5.7 hours. Plasma Zovinex levels dropped approximately 60% during dialysis.
In a clinical study in which morbidly obese female patients (n=7) were dosed with intravenous Zovinex 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.

Distribution

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.

Elimination

In adults, the terminal plasma half-life of Zovinex after administration of Zovinex is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of Zovinex is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. 9-carboxymethoxy-methylguanine is the only significant metabolite of Zovinex and accounts for 10 to 15% of the dose excreted in the urine. When Zovinex 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.

5.3 Preclinical safety data

Mutagenicity:

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

Carcinogenicity:

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

Teratogenicity:

Systemic administration of Zovinex in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits 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 Zovinex greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of Zovinex on fertility.
Data to evaluate a potential effect on the environment is currently limited (see item 6.6 – disposal of Zovinex).

6. Pharmaceutical Particulars

6.1 List of Excipients

There are no excipients used in the formulation.

6.2 Incompatibilities

Zovinex must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-Life

Sealed pack: 3 years.
After reconstitution and/or dilution:
For reconstituted solutions, chemical and physical in-use stability has been demonstrated for 12 hours at 25° C or in a refrigerator (2° C – 8° C).
From a microbiological point of view, once opened, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2-8° C, unless reconstitution has taken place in controlled and validated aseptic conditions.
Following dilution using the fluids detailed in section 6.6, chemical and physical in-use stability has been demonstrated for:

	Room temperature (15° C – 25° C)	**Refrigerator (2° C – 8° C)**
Sodium Chloride Intravenous Infusion (0.9% w/v)	24 hours	24 hours
Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion	12 hours	Do not refrigerate or freeze
Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion	24 hours	8 hours
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution) – after reconstituted with purified water	Do not store below 25° C	12 hours
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution) - after reconstituted with Sodium Chloride (0.9% w/v)	Do not store below 25° C	8 hours

6.4 Special Precautions for storage

Store in the original package.

For storage conditions after reconstitution and/or dilution of the medicinal product, see section 6.3.

6.5 Nature and Content of container

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

6.6 Special precautions for disposal and other handling

For single use only.

Prepare immediately prior to use.

Reconstitution:

Zovinex should be reconstituted using the following volumes of either Water for Injections or Sodium Chloride Intravenous Injection (0.9% w/v) to provide a solution containing 25 mg Zovinex per ml:

Formulation	*Volume of fluid for reconstitution*
250 mg vial	10 ml

Volume following reconstitution: 10.1-10.2 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.

The solution reconstituted with Water for Injections or sodium chloride intravenous injection (0.9% w/v) is stable for a period of 12 hours at temperature below 25° C or in a refrigerator (2° C – 8° C).

Administration:

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

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

Alternatively, the reconstituted solution may be further diluted to give a Zovinex 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 Zovinex) 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 a Zovinex 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 Zovinex (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 mg and 1000 mg.

When diluted in accordance with the recommended schedules, Zovinex is known to be compatible with the following infusion fluids:
- Sodium Chloride Intravenous Infusion (0.9% w/v).
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion.
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion.
- Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution)

Zovinex when diluted in accordance with the above schedule will give a Zovinex 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.
Discard any unused solution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

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
CTD10778

9. Date of first authorization/renewal of the authorization
09/02/2024

10. Date of revision of the text
10th May, 2025