Aciclovir

Core Safety Profile (systemic)

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 and Powder for I.V. infusion:

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).

Oral formulations:

Hydration status: Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

Powder for I.V. infusion:

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.

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.

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.

Care is also required (with monitoring for changes in renal function) if administering i.v. aciclovir with drugs which affect other aspects of renal physiology (e.g. **cyclosporin, tacrolimus**).

4.6. Pregnancy and Lactation

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.

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.

Core Safety Profile (topical)

4.3. Contraindications

Cream:

Aciclovir cream is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir, propylene glycol or any of the excipients of aciclovir cream.

Ophthalmic Ointment:

Aciclovir ophthalmic ointment is contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir, or any of the excipients.

4.4. Special warnings and precautions for use

Cream:

Aciclovir cream is not recommended for application to mucous membranes, such as in the mouth, eye or vagina, as it may be irritant. Particular care should be taken to avoid accidental introduction into the eye.

In severely immune-compromised patients (e.g. AIDS patients or bone marrow transplant recipients) oral aciclovir dosing should be considered. Such patients should be encouraged to consult a physician concerning the treatment of any infection.

The excipient propylene glycol can cause skin irritations and the excipient cetyl alcohol can cause local skin reactions (e.g. contact dermatitis).

Ophthalmic Ointment:

Patients should be informed that transient mild stinging immediately following application may occur.

Patients should avoid wearing contact lenses when using aciclovir ophthalmic ointment.

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

No clinically significant interactions have been identified.

4.6. Pregnancy and Lactation

Fertility

See Clinical Studies in section 5.2

Pregnancy

Cream:

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks however the systemic exposure to aciclovir from topical application of aciclovir cream is very low.

Ophthalmic Ointment:

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

Cream and Ophthalmic Ointment:

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

Limited human data show that the drug does pass into breast milk following systemic administration. However, the dosage received by a nursing infant following maternal use of aciclovir cream or ophthalmic ointment would be insignificant.

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

Ophthalmic Ointment:

Eye ointments can affect visual ability and therefore caution is advised when driving or using machines.

4.8. Undesirable effects

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.

Clinical trial data have been used to assign frequency categories to adverse reactions observed during clinical trials with aciclovir 3% ophthalmic ointment. Due to the nature of the adverse events observed, it is not possible to determine unequivocally which events were related to the administration of the drug and which were related to the disease. Spontaneous reporting data has been used as a basis for allocating frequency for those events observed post-marketing.

Cream:

Skin and subcutaneous tissue disorders

Uncommon: Transient burning or stinging following application of aciclovir cream.

Mild drying or flaking of the skin.

Itching.

Rare: Erythema. Contact dermatitis following application. Where sensitivity tests have been conducted, the reactive substances have most often been shown to be components of the cream rather than aciclovir.

Cream and Ophthalmic Ointment:

Immune system disorders

Very rare: Immediate hypersensitivity reactions including angioedema and urticaria.

Ophthalmic Ointment:

Eye disorders

Very common: Superficial punctate keratopathy

This did not necessitate an early termination of therapy and healed without apparent sequelae.

Common: Transient mild stinging of the eye occurring immediately following application, conjunctivitis

Rare: Blepharitis

Local irritation and inflammation such as blepharitis and conjunctivitis have been reported in patients receiving aciclovir ophthalmic ointment.

4.9. Overdose

No untoward effects would be expected if the entire contents of the tube containing 500 mg of aciclovir (cream) or 135 mg aciclovir (ophthalmic ointment) were ingested orally.