Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax I.V. 500 mg, Powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg acyclovir (as sodium salt).
The quantity after reconstitution is 25 mg acyclovir per ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zovirax I.V. is indicated for: Treatment of herpes simplex virus infections. Prophylaxis of herpes simplex infections in immunocompromised patients. Treatment of varicella zoster infections. Treatment of herpes simplex infections in the neonate.

4.2 Posology and method of administration

Dosage and administration.

Dosage in adults: Patients with herpes simplex (except herpes simplex encephalitis) or varicella zoster infections should be given Zovirax I.V. in doses of 5mg/kg bodyweight every 8 hours.

Immuno-compromised patients with varicella zoster infections or patients with herpes simplex encephalitis should be given Zovirax I.V. in doses of 10mg/kg bodyweight every 8 hours provided renal function is not impaired.

Dosage in children: The dose of Zovirax I.V. for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children with herpes simplex (except herpes simplex encephalitis) or varicella zoster infections should be given Zovirax I.V. in doses of 250mg per square metre of body surface area every 8 hours.

In immunocompromised children with varicella zoster infections or children with herpes simplex encephalitis, Zovirax I.V. should be given in doses of 500mg per square metre of body surface area every 8 hours if renal function is not impaired.

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

Dosage in neonates: The dosage of Zovirax I.V. in neonates is calculated on the basis of bodyweight. Neonates with herpes simplex infections should be given Zovirax I.V. in doses of l0mg/kg every 8 hours.

Dosage in the 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 I.V. to patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine Clearance	**Dosage**
25-50 ml/min	The dose recommended above (5 or 10mg/kg) should be given every 12 hours.
10-25 ml/min	The dose recommended above (5 or 10mg/kg) should be given every 24 hours.
0 (anuric) - 10ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10mg/kg) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg) should be halved and administered every 24 hours and after dialysis.

A course of treatment with Zovirax I.V. usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes simplex encephalitis usually lasts l0 days.

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

4.3 Contraindications

Zovirax I.V. is contra-indicated in patients known to be previously hypersensitive to acyclovir.

4.4 Special warnings and precautions for use

The dose of Zovirax I.V. must be adjusted in patients with impaired renal function in order to avoid accumulation of acyclovir in the body. In patients receiving Zovirax I.V. at higher doses (e.g. for herpes simplex encephalitis), specific care regarding renal function should be taken, particularly with patients who are dehydrated or have renal impairment.

Reconstituted Zovirax I.V. has a pH of approximately 11.0 and should not be administered by mouth.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid increases the acyclovir mean half-life and area under the plasma concentration time curve. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of acyclovir. However, clinical experience has not identified other drug-interactions with acyclovir.

4.6 Pregnancy and lactation

Limited data are available on the use of acyclovir during pregnancy. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard. Systemic administration of acyclovir 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.

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

Fertility: Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs

have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of (orally administered) acyclovir on fertility. There is no experience of the effect of Zovirax I.V. on human fertility. Zovirax tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

4.7 Effects on ability to drive and use machines

Zovirax 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 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 ≥1/100, 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: Decrease 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 reversible events are usually seen in medically complicated cases.

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.

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.

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 I.V. for Infusion has been inadvertently infused into extracellular tissues.

4.9 Overdose

Single doses of Zovirax I.V. up to 80mg/kg bodyweight have been inadvertently administered with no adverse consequences. Acyclovir is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of Action: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including herpes simplex virus (HSV) types I and II and varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, acyclovir 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 acyclovir for HSV I, HSV II, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non-infected cells does not use acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Prolonged or repeated courses of acyclovir in severely immunocompromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued acyclovir 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 acyclovir 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 acyclovir therapy is not clear. All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

5.2 Pharmacokinetic properties

In adults the terminal plasma half-life of acyclovir after administration of intravenous acyclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of acyclovir 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 acyclovir, and accounts for approximately 10-15% of the administered dose recovered from the urine. When acyclovir is given one hour after 1 gram of probenecid the terminal half-life and area under the plasma concentration-time curve is extended by 18% and 40% respectively.

In adults, mean C^{ss}max levels following a one hour infusion of 2.5mg/kg, 5mg/kg and 10mg/kg were 22.7 microMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding C^{ss}min levels 7 hours later were 2.2 microMol (0.5 micrograms/ml) 3.1 microMol (0.7 micrograms/ml) and 10.2 microMol (2.3 micrograms/ml), respectively. In children, over 1 year of age similar mean C^{ss}max and C^{ss}min levels were observed when a dose of 250 mg/m^2 was substituted for 5mg/kg and a dose of 500mg/m^2 was substituted for 10mg/kg. In neonates and young infants (0-3 months of age) treated with doses of 10mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}max was found to be 61.2 microMol (13.8 micrograms/ml) and the C^{ss}min to be 10.1 microMol (2.3 micrograms/ml). The terminal plasma half-life in these patients was 3.8 hours. 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.

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

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 tests *in vitro* and *in vivo* indicate that acyclovir is unlikely to pose a genetic risk to man. Acyclovir was not found to be carcinogenic in long-term studies in the rat and mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

6.2 Incompatibilities

None known.

6.3 Shelf Life

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 acyclovir, 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 (15° to 25°C).

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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 covers.

Pack size 5 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Prepare immediately prior to use. Discard any unused solution. For intravenous infusion only.

Reconstitution: Each 500mg vial should be reconstituted using 20ml of either Water for Injections BP or Sodium Chloride Intravenous Injection BP (0.9% w/v) to provide a solution containing 25mg acyclovir 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.

Administration: The required dose of Zovirax I.V. should be administered by slow intravenous infusion over a one-hour period.

After reconstitution Zovirax I.V. 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 5mg/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 4ml reconstituted solution (100mg acyclovir) added to 20ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100ml of infusion fluid be used, even when this would give an acyclovir concentration substantially below 0.5% w/v. Thus one 100ml infusion bag may be used for any dose between 250mg and 500mg acyclovir (10 and 20ml of reconstituted solution), but a second bag must be used for doses between 500 and 1000mg.

When diluted in accordance with the recommended schedules, Zovirax I.V. is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15^{o} to 25^{o}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 I.V. when diluted in accordance with the above schedule will give an acyclovir concentration not greater than 0.5% w/v.

Zovirax I.V. contains no antimicrobial preservatives. Reconstitution and dilution should therefore be carried out either under full aseptic conditions or immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated. Should any visible turbidity or crystallisation appear in the solution, before or during the infusion, the preparation should be discarded.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
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8 MARKETING AUTHORISATION NUMBER

PA 1077/84/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 1997

Date of last renewal: 24 April 2002

10 DATE OF REVISION OF THE TEXT

January 2006