Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aciclovir 25mg/ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25 mg aciclovir as aciclovir sodium
Each vial of 10 ml of solution contains 250 mg aciclovir (sodium salt formed *in situ*)
Each vial of 20 ml of solution contains 500 mg aciclovir (sodium salt formed *in situ*)

Excipient(s) with known effect:
Each ml of solution contains 2.67 mg of sodium

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
A clear, colourless solution, free from visible particles
pH of the solution is between 10.70 and 11.70 and osmolarity of the solution is 353.01 mosmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Aciclovir is indicated for the treatment of Varicella zoster infections.

Aciclovir is indicated for the treatment of herpes encephalitis.

Aciclovir 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 Aciclovir 25 mg/ml Concentrate for solution for infusion 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 Aciclovir 25 mg/ml Concentrate for solution for infusion is determined by the duration of the period at risk.

Dosage in adults:

Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given Aciclovir 25 mg/ml Concentrate for solution for infusion in doses of 5 mg/kg bodyweight 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 Aciclovir 25 mg/ml Concentrate for solution for infusion in doses of 10 mg/kg bodyweight every 8 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.

Paediatric Population: The dose of Aciclovir 25 mg/ml Concentrate for solution for infusion 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 Aciclovir 25 mg/ml Concentrate for solution for infusion 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, Aciclovir 25 mg/ml Concentrate for solution for infusion 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 Aciclovir 25 mg/ml Concentrate for solution for infusion 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

acyclovir 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 and dosage should be adjusted accordingly (see *Dosage in renal impairment below*).

Adequate hydration should be maintained.

Dosage in renal impairment: Caution is advised when administering Aciclovir 25 mg/ml Concentrate for solution 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/1.73m2 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 adjustments in infants and children:

Creatinine Clearance	Dosage
25 to 50 ml/min/1.73 m^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/1.73 m^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/1.73 m^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 25 mg/ml Concentrate for solution for infusion should be administered by slow intravenous infusion over a one-hour period and adequate hydration should be established.

Aciclovir 25 mg/ml Concentrate for solution for infusion may be administered by a controlled-rate infusion pump.

Refer to Section 6.6 for instructions on use, preparation and handling.

4.3 Contraindications

Hypersensitivity to aciclovir and valaciclovir or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

Solutions of aciclovir are alkaline (pH of approximately 11) and intended for intravenous infusion only and should not be used by any other route.

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 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 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 25 mg/ml concentrate for solution 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.

Aciclovir should not be administered by mouth. Product contains sodium (26mg, approx. 1,13mmol). To be taken into consideration by patients on a controlled sodium diet.

Aciclovir 25 mg/ml concentrate for solution for infusion contains no antimicrobial preservative. dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. diluted solutions should not be refrigerated.

Other warnings and precautions
The labels shall contain the following statements:
For intravenous infusion only
Keep out of the reach and sight of children
Store below 25°C
Prepare immediately prior to use
Discard unused solution
This medicinal product contains 0.116 mmol (or 2.67 mg) sodium per ml, 1.16 mmol (or 26.7 mg) sodium per 10 ml vial & 2.32 mmol (or 53.4 mg) sodium per 20 ml vial. This has to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

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 coadministered.

If **lithium** is administered concurrently with high dose aciclovir IV, the lithium serum concentration should be closely monitored because of the risk of lithium toxicity.

Care is also required (with monitoring changes in renal function) if administering Aciclovir 25 mg/ml Concentrate for solution for infusion with drugs which affect other aspects of renal physiology (e,g, cyclosporine, tacrolimus).

An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered theophylline with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

4.6 Fertility, pregnancy and lactation

Pregnancy:
A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Aciclovir 25 mg/ml Concentrate for solution for infusion. The registry findings have not shown an increase in the number of birth defects amongst Aciclovir 25 mg/ml Concentrate for solution for infusion 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 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 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, 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 body weight/day. Caution is therefore advised if Aciclovir 25 mg/ml concentrate for solution for infusion is to be administered to a nursing woman.

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.
See clinical studies in section 5.2

4.7 Effects on ability to drive and use machines

Aciclovir 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 aciclovir 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: decrease in haematological indices (anemia, 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: diarrhea, abdominal pain.

Hepatobiliarydisorders:
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 the 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 Aciclovir 25 mg/ml Concentrate for solution for infusion has been inadvertently infused in to extra cellular 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971 FREE; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Toxicity and treatment of overdosage

Overdosage of intravenenous 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.
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: Direct acting Antivirals, nucleosides and nucleotidesexcludingreverse transcriptaseinhibitors
ATC Code: J05A B01.

Aciclovir 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 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 in to the viral DNA.

Mechanism of Resistance:
Resistance to aciclovir is rare, but is more common in patients on chronic antiviral prophylaxis (transplant recipients, people with acquired immunodeficiency syndrome due to HIV infection). Mechanisms of resistance in HSV include deficient viral thymidine kinase; and mutations to viral thymidine kinase and/or DNA polymerase, altering substrate sensitivity. Acyclovir has also shown cross-resistance with valacyclovir and famcyclovir.

5.2 Pharmacokinetic properties

In adults, the terminal plasma half-life of aciclovir after administration of Aciclovir 25 mg/ml Concentrate for solution for infusion is about 2.9 hours.

Absorption:
In adults, mean steady state peak (C^{ss}max) plasma concentrations following a one-hour infusion were;

	2.5 mg/kg	5 mg/kg	10 mg/kg
C^{ss} max in µmol or in (µg/ml)	22.7 (5.1)	43.6 (9.8) 43.6 (9.8)	92 (20.7) 92 (20.7)
C^{ss} min, after 7 hours, in µmol or in (µg/ml)	2.2 (0.5)	3.1 (0.7) 3.1 (0.7)	10.2 (2.3) 10.2 (2.3)

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/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 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).

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.

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:
Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.
Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels.

Biotransformation:
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.

Elimination:
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.

Renal Impairment:
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.

5.3 Preclinical safety data

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.

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.

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 aciclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

None known.

6.3 Shelf life

Unopened: 24 months.
After dilution: Chemical and physical in-use stability has been demonstrated for 12 hours at 25^{o}C.
From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Keep this medicine out of the sight and reach of children

Do not store this medicine above 25°C. Do not refrigerate.
Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Glass vials closed with Teflon coated rubber stopper and flip-off seal.

5, 10 and 20 x 10ml
5, 10 and 20 x 20ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Refrigeration is not recommended as precipitation may occur.

Administration:

The required dose of Aciclovir 25 mg/ml concentrate for solution for infusion should be administered by slow intravenous infusion over a one hour period.

Aciclovir product can be 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 Aciclovir product to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs.

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 but a second bag must be used for any doses between 500 and 1000 mg. Aciclovir 25 mg/ml Concentrate for solution for infusion should not be diluted to a concentration greater than 5 mg/ml (0.5%w/v) for administration by infusion. After addition of Aciclovir 25 mg/ml Concentrate for solution for infusion to an infusion solution, the mixture should be shaken to ensure thorough mixing.

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 of solution (100 mg aciclovir) added to 20 ml of infusion fluid.

When diluted in accordance with the recommended schedules, Aciclovir 25 mg/ml Concentrate for solution for infusion is known to be compatible with the following infusion fluids and stable for up to 12 hours at room temperature (15^0 C to 25^0 C):

Sodium Chloride Intravenous Infusion BP (0.45% w/v 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 (Hartmann's Solution).

Dilutions of Aciclovir in the above mentioned diluents have been demonstrated to be stable in Non polyvinyl chloride (Non-PVC) infusion bags.

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 crystallisation appear in the solution before or during infusion, the preparation should be discarded.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/041/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 27th March 2013
Date of Last Renewal: 16th December 2017

10 DATE OF REVISION OF THE TEXT

October 2018