

## SUMMARY OF PRODUCT CHARACTERISTICS

### 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/aluminium 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 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 the 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, a 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 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 Contraindications**

Known hypersensitivity to aciclovir and valaciclovir or to any of the excipients

### **4.4 Special warnings and precautions for use**

Aciclovir should be administered with caution to patients with renal or hepatic impairment and may aggravate existing renal dysfunction.

Use in patients with renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see 4.2 Posology and Method of Administration). Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment 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 4.8 Undesirable Effects).

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.)

There have been occasional reports of resistance to aciclovir.

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

### **4.5 Interaction 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, an immunosuppressant agent used in transplant patients 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**

##### **Fertility:**

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

In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

(Also see Section 5.3)

##### **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 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**

There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of the active substance, but the adverse event profile of aciclovir and the clinical status of the patient should be borne in mind.

#### 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  $\geq 1/10$ , common  $\geq 1/100$  and  $< 1/10$ , uncommon  $\geq 1/1000$  and  $< 1/100$ , rare  $\geq 1/10,000$  and  $< 1/1000$ , very rare  $< 1/10,000$ .

*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 4.4 Special warnings and precautions for use).

*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 and crystalluria.

*General disorders and administration site conditions:*

Common: Fatigue, fever.

## **4.9 Overdose**

### **Symptoms and Signs**

Aciclovir is only partly absorbed from the G.I.T. Patients have ingested overdoses of up to 20g 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).

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.

## **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 II and varicella zoster virus (VZV). This activity is due to intracellular conversion of aciclovir by viral thymidine kinase to the 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 HSV I, HSV II 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.

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 $\mu$ g/ml, respectively, were reported: equivalent trough plasma levels were 0.4, 0.6 and 0.9 $\mu$ g/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 $\mu$ g/ml, respectively. The corresponding trough levels 7 hours later were 0.5, 0.7 and 2.3 $\mu$ g/ml, respectively. Similar mean peak and trough levels were observed in children aged over one year when doses of 250mg/m<sup>2</sup>, 500mg/m<sup>2</sup> 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 $\mu$ g/ml and a corresponding trough level of 2.3 $\mu$ g/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. 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.

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 container**

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

### **6.6 Special precautions for disposal**

Use as directed by physician

## **7 MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Limited  
NLA Tower  
12-16 Addiscombe Road  
Croydon  
Surrey  
CR0 0XT  
United Kingdom

**8     MARKETING AUTHORISATION NUMBER(S)**

PL 12762/0105

**9     DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

25/07/2001

**10    DATE OF REVISION OF THE TEXT**

30/03/2011