Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax IV for Infusion 250 mg, Powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg aciclovir (as the sodium salt).
The quantity after reconstitution is 25 mg aciclovir per mL.
Each vial contains 28.03 mg of sodium.
The quantity of sodium after reconstitution in 10 mL of water for injection is approximately 2.789 mg/mL.
The quantity of sodium after reconstitution in 10 mL of NaCl (0.9 % w/v) is approximately 6.403 mg/mL.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion
A white to off white freeze-dried sterile powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zovirax IV is indicated for:

Immunocompetent Patients	Immunocompromised Patients
Severe initial genital herpes	Herpes simplex infection
Recurrent varicella zoster virus infection	Primary and recurrent varicella zoster infection
	Prophylaxis of herpes simplex infection
Herpes simplex encephalitis	Herpes simplex encephalitis

4.2 Posology and method of administration

The required dose of Zovirax IV should be administered by slow intravenous infusion over 1 hour.

A course of treatment with Zovirax IV 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 usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for dissemination or central nervous system disease.

The duration of prophylactic administration of Zovirax IV is determined by the duration of the period at risk.

Table 1: Dosage for IV aciclovir in patients with normal renal function

Age group	Indication	Dosage
Adults and adolescents (≥12 years)	Immunocompetent and immunocompromised patients with *herpes simplex* (except herpes encephalitis) or immunocompetent patients with *varicella zoster*	5 mg/kg body weight every 8 hours
	Immunocompromised patients with *varicella zoster* infections or immunocompetent and immunocompromised patients with herpes encephalitis	10 mg/kg body weight every 8 hours

Infants and children (≥ 3 months to <12 years)	Immunocompetent and immunocompromised patients with *herpes simplex* (except herpes encephalitis) or immunocompetent patients with *varicella zoster*	10 mg/kg body weight every 8 hours
	Immunocompromised patients with *varicella zoster* infections or immunocompetent and immunocompromised patients with herpes encephalitis	20 mg/kg body weight every 8 hours
Neonates (<3 months)	Patients with known or suspected neonatal herpes (disseminated and CNS disease)	20 mg/kg body weight IV every 8 hours for 21 days
	Patients with known or suspected neonatal herpes limited to the skin and mucous membranes	20 mg/kg body weight IV every 8 hours for 14 days

Patients with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Renal impairment)

In obese patients who receive aciclovir intravenously based on their actual body weight, increased plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). A dose reduction should therefore be considered in obese patients, especially in patients with renal impairment or in elderly patients.

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

Renal impairment*:*
Caution is advised when administering aciclovir IV 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.

The following adjustments in dosage are recommended:

Table 2: Dosage adjustments for IV aciclovir in **adults and adolescents 12 years or older** with renal impairment for treatment of herpes simplex or varicella zoster virus infections

Creatinine Clearance	Dosage for herpes simplex infection (immunocompetent and immunocompromised patients) or varicella zoster (immunocompetent patients)	Dosage for herpes encephalitis (immunocompetent and immunocompromised patients) or varicella zoster (immunocompromised patients)
25 to 50 mL/min	5 mg/kg body weight given every 12 hours.	10 mg/kg body weight given every 12 hours.
10 to 25 mL/min	5 mg/kg body weight given every 24 hours.	10 mg/kg body weight given every 24 hours.

0 (anuric) to 10 mL/min	2.5 mg/kg body weight given every 24 hours.	5 mg/kg body weight given every 24 hours.
Patients on haemodialysis	2.5 mg/kg body weight given every 24 hours after dialysis.	5 mg/kg body weight given every 24 hours after dialysis.

Table 3: Dosage adjustments for IV aciclovir in **neonates, infants and children <12 years** with renal impairment for treatment of herpes simplex or varicella zoster virus infections

Creatinine Clearance (mL/min/1.73 m2)	Dosage for herpes simplex infection (immunocompetent and immunocompromised patients) or varicella zoster (immunocompetent patients)	Dosage for herpes encephalitis (immunocompetent and immunocompromised patients) or varicella zoster (immunocompromised patients)
25 to 50 mL/min/1.73m^2	10 mg/kg body weight given every 12 hours.	20 mg/kg body weight given every 12 hours
10 to 25 mL/min/1.73m^2	5 mg/kg body weight given every 12 hours.	10 mg/kg body weight given every 12 hours
0 (anuric) to 10 mL/min/1.73m^2	2.5 mg/kg body weight given twice a day.	5 mg/kg body weight given every 12 hours
Patients on haemodialysis	2.5 mg/kg body weight given twice a day after dialysis.	5 mg/kg body weight given every 12 hours

4.3 Contraindications

Zovirax IV is contraindicated in patients known to be hypersensitive to aciclovir and valaciclovir or to any of the excipients as listed in section 6.1.

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 adjusted in patients with renal impairment (see section 4.2).

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).

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 aciclovir IV 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 Zovirax IV has a pH of approximately 11 and should not be administered by mouth.

This medicinal product contains 28.03 mg sodium per vial, equivalent to 1.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 IV 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 coadministered.

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

4.6 Fertility, pregnancy and lactation

Fertility
See Clinical Studies in section 5.3

Pregnancy
The use of Zovirax Powder for IV Infusion 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 Zovirax. The registry findings have not shown an increase in the number of birth defects amongst Zovirax exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

Breast-feeding
Following oral administration of 200 mg aciclovir 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 Zovirax is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Zovirax IV 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 Zovirax 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 to <1/10); uncommon (>1/1000 to <1/100) rare (>1/10,000 to <1/1000); 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 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, 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 peakplasma levels and the state of hydration of the patient. To avoid this effect, when administered intravenously 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 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.

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 Zovirax IV for Infusion 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

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 an option in the management of overdose of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: group Anti infective, ATC code J05AB01.

Mechanism of Action

Aciclovir is an antiviral agent which is highly active *in vitro* against Herpes simplex virus (HSV) types I and II and Varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase.

Aciclovir triphosphate acts as an inhibitor of and substrate for the herpes specified DNA polymerase preventing further viral DNA synthesis without affecting normal cellular processes.

5.2 Pharmacokinetic properties

Elimination
In adults, the terminal plasma half-life has been determined as about 2.9 hours.

Most of the drug is excreted unchanged in 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 10-15% of the dose excreted in the urine.

When aciclovir 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.

Absorption
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 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 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. 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.

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.

5.3 Preclinical safety data

- **Fertility**

There is no information on the effect of aciclovir oral formulations or IV. for infusion 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.

- **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.

NON-CLINICAL INFORMATION

- **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.

- **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

This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Prior to reconstitution: 5 years.

From a microbiological point of view, the reconstituted product 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 room temperature, unless reconstitution has taken place in controlled and validated aseptic conditions.

Following further dilution to give a concentration not greater than 0.5% w/v of aciclovir, Zovirax is known to be compatible and stable for up to 12 hours (in the named infusion fluids listed in section 6.6) when stored at room temperature (15ºC to 25ºC).

The reconstituted or diluted solutions should not be refrigerated.

6.4 Special precautions for storage

Do not store above 25°C.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Clear colourless, Type I glass bottle (Ph. Eur.) with bromobutyl rubber stoppers or with a bromobutyl rubber stopper with a fluorinated polymer coating and aluminium collars with a polypropylene flip-top cover.

Pack size: 5 vials.

6.6 Special precautions for disposal and other handling

Prepare immediately prior to use. Discard any unused solution. Any unused product or waste materials should be disposed of in accordance with local requirements.

For intravenous infusion only.

For single use only.

Reconstitution: Each vial (containing the equivalent of 250 mg aciclovir) should be reconstituted by the addition of 10mL of either Water for Injections BP or Sodium Chloride Intravenous Infusion BP (0.9% w/v). This provides a solution containing 25 mg aciclovir per mL.

From the calculated dose, determine the appropriate number 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.

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

The reconstituted or diluted solutions should not be refrigerated. Should visible turbidity or crystallisation appear in the solution, before or during the infusion, the mixture should be discarded.

Administration: The required dose of Zovirax IV for infusion should be administered by slow intravenous infusion over a one-hour period. After reconstitution Zovirax IV for Infusion may be administered by a controlled-rate infusion pump. Alternately, 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.

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. Zovirax when diluted in accordance with the above schedules to give a concentration not greater than 0.5% w/v of aciclovir, is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15ºC to 25°C).

Sodium Chloride Intravenous Infusion BP (0.45% and 0.9% w/v).
Sodium Chloride (0.18% w/v) and Dextrose (4% w/v) Intravenous Infusion BP.
Sodium Chloride (0.45% w/v) and Dextrose (2.5% w/v) Intravenous Infusion BP.
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's solution).

7 MARKETING AUTHORISATION HOLDER

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12 Riverwalk
Citywest Business Campus
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