SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir Agila 25mg/ml powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the reconstituted solution for infusion contains aciclovir sodium dihydrate equivalent to 25 mg of aciclovir. .

Each 10 ml vial contains aciclovir sodium dihydrate equivalent to 250 mg of aciclovir.

Each 20 ml vial contains aciclovir sodium dihydrate equivalent to 500 mg of aciclovir.

This medicinal product contains 24.5 mg sodium per dose.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion

White to off white lyophilized powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Aciclovir Agila is indicated for the treatment of *Varicella zoster* infections in immune-competent patients in whom a severe course can be anticipated.

Aciclovir Agila is indicated for the treatment of herpes encephalitis.

Aciclovir Agila 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

Posology

Dosage in adults:
Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given Aciclovir Agila 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 Aciclovir Agila 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 aciclovir based on their actual body weight, higher plasma concentrations may be obtained (see section 5.2). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

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

Children 3 months of age or older with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given Aciclovir Agila 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 Agila 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 Agila 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 Agila 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/1.73m^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

Method of administration:
For intravenous use
Slow intravenous infusion over 1 hour.

A course of treatment with Aciclovir Agila 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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Aciclovir Agila is contra-indicated in patients with known hypersensitivity to aciclovir or valaciclovir or to any of the excipients

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 Agila 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.

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."

Reconstituted Aciclovir Agila has a pH of approximately 11 and should not be administered by mouth. Extravascular infusion can cause a severe local inflammation, possibly with tissue necrosis.

Contact with the eyes and the unprotected skin must be avoided.

This medicinal product contains less than 1 mmol sodium (24.5 mg) per dose, i.e. essentially 'sodium- free.

4.5 Interaction with other medicinal products and other forms of interaction

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 Agila 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.

In certain case reports, intra venous aciclovir co-administered with lithium led to a fourfold increase of the plasmatic levels of lithium. Concomitant administration with interferon may possibly lead to a mutual potentiation.

Care is also required (with monitoring for changes in renal function) if administering intravenous Aciclovir Agila with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus) because they may influence the nephrotoxic effect of aciclovir.

According to one case report, co-administration of intravenous aciclovir and lithium caused a four-fold increase in lithium serum concentrations. Lithium concentrations should be closely monitored and reduced lithium dose may be needed.

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

When aciclovir is administered concomitantly with theophylline, close monitoring of theophylline concentrations and possible theophylline dose reduction is recommended An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered theophylline with approximately 50%.

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.

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

Animal studies do not indicate reproductive toxicity in internationally accepted standards tests (see Section 5.3).

The use of Aciclovir Agila should be considered only when the potential benefits outweight any possible unknown risks.

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 Agila 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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).

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 Aciclovir Agila 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 (see details below).

[To be completed nationally]

4.9 Overdose

Symptoms and Signs
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.

Treatment
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

ATC Code: J05A B01
Pharmacotherapeutic group: Direct Acting Antiviral; Nucleosides and nucleotides excl. reverse transcriptase inhibitors

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 into the viral DNA.

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype which results in a virus which is disadvantaged in the natural host. Reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent host and is found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

5.2 Pharmacokinetic Properties

Distribution

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/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).

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.

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 Agila is about 2.9 hours. 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 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, 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 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 (orally administered) aciclovir on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

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

6.3 Shelf life

2 years

Following dilution using the solutions in section 6.6: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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.

For reconstituted solutions, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml Ph Eur Type I glass vial with bromobutyl rubber stopper and light blue aluminium flip off seal.

20 ml Ph Eur Type I glass vial with bromobutyl rubber stopper and dark green aluminium flip off seal.

Pack sizes: 1, 5 or 10 vials in a carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution: Aciclovir Agila should be reconstituted using the following volumes of either Water for Injections or Sodium Chloride 9mg/ml (0.9% w/v) *solution for infusion* to provide a solution containing 25 mg aciclovir per ml:

Formulation	*Volume of solution for reconstitution*
250 mg vial	10 ml
500 mg vial	20 ml

From the calculated dose, determine the appropriate number and size of vials to be used. To reconstitute each vial add the recommended volume of infusion solution and shake gently until the contents of the vial have dissolved completely.

Administration:

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

Alternatively, 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 solution 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 solution.

For adults, it is recommended that infusion bags containing 100 ml of infusion solution 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 mg and 1000 mg.

When diluted in accordance with the recommended schedules, Aciclovir Agila is known to be compatible with the following infusion solutions and stable for up to 24 hours at room temperature (25°C):

Sodium Chloride 4.5 mg/ml (0.45%) and 9 mg/ml (0.9% w/v) *solution for infusion*

Sodium Chloride 1.8 mg/ml (0.18% w/v) and Glucose (4% w/v) *solution for infusion*

Sodium Chloride 4.5 mg/ml (0.45% w/v) and Glucose (2.5% w/v) *solution for infusion*

Compound Sodium Lactate (Hartmann's Solution) *solution for infusion*.

Aciclovir Agila when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

This medicinal product is for single use only.

Aciclovir Agila contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.

The medicinal product is to be visually inspected prior to use (also after dilution). *Only clear solutions practically free from particles should be used*. Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

Displacement value for the powder is 0.50mL and the final volume in the container after reconstitution is 10.50mL

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally