



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir Powder for Infusion 250mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION (Active)

Each vial contains 250mg Aciclovir (as the sodium salt) in a freeze-dried sterile powder form.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Powder for Solution for Infusion

Sterile powder for infusion packaged in colourless 20ml glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment and prophylaxis of *Herpes simplex* virus infections in immunocompromised patients.
- Treatment of severe initial genital herpes in non-immunocompromised patients.
- Treatment of *Herpes simplex* encephalitis.
- Treatment of *Varicella zoster* infections.
- Treatment of *Herpes simplex* infections in the neonate and in infants up to age 3 months.

4.2 Posology and method of administration

Route of administration: Slow intravenous infusion

The duration of intravenous therapy with Aciclovir is usually 5 days and may be adjusted in accordance with the condition of the patient and the response to therapy. For herpes encephalitis and neonatal *Herpes simplex* infections, the duration of therapy is usually 10 days.

When used for prophylaxis, the duration of intravenous administration of Aciclovir is determined by the duration of the risk period.

Dosage in adults : The recommended dosage for adults with *Herpes simplex* (excluding herpes encephalitis) or *Varicella zoster* infections is 5mg per kg bodyweight every 8 hours, provided that renal function is not impaired.

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Aciclovir intravenously in doses of 10mg per kg bodyweight every 8 hours, provided that renal function is not impaired.

Dosage in children : The recommended dosage for children with *Herpes simplex* (excluding herpes encephalitis) or *Varicella zoster* infections is 250mg per square metre of body surface area every 8 hours.

Immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis should be given Aciclovir intravenously in doses of 500mg per square metre of body surface area every 8 hours if renal function is not impaired.

For children with renal impairment, the dosage should be modified, appropriately, according to the degree of impairment.

Dosage in neonates and infants up to age 3 months : The recommended dosage for treatment of *Herpes simplex* infections is 10mg per kg bodyweight every 8 hours. For neonatal *Herpes simplex* infections, the usual duration of treatment is 10 days.

Dosage in the elderly : The total body clearance of Aciclovir in the elderly declines in parallel with creatinine clearance. In elderly patients with impaired creatinine clearance, particular attention should be given to dosage reduction.

Dosage in renal impairment : Particular care should be taken when administering Aciclovir intravenously to patients with impaired renal function. Dosage adjustments are suggested as follows :

<i>Creatinine Clearance</i> (ml/min.)	<i>Dosage</i>
25 - 50	The doses recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be given every 12 hours.
10 - 25	The doses recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be given every 24 hours.
0 (anuric) - 10	For patients receiving continuous ambulatory peritoneal dialysis (CAPD) the doses recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be halved and given every 24 hours. For patients receiving haemodialysis, the doses recommended above (5 or 10mg/kg bodyweight or 500mg/m ²) should be halved and administered every 24 hours <i>and</i> after dialysis.

4.3 Contra-indications

Known hypersensitivity to aciclovir or valaciclovir.

4.4 Special warnings and special precautions for use

If renal function is impaired, the intravenous dose must be adjusted in order to avoid accumulation of Aciclovir in the body (see *Dosage in renal impairment* above).

When higher doses of Aciclovir are administered (e.g. for herpes encephalitis), specific care regarding renal function should be exercised, especially if the patient is dehydrated or has any renal impairment.

The reconstituted solution is highly alkaline and should not be administered orally.

Aciclovir Powder for Infusion 250mg does not contain an antimicrobial preservative. Reconstitution and dilution should, therefore, be performed under full aseptic conditions, immediately before use, and any unused solution should be discarded. Reconstituted or diluted solutions should not be refrigerated.

Other warnings and precautions:

The labels shall contain the following statements:

For intravenous infusion only

Keep out of reach of children

Do not store above 25°C

After reconstitution and dilution use immediately

Discard any unused portion.

4.5 Interactions with other medicaments and other forms of interaction

No clinically significant interactions have been identified.

Aciclovir is eliminated mainly unchanged in the urine via active renal tubular secretion. Concomitant administration of any drugs that compete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce its renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Caution is required during concurrent intravenous administration of aciclovir 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, including monitoring for changes in renal function, if administering intravenous aciclovir with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus)

4.6 Pregnancy and lactation

As only limited data on the use of Aciclovir in human pregnancy are available, caution is required and the potential benefits of treatment should be weighed against any possible unknown risks.

Following oral administration of Aciclovir 200mg five times a day, the drug has been detected in breast milk in concentrations of between 0.6 to 4.1 times the corresponding plasma levels. As these levels could potentially expose nursing infants to dosages of Aciclovir of up to 0.3mg/kg/day, caution is advised if the drug is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Gastrointestinal: Nausea and vomiting have been reported.

Haematological: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia)

Hypersensitivity and Skin: Rashes including photosensitivity, urticaria, pruritus, fevers and rarely dyspnoea, angioedema and anaphylaxis.

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when aciclovir I.V. has been inadvertently infused in extravascular tissues.

Kidney: Rapid increases in blood urea and creatinine levels may occasionally occur in patients given aciclovir I.V., putatively in relation to peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should be given by slow infusion over a one hour period, and not as an intravenous bolus injection.

Adequate hydration of the patient should be maintained. If renal impairment develops during intravenous administration of aciclovir, it 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.

Liver: Reversible increases in bilirubin and liver-related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Neurological: Reversible neurological reaction such as confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with aciclovir I.V. therapy, usually in medically complicated cases.

4.9 Overdosage

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. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. *In-vitro* and *in-vivo*, Aciclovir demonstrates antiviral 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, aciclovir has the greatest antiviral activity against HSV-I, followed in decreasing order of potency by HSV-II, VZV, EBV and CMV. This activity is due to intracellular conversion of Aciclovir by viral thymidine kinase to aciclovir monophosphate with subsequent conversion to the diphosphate and then to the active triphosphate form. Aciclovir triphosphate inhibits viral DNA synthesis and replication by inhibiting the viral DNA polymerase enzyme as well as being incorporated into the viral DNA. The inhibitory activity of Aciclovir against HSV1, HSV11 and VZV is highly selective for infected cells : thymidine kinase in normal, non-infected cells does not use Aciclovir effectively as a substrate, therefore, toxicity to the host cells is low.

5.2 Pharmacokinetic properties

Following intravenous administration of Aciclovir in adults, the terminal plasma half-life is about 2.9 hours. Aciclovir is excreted through the kidney by both glomerular filtration and tubular excretion, mainly as unchanged drug with 10 to 15% appearing in the urine as the 9-carboxymethoxymethylguanine metabolite. Prior administration of probenecid increases the half-life and the area under the plasma concentration/time curve of Aciclovir.

Infusion over one hour of 2.5mg, 5mg, 10mg and 15mg Aciclovir per kg body weight in adults has produced mean steady state peak plasma concentrations of 5.1, 9.8, 20.7 and 23.6µg/ml, respectively. The corresponding trough levels 7 hours later were 0.5, 0.7, 2.3 and 2.0µg/ml, respectively. Similar mean peak and trough levels were observed in children aged over one year when doses of 250mg/m² and 500mg/m² were substituted for 5mg/kg and 10mg/kg respectively. A dose of 10mg/kg infused over a one hour period every 8 hours in neonates of up to 3 months of age produced a mean steady state peak plasma concentration of 13.8µg/ml and a corresponding trough level of 2.3µg/ml. The terminal plasma half-life in these patients was 3.8 hours.

Although there is little change in the terminal plasma half-life of Aciclovir in the elderly, there is an age-related decrease in total body clearance associated with decreases in creatinine clearance.

In patients with chronic renal failure, the mean terminal half-life was found to be 19.5 hours. During haemodialysis, the mean half-life of Aciclovir was 5.7 hours and plasma levels of the drug declined by approximately 60% during dialysis.

Concentrations of Aciclovir in cerebrospinal fluid are approximately 50% of those achieved in plasma. Protein binding ranges from 9 to 33% and drug interactions that involve displacement from binding sites are not anticipated.

Aciclovir crosses the placenta and is excreted in breast milk.

5.3 Preclinical safety data

Results of various *in-vivo* and *in-vitro* mutagenicity tests indicate that Aciclovir is unlikely to pose a genetic risk in man. Aciclovir did not show any carcinogenic activity in lifetime studies in rats and mice.

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 only after such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

At doses of Aciclovir greatly in excess of those used therapeutically, largely reversible effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported. Aciclovir tablets have been shown to have no definite effects on sperm count, morphology or motility in man.

There is no experience of the effect of Aciclovir intravenous infusions on human female fertility. Two-generation studies in mice did not reveal any effects of orally administered Aciclovir on fertility.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients (Qualitative)

Sodium Hydroxide

Water for Injections *

*almost completely removed during lyophilization.

6.2 Incompatibilities

Aciclovir Powder for Infusion 250mg is compatible with the infusion fluids listed below (see Instructions for use and handling 6.6, below). Compatibility with other agents has not been established.

6.3 Shelf life

Unopened : 3 years
 After first opening : not applicable.

6.4 Special precautions for storage

Do not store above 25°C. Store the vials in the original packaging.
 After reconstitution use immediately. Discard any unused portion

6.5 Nature and contents of container

Colourless glass type 1 vials closed with bromobutyl rubber stopper and aluminium seal with a blue flip-off cap.

Pack sizes : Vials of 20ml each containing the equivalent of 250mg of Aciclovir packaged per 1 or 5 in a box.

6.6 Instructions for use/handling

Reconstitution : The contents of each vial (equivalent to 250mg Aciclovir) should be reconstituted by adding 10ml of Water for Injections B.P. and shaking gently until the powder has fully dissolved. This provides a solution containing Aciclovir 25mg per ml. The calculated dose can be used to determine the number of vials to be used.

Administration : The required dose of Aciclovir should be administered by slow intravenous infusion over a one hour period.

After reconstitution, the solution containing 25mg Aciclovir per ml 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 5mg per ml (0.5% w/v) for administration by infusion.

The required volume of reconstituted solution (containing 25mg Aciclovir per ml) should be added to the chosen infusion solution, as recommended below, and then shaken well to ensure adequate mixing.

For children and neonates, where lower infusion volumes are generally required, the recommended dilution is based on the addition of 4ml reconstituted solution (Aciclovir 100mg) to 20ml of infusion fluid.

For adults, use of infusion bags containing 100ml of infusion fluid is recommended, even when this would result in an Aciclovir concentration significantly below 0.5% w/v. A 100ml infusion bag may be used for any dose between 250 - 500mg Aciclovir but a second bag must be used for doses between 500 - 1,000mg.

When diluted as recommended, the drug is compatible with the following infusion fluids and is stable for up to 12 hours at room temperature (15°C to 25°C) :

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

Reconstitution and dilution should be performed immediately before use, under full aseptic conditions, and any unused solution should be discarded. The formulation does not contain an antimicrobial preservative.

The reconstituted or diluted solution should not be refrigerated.
If turbidity or crystallisation appear in the solution prior to or during an infusion, the solution should be discarded.

Please refer to enclosed patient information leaflet

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd
Roscrea
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

PL 02848/0190

9. DATE OF FIRST AUTHORISATION

27 February 2002

10. DATE OF (PARTIAL) REVISION OF THE TEXT