Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ACIC 250 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg aciclovir as the freeze-dried sodium salt.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ACIC is indicated for:

Non-Immuno-compromised Patients	**Immuno-compromised Patients**
Severe initial genital herpes	Herpes simplex infection
Recurrent varicella Zoster virus infection	Primary and recurrent varicella zoster infection Prophylaxis of herpes simplex infection
Herpes simplex encephalitis	Herpex simplex encephalitis

4.2 Posology and method of administration

Route of Administration: Intravenous.

Recommended Dosage Schedule:

Indication	**Immune Status**	**Dosage**
Herpes simplex infections	Normal or Immuno-compromised	5 mg/kg every 8 hours
Recurrent varicella zoster infections	Normal	5 mg/kg every 8 hours
Primary and recurrent varicella zoster infections	Immuno-compromised	10 mg/kg every 8 hours
Herpes simplex encephalitis	Normal or Immuno-compromised	10 mg/kg every 8 hours

The required dose of ACIC should be administered by slow intravenous infusion over a one-hour period.

A course of treatment with ACIC 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 10 days.

The duration of prophylactic administration of ACIC is determined by the duration of the period at risk.

Patients with renal impairment should be administered ACIC with caution. The following modifications in dosage are recommended:

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

Dosage in children: The dosage of ACIC in neonates is calculated on the basis of bodyweight. Although its use in neonatal, herpes is still experimental, doses of 10mg/kg have been employed.

The dose of ACIC 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 ACIC in doses of 250 mg per square metre of body surface area every 8 hours.

In immunocompromised children with varicella zoster infections or children with herpes simplex encephalitis, ACIC should be given in doses of 500 mg per square metre 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 the elderly: In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Administration: The required dose of ACIC for infusion should be administered by slow intravenous infusion over a one-hour period. After reconstitution ACIC for Infusion may be administered by a controlled-rate infusion pump. Alternately, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5mg/ml (0.5% w/v) for administration by infusion.

4.3 Contraindications

Contra-indications: ACIC is contra-indicated in patients known to be previously hypersensitive to aciclovir.

Precautions: The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long-term studies in the rat and mouse.

Aciclovir should be administered with caution to patients with hepatic or renal impairment and in the elderly.

The dosage of ACIC for Infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body. In patients receiving ACIC 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 of the patient should be maintained, to avoid rapid increases in blood urea and creatinine associated with I.V. aciclovir and inadequate hydration.

Aciclovir should be administered by slow infusion over one hour and not as a bolus intravenous injection.

Reconstituted ACIC has a pH of approximately 11 and should not be administered by mouth.

4.4 Special warnings and precautions for use

No special precautions necessary.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Experience in humans is limited, so the use of ACIC should be considered only when the potential benefits outweigh the possibility of unknown risks.

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.

Following oral administration of 200mg 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 doses of up to 0.3 mg/kg bodyweight/day. Caution is therefore advised if ACIC is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

No specific studies have been conducted, but there is no evidence to suggest that aciclovir will adversely affect ability to drive and operate machines.

4.8 Undesirable effects

Rapid increases in blood urea and creatinine levels may occasionally occur in patients given ACIC. This is believed to be related to 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. Adequate hydration of the patient should be maintained.

Renal impairment developing during treatment with ACIC usually responds rapidly to hydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

Severe local inflammatory reactions, leading to breakdown of the skin, has occurred when ACIC has been inadvertently infused into extravascular tissues.

Reversible neurological reactions, usually consisting of tremor sometimes associated with confusion and electroencephalographic changes have been associated with ACIC therapy.

Nausea and vomiting have been reported in patients receiving therapy with ACIC.

Other events reported in patients receiving ACIC include increases in liver-related enzymes, increases in levels of bilirubin, and rashes.

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.

ACIC Tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

There has been no experience of the effect of ACIC on human female fertility. Two-generation studies in mice did not reveal any effect of aciclovir on fertility.

4.9 Overdose

Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialysable by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV and CMV. The inhibitory activity of aciclovir 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 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.

Properties: Aciclovir, converted to the active compound by viral thymidine kinase, inhibits the herpes virus DNA polymerase. Absorption from the oral route is variable. The drug is poorly protein bound and is excreted mainly through the kidney with a T ½ of 3-4 hours.

Prolonged or repeated courses of aciclovir in severely immunocompromised 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.

5.2 Pharmacokinetic properties

In adults the terminal plasma half life of aciclovir after administration of intravenous aciclovir 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- Carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for approximately 10-15% of the administered dose recovered from the urine. When aciclovir 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 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 mMol (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 5 mg/kg and a dose of 500 mg/m 2 was substituted for 10 mg/kg.

In neonates and young infants (0-3 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 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 aciclovir half life during haemodialysis was 5.7 hours. Plasma aciclovir 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 aciclovir is unlikely to pose a genetic risk to man. Aciclovir was not carcinogenic in long term studies in the rat and the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide

6.2 Incompatibilities

None known.

6.3 Shelf Life

2 years.

Chemical and physical in-use stability for the reconstituted solution and the diluted solution has been demonstrated for 24 hours at 2 to 8°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 and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

ACIC is packed in 25ml colourless type I Ph. Eur. glass vials with red coloured rubber stopper, composed of chlorobutylastomer, B-50-1-05-B, type 1 Ph. Eur., and aluminium flip-off seal with PP-disc. It is available in packs of 10 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

Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions immediately before use and any unused solution should be discarded. Should visible turbidity or crystallisation appear in the solution, before or during the infusion, the mixture should be discarded.

Reconstitution: Each vial (containing the equivalent of 250 mg aciclovir) should be reconstituted by the addition of 10 ml of either Dextrose (5% w/v) or Sodium Chloride injection (0.9% w/v). This provides a solution containing 25 mg aciclovir per ml.

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 aciclovir) added to 20ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus one 100ml infusion bag may be used for any dose between 250mg and 500mg aciclovir (10 and 20ml of reconstituted solution), but a second bag must be used for does between 500 and 1000mg. ACIC when diluted in accordance with the above schedules to give a concentration not greater than 0.5% w/v of aciclovir, is known to be compatible with the following infusion fluids and stable for up to 24 hours at 2 to 8°C).

Sodium Chloride (0.9% w/v).

Dextrose (5% w/v).

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Newtown
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/17/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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