SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aciclovir 800mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Aciclovir 800 mg

Excipient with known effect: Each tablet contains 128mg lactose (as lactose monohydrate)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

A white or almost white, capsule shaped biconvex scored tablet of 9mm x 19mm, coded: ACY 800 on one side

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children). Suppression of recurrent herpes simplex infections. Prevention of herpes simplex infections in immunocompromised patients. Treatment of herpes zoster infections. Treatment of varicella (chickenpox) infections.

4.2 Posology and method of administration

Posology

Treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes.

Adults:

200mg five times daily for five days; in severe infections, the duration of treatment may have to be extended beyond 5 days, but in severe initial infections this may have to be extended. Treatment should begin as early as possible after the first sign of outbreak. In severely immunocompromised patients: (e.g. after bone marrow transplant or in patients with impaired absorption from the gut), the dosage can be doubled to 400mg five times daily or alternatively, intravenous dosing could be considered.

Dosing should begin as early as possible after the start of an infection: for recurrent episodes this should preferably be during the prodromal period for when lesions first appear.

Dosage reduction in renal impairment: At creatinine clearance <10 ml/minute 200mg twice daily for five days.

Children:

Children over the age of 2 years: Adult dosage.

Children under the age of 2 years: Half the adult dosage.

Suppression of recurrent herpes simplex infections:

Adults:

800mg divided in two to four daily doses, dosage reduction to 400-600mg daily can be tried. The duration of administration is determined by the duration of the period of risk. Some patients may experience break-through infection on total daily doses of 800mg Aciclovir. Therapy should be interrupted at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.

Dosage reduction in renal impairment:

At creatinine clearance <10 ml/minute 200mg twice daily.

Children:

Children 2-14 years of age: Adult dosage.

Children under the age of 2 years: Half the adult dosage.

Prevention of herpes simplex infections in immunocompromised patients:

Adults:

200mg four times daily. Some patients may experience break-through infections on total daily doses of 800mg aciclovir. In severely immunocompromised patients or in patients with impaired absorption from the gut, the dose may be raised to 400mg four times daily or, alternatively, intravenous dosing could be considered. The duration of administration is determined by the duration of the period of risk, Dosage reduction in renal impairment: At creatinine clearance <10 ml/minute 200mg twice daily.

Children:

Children: 2-14 years of age: Adult dosage.

Children under the age of 2 years: Half the adult dosage.

Treatment of herpes zoster infections:

Adults:

800mg five times daily for seven days. Treatment of herpes zoster must begin as early as possible and not later than three days after the first sign of outbreak. In immunocompromised patients or in patients with impaired absorption from the gut consideration should be given to intravenous dosing. Dosage reduction in renal impairment: At creatinine clearance 10-25 ml/minute 800mg three to four times daily. At creatinine clearance <10 ml/minute 800mg twice daily.

Treatment of varicella (chickenpox) infections*:*

Adults:

800mg five times daily for seven days at approximately four hourly intervals omitting the night time dose. Treatment should begin within 24 hours after the onset of rash. In immuncompromised patients or patients with impaired absorption from the gut consideration should be given to intravenous dosing.

Dosage reduction in renal impairment: at creatinine clearance 10-25m/minute 800mg three to four times daily. At creatinine clearance <10ml/minute 800mg twice daily.

Children:

Children aged 6 years and over: 800mg four times daily for five days

Children aged 2-5 years: 400mg four times daily for five days
Children 3 months-2 years: 200mg four times daily for five days

The dosage may be determined on the basis of 20mg per kg body weight (max 800mg) four times daily for five days. In immunocompromised children aciclovir should be administered i.v. for at least 5 days before commencing oral dosing.

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).

Method of administration: Orally.

4.3 Contraindications

Aciclovir tablets, are contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir or any of the excipients.

4.4 Special warnings and precautions for use

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). In patients with severe renal impairment (creatinine clearance <10 ml/minute) the daily doses should be reduced by approx. 50 per cent by increasing dosage intervals. 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).

Hydration status: Adequate hydration should be maintained, especially in the elderly and, in patients with impaired renal function or those receiving high doses of aciclovir.

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

The data currently available from clinical studies is not sufficient to conclude that treatment with aciclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.

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).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose

4.5 Interaction with other medicinal products and other forms of interaction

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 immunosuppresant 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.

Care should be taken when using aciclovir in combination with compounds known to have nephrotoxic effects, e.g. cyclosporin and tacrolimus.

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.

4.6 Fertility, pregnancy and lactation

Fertility

There is no information on the effect of aciclovir 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.

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 described amongst aciclovir exposed subjects compared with the general population, and any birth defects have not shown any 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.

Findings from reproduction toxicology studies are included in Section 5.3.

Breas-feeding

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 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. The clinical status of the patient and the adverse event profile should be borne in mind when considering the patients's ability to drive or 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.

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 and crystalluria.

General disorders and administration site conditions:

Common: Fatigue, fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the internet at www.mhra.gov.uk/yellowcard.

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. 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 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 acyclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anatomical Therapeutical Chemical Classification: ATC code J05A B01.

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). The inhibitory activity of Aciclovir for HSV I and HSV II and VZV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use Aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV and VZV 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.

Prolonged or repeated courses of Aciclovir in severely immuno-compromised 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 viral 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

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations ($C^{ss}max$) following doses of 800 mg Aciclovir administered four-hourly were 8 microMol (1.8 micrograms/ml) and equivalent trough plasma levels were 4 microMol (0.9 micrograms/ml).

In adults the terminal plasma half-life 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-carboxymethoxymethyl-guanine is the only significant metabolite of Aciclovir, and accounts for 10-15% of the dose excreted in the urine. When Aciclovir is given one hour after 1 gram of probenecid the terminal half-life and the area under the plasma concentration time curve is extended by 18% and 40% respectively.

In adults, mean steady state peak plasma concentrations ($C^{ss}max$) following a one hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 microMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding trough levels ($C^{ss}min$) 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 peak (C^{ss}max) and trough (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 to 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 C^{ss}min to be 10.1 microMol (2.3 micrograms/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/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

Mutagenicity:- 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.

Carcinogenicity:- Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse.

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

Fertility:- 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. Two generation studies in mice did not reveal any effect of aciclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, potato starch, gelatin, cellulose, microcrystalline, sodium starch glycollate (Type A), sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years (Al/PVC blister).
2 years (polyethylene tablet container and screw cap).

6.4 Special precautions for storage

None. Storage temperature: Do not store above 25°C.

6.5 Nature and contents of container

Blister (A1/PVC) or polyethylene tablet container and screw cap.

Pack size:

800 mg: 35 tablets

6.6 Special precautions for disposal and other handling

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0200

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