

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir 200mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of Aciclovir B P

3. PHARMACEUTICAL FORM

200mg tablets packaged in PVC/aluminum strips

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir tablets are indicated for

- The treatment of herpes simplex virus (HSV) infections of the skin and the mucous membranes including initial and recurrent genital herpes,
- The suppression (prevention of recurrence) of recurrent herpes simplex infections in immunocompetent patients,
- The prophylaxis of herpes simplex infections in immunocompromised patients,
- The treatment of herpes zoster (shingles) and varicella (chickenpox) infections

4.2 Posology and method of administration

Method of administration. Oral.

Adults:

Treatment of herpes simplex infections- 200mg five times daily at approximately 4-hourly intervals Treatment should continue for 5 days, but may need to be extended in severe initial infections.

If patients are severely immunocompromised (e g following marrow transplant) or if absorption from G.I.T is impaired, the dose may be doubled to 400mg. Alternatively, intravenous therapy may be considered

Treatment should commence as soon as possible after the start of an infection and, for recurrent infections, this should preferably be during the prodromal period or as soon as the lesions first appear

Suppression of herpes simplex infections in immunocompromised patients 200mg four times daily at approximately 6-hourly intervals Many patients may be managed conveniently on a dosage of 400mg twice daily at approximately 12-hour intervals.

It may be possible to titrate the dosage down to 200mg three times daily at approximately 8-hourly intervals or even twice daily at approximately 12-hourly intervals, with good effect

Break-through infections may occur in some patients on total daily doses of 800mg

Therapy should be interrupted every 6 to 12 months to allow reassessment of the condition.

Prophylaxis of herpes simplex infections in immunocompromised patients- 200mg four times daily at approximately 6-hourly intervals

If patients are severely immunocompromised (e.g. following marrow transplant) or if absorption from the G.I.T is impaired, the dose may be doubled to 400mg. Alternatively, intravenous therapy may be considered.

The duration of the risk period will determine the duration of therapy

Treatment of herpes zoster (shingles) and Varicella (chickenpox) infections 800mg five times daily at approximately 4-hourly intervals for 7 days. If patients are severely immunocompromised (e.g. following marrow transplant) or if absorption from the G.I.T is impaired, intravenous therapy should be considered.

Treatment should commence as soon as possible after the start of an infection in herpes zoster, better results are obtained if treatment is initiated as soon as possible after the onset of the rash

Treatment of chickenpox in immunocompetent patients should begin within 24 hours of the onset of the rash

Children

Treatment of herpes simplex infections and prophylaxis of herpes simplex in immunocompromised patients Children aged 2 years and over should be given adult dosages and children under 2 years of age should be given half the adult dose.

Treatment of varicella infections.

Age 6 years and over 800mg four times daily

Age 2-5 years 400mg four times daily.

Under 2 years 200mg four times daily

Calculating the dosage as 20mg per kg body weight (not to exceed 800mg) four times daily is more precise. Treatment should continue for 5 days. There are no specific data available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children. When treatment of herpes zoster infections is required in immunocompromised children, intravenous therapy should be considered.

Dosage in renal impairment- Aciclovir is excreted via the kidney. In the management of herpes simplex infections in patients with impaired renal function, the usual recommended oral doses will not result in accumulation of Aciclovir above levels that have been established with intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10ml per minute), a dosage of 200mg twice daily at approximately 12-hourly intervals is recommended. In the treatment of herpes zoster infections and varicella, dosage of 800mg twice daily at approximately 12-hourly intervals is recommended for patients with severe renal impairment (creatinine clearance less than 10ml per minute) and 800mg three times daily at approximately 6 to 8 hourly intervals is recommended for patients with moderate renal impairment (creatinine clearance in the range of 10 - 25ml per minute).

Elderly

The total aciclovir body clearance declines along with creatinine clearance in the elderly

Adequate hydration should be ensured in elderly patients receiving high oral doses of Aciclovir

Particular attention should be given to dosage reduction in elderly patients who have impaired renal function

4.3 Contra – indications

Aciclovir tablets are contra-indicated in patients known to be hypersensitive to aciclovir or valaciclovir or any of the excipients

4.4 Special Warnings and special Precautions for Use

Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens eg , for the treatment of herpes zoster infection (4 g daily), in order to avoid the risk of possible renal toxicity

The data currently available from clinical studies are not sufficient to conclude that aciclovir therapy reduces the incidence of chickenpox-related complications in immunocompetent patients

Results of various in-vitro and in-vivo mutagenicity tests indicate that aciclovir does not pose a genetic risk in man

Aciclovir tablets have been shown to have no definite effects on sperm count, morphology or motility in man.

(Also see Section 5.3)

4.5 Interactions with other medicinal products and other forms of Interaction

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 have been shown when the drugs are co-administered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

4.6 Pregnancy and Lactation

As experience with the use of aciclovir in human pregnancy is limited, caution is required and the benefits of treatment should be weighed against any possible unknown risks

There is no experience of the effect of aciclovir tablets on human female fertility.

(Also see Section 5.3)

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

Reversible neurological effects have occasionally been reported (see 'undesirable effects' under 4.8 below) and patients should be advised not to drive or to operate machinery if affected.

4.8 Undesirable Effects

Gastrointestinal Nausea, vomiting, diarrhoea and abdominal pains have been reported in some patients In clinical studies, no difference was found between placebo and aciclovir in the incidence of gastrointestinal events

Haematological Very rarely, anaemia, leucopema and thrombocytopenia.

Hypersensitivity and skin Rashes including photosensitivity, urticaria, pruritis and rarely dyspnoea, angioedema and anaphylaxis

Kidney Rare reports of increases in blood urea and creatinine Acute renal failure has been reported on very rare occasions.

Liver Rare reports of reversible rises in bilirubin and liver related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Neurological Headaches Occasionally, reversible neurological reactions, notably dizziness, confusional states, hallucinations, somnolence, convulsions and coma have been reported, usually in patients with renal impairment in whom the dosage was in excess of that recommended or with other predisposing factors.

Other: Fatigue Occasional reports of accelerated diffuse hair loss As this type of hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain

4.9 Overdose

Symptoms and Signs: Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20g aciclovir on a single occasion, usually without toxic effects. Accidentally, 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)

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 intravenous overdosage.

Management: 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.

5 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 varicella zoster virus (VZV). This activity is due to intracellular conversions of aciclovir by viral thymidine kinase to the monophosphate with subsequent conversions 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 HSVI, HSVII and VZV is highly selective for infected cells, thymidine kinase in normal, non-affected cells does not use aciclovir effectively as a substrate, therefore, toxicity to the host cells is low

Prolonged or repeated therapy with aciclovir in severely immunocompromised patients may result in selection of viral strains with reduced sensitivity, which may not respond to continued aciclovir therapy a relative deficiency in viral thymidine kinase is the usual underlying mechanism, although strains with altered specificity of this enzyme or with reduced sensitivity of their DNA polymerase have also been reported

In-vitro exposure of HSV isolates to aciclovir can also result in the emergence of less sensitive strains. The relationship between the in-vitro-determined sensitivity of HSV isolates and the clinical response to aciclovir therapy has not been clarified

5.2 Pharmacokinetic Properties

Approximately 15-30% of an oral dose of aciclovir is absorbed from the gastro-intestinal tract. Following oral administration of 200, 400 and 800mg doses of aciclovir every four hours, mean steady state peak plasma concentrations of 0.7, 1.2 and 1.8 µg/ml, respectively, were reported-equivalent trough plasma levels were 0.4, 0.6 and 0.9 µg/ml.

Following intravenous administration of aciclovir in adults, the terminal plasma half-life is reported to be 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 and 10mg aciclovir per kg body weight in adults has produced mean steady state peak plasma concentrations of 5.1, 9.8 and 20.7 µg/ml respectively. The corresponding trough levels 7 hours later were 0.5, 0.7 and 2.3 µg/ml, respectively. Similar mean peak and trough levels were observed in children aged over one year when doses of 250mg/m², 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 has produced a mean steady state peak plasma concentration of 13.8 µg/ml and a corresponding trough level of 2.3 µg/ml. The terminal 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

Aciclovir did not show any carcinogenic activity in lifetime studies in rats and mice.

At doses of aciclovir greatly in excess of those used therapeutically, largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported. Two generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats and 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose Ph Eur
Sodium Starch Glycollate B P
Polyvidone K25 Ph Eur
Magnesium Stearate Ph.Eur.
Colloidal Anhydrous Silica Ph.Eur.
Purified Water Ph Eur

6.2 Incompatibilities

None Known

6.3 Shelf life

4 years

6.4 Special Precautions for Storage

Store below 25°C. Store in a dry place in its original packaging

6.5 Nature and Contents of Containers

Blister pack containing 25 (5x5) or 60 (6x10) tablets in PVC (250µm)/aluminum strip (20µm)

6.6. Instructions for Use and Handling (and Disposal)

Use as directed by physician

7 MARKETING AUTHORISATION HOLDER

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Surrey
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25 July 2001

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