ZOVIRAX IV
Aciclovir

POWDER FOR I.V. INFUSION

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
ZOVIRAX 250 mg: The sodium ion content is approximately 26 mg per vial.

2. PHARMACEUTICAL FORM
Freeze dried powder for Injection.

3. CLINICAL PARTICULARS
3.1. Indications
ZOVIRAX IV for infusion is indicated for the treatment of herpes simplex infections in immune-compromised patients.

ZOVIRAX IV for infusion is indicated for the prophylaxis of herpes simplex infections in severely immune-compromised patients.

ZOVIRAX IV for infusion is indicated in the treatment of severe initial genital herpes.

ZOVIRAX IV for infusion is indicated in the treatment of primary and recurrent varicella zoster infections in immune-compromised patients.

ZOVIRAX IV for infusion is indicated in the treatment of shingles (recurrent varicella zoster infection) in patients with normal immune response.

ZOVIRAX IV for infusion is indicated for herpes simplex encephalitis patients over age 6 months.

3.2. Dosage and Administration
Dosage in Adults
Patients with herpes simplex (except herpes encephalitis) infections should be given *ZOVIRAX IV* for infusion in doses of 5 mg/kg bodyweight infused at a constant over a 1 hour period every 8 hours (15 mg/kg/day) for 7 days in patients with normal renal function.

For severe initial episode herpes simplex genitalis the same dosage as above are administered for 5 days.

For herpes simplex encephalitis, 10 mg/kg bodyweight infused at a constant rate over 1 hour period every 8 hour for 10 days with provided renal function is not impaired.

Immune-compromised patients with varicella zoster infection should be given 10 mg/kg bodyweight over 1 hour period every 8 hours for 7 days with provided renal function is not impaired.

Dosage in Children
The dose of *ZOVIRAX IV* for infusion for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children with herpes simplex infection should be given *ZOVIRAX IV* for infusion 250 mg/m^2 infused at a constant rate over a 1 hour period every 8 hours (750 mg/m^2/day) for 7 days.

In immune-compromised children with varicella zoster infection 500 mg/m^2 over a 1 hour period every 8 hours for 7 days.

For children in 6 months to 12 years with herpes simplex encephalitis, more accurate dosing is achieved by infusing 500 mg/m^2 at a constant rate over at least 1 hour every 8 hours for 10 days.

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Dosage in Elderly
In the elderly total acyclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Dosage in Renal Impairment
Caution is advised when administering *ZOVIRAX IV* for infusion to patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine clearance	Dosage
>50 mL/min	The dosage recommendation above (5 or 10 mg/kg bodyweight) should be given every 8 hours
25-50 mL/min	The dosage recommendation above (5 or 10 mg/kg bodyweight) should be given every 12 hours
10-25 mL/min	The dosage recommendation above (5 or 10 mg/kg bodyweight) should be given every 12 hours
0 (anuric)-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

3.3. Contraindications
ZOVIRAX IV for infusion is contra-indicated in patients known to be hypersensitive to aciclovir or valaciclovir.

3.4. Warnings and Precautions
In patients receiving *ZOVIRAX 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* for infusion has a pH of approximately 11.0 and should not be administered by mouth.

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 Dosage and Administration*). 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 Adverse Reactions*).

3.5. Interactions
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 *ZOVIRAX*, 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 *ZOVIRAX* with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

3.6. Pregnancy and Lactation

Pregnancy

A post-marketing *ZOVIRAX* pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of *ZOVIRAX*. The birth defects described amongst *ZOVIRAX* exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause.

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

Lactation

Following oral administration of 200 mg *ZOVIRAX* five times a day, aciclovir has been detected in 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/day. Caution is therefore advised if *ZOVIRAX* is to be administered to a nursing woman.

3.7. 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 aciclovir on driving performance or the ability to operate machinery.

3.8. Adverse Reactions

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 ≥1/1000 and <1/100, rare ≥1/10,000 and <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 Warnings and Precautions*).

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, 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 inadvertantly infused into extracellular tissues.

3.9. 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.

4. PHARMACOLOGICAL PROPERTIES
4.1. Pharmacodynamic Properties
Mechanism of Action
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, 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, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non-infected 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.

4.2. Pharmacodynamic 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.

Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK however, strains with altered viral TK or DNA polymerase have also been reported. In vitro exposure of HSV isolates to aciclovir can also lead to the emergence of less sensitive strains. The relationship between the in-vitro determined sensitivity of HSV isolates and clinical response to aciclovir therapy is not clear.

All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

4.3. Pharmacokinetic Properties

Absorption

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 22.7 micromoles (5.1 micrograms/mL), 43.6 micromoles (9.8 micrograms/mL), 92 micromoles (20.7 micrograms/mL) and 105 micromoles (23.6 micrograms/mL), respectively. The corresponding trough levels (C_{ssmin}) 7 h later were 2.2 micromoles (0.5 micrograms/mL), 3.1 micromoles (0.7 micrograms/mL), 10.2 micromoles (2.3 micrograms/mL) and 8.8 micromoles (2.0 micrograms/mL), respectively. In children over 1 year of age similar mean peak (C_{ssmax}) and trough (C_{ssmin}) 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.

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 aciclovir after administration of aciclovir i.v. for infusion is about 2.9 h. 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-carboxymethoxy-methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10 to 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 is extended by 18% and 40% respectively.

Special Patient Populations

In patients with chronic renal failure the mean terminal half life was found to be 19.5 h. The mean aciclovir half life during haemodialysis was 5.7 h. Plasma aciclovir levels dropped approximately 60% during dialysis.

In the elderly total body clearance falls with increasing age, associated with decreases in creatinine clearance, although there is little change in the terminal plasma half life.

4.4. Clinical Studies

There is no information on the effect of *ZOVIRAX 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 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

4.5. Preclinical Safety Data

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.

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

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.

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.

5. PHARMACEUTICAL PARTICULARS

5.1. List of Excipients
As registered locally.

5.2. Incompatibilities
No data.

5.3. Shelf Life
The expiry date is indicated on the packaging.
Store below 30°C.

5.4. Special Precautions for Storage
As registered locally.

5.5. Nature and Contents of Container
As registered locally.

5.6. Instructions for Use/Handling
Reconstitution
The required dose of *ZOVIRAX IV* for infusion should be administered by slow i.v. infusion over a one-hour period.

ZOVIRAX IV for infusion should be reconstituted using the following volumes of either water for injections BP or sodium chloride injection BP (0.9% w/v) to provide a solution containing 25 mg *ZOVIRAX* per mL:

Formulation	**Volume of fluid for reconstitution**
125 mg vial	5 mL
250 mg vial	10 mL
500 mg vial	20 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.

After reconstitution *ZOVIRAX IV* for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an *ZOVIRAX* 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, 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 *ZOVIRAX*) 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 *ZOVIRAX* 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 *ZOVIRAX* (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, *ZOVIRAX IV* for infusion is known to be compatible with the following infusion fluids and stable for up to 12 h 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).

ZOVIRAX IV for infusion when diluted in accordance with the above schedule will give an *ZOVIRAX* concentration not greater than 0.5% w/v.

When reconstituted as directed, *ZOVIRAX IV* for infusion has a pH of approximately 11.

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 solutions should not be refrigerated.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

5.7. Package Quantity and Reg. No.
Box contains 5 vials @ 250 mg. Reg. No. XXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Manufactured by
GlaxoSmithKline Manufacturing S.p.A.,
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