Aciclovir

Core Safety Profile (systemic)

4.2 Posology and method of administration

Oral formulations:

Dosage in the elderly:
The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Dosage in renal impairment below).
Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

Dosage in renal impairment:
Caution is advised when administering aciclovir to patients with impaired renal function.
Adequate hydration should be maintained.
In the management of herpes simplex infections in patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.
In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800 mg aciclovir twice daily at approximately twelve - hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800 mg aciclovir three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10 – 25 ml/minute).

Powder for I.V. infusion:

Elderly:
The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Renal impairment below).
Adequate hydration should be maintained.

Dosage in children
Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).

Renal impairment:
Caution is advised when administering aciclovir i.v. for infusion to patients with impaired renal function.
Adequate hydration should be maintained.

~~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.

Oblikovano: Pisava: 12 pt, Krepko
Oblikovano: Na sredini
Oblikovano: Pisava: 12 pt
Oblikovano: Pisava: 12 pt, Krepko
Oblikovano: Pisava: 12 pt
Oblikovano: angleščina (Združeno kraljestvo)

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/1.73m2	The dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min/1.73m2	The dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be given every 24 hours.
0(anuric) to 10 ml/min/1.73m2	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m2 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/m2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis

Oblikovano: nizozemščina (Nizozemska)

4.3. Contraindications

Aciclovir tablets, suspension and i.v. for infusion are contraindicated in patients known to be hypersensitive to aciclovir and valaciclovir or to any of the excipients.

4.4. Special warnings and precautions for use

Oral formulations:

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

The risk of renal impairment is increased by use with other nephrotoxic drugs.

Use in patients with renal impairment and in elderly patients:
Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction 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).

Powder for I.V. infusion:

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.

Use in patients with renal impairment and in elderly patients:
Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction 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).

In patients receiving aciclovir i.v. 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.

Reconstituted aciclovir i.v. for infusion has a pH of approximately 11.0 and should not be administered by mouth.

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).

Product contains sodium (26mg, approx. 1,13mmol).

4.5. Interactions with other medicinal products and other forms of interaction

Oral formulations:
~~No clinically significant interactions have been identified.~~
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. Similarly 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. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

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.
Powder for I.V. infusion:
~~No clinically significant interactions have been identified.~~
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 i.v. 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.

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.

Fertility
See Clinical Studies in section 5.2

Pregnancy
The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.
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. 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.

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

4.7. Ability to perform tasks that require judgement, motor or cognitive skills

Oral formulations:
The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patients's ability to drive or operate machinery.
There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

Powder for I.V. Infusion:
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 ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Oral formulations

Blood and lymphatic system disorders
Very rare: Anaemia, leukopenia, thrombocytopenia

Immune system disorders
Rare: Anaphylaxis

Psychiatric and nervous system disorders
Common: Headache, dizziness
Very rare: 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 section 4.4).

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, abdominal pains

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes
Very rare: Hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: Pruritus, rashes (including photosensitivity)
Uncommon: Urticaria, accelerated diffuse hair loss.

Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Rare: Angioedema

Renal and urinary disorders
Rare: Increases in blood urea and creatinine
Very rare: Acute renal failure, renal pain

Renal pain may be associated with renal failure.

General disorders and administration site conditions
Common: Fatigue, fever

Powder for I.V. Infusion:

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 section 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 i.v. bolus injection but by slow infusion over a 1 h period.

Very rare: Renal impairment, acute renal failure, renal pain

Adequate hydration should be maintained. Renal impairment usually responds rapidlyto 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.

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 i.v. for infusion has been inadvertantly infused into extracellular tissues.

4.9. Overdose

Symptoms and Signs

Oral formulations:
Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

Oral formulations and Powder for I.V. infusion:

Overdosage of i.v. 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
Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.