1. Name of the medicinal product

Aciclovir Tablets 800mg BP

2. Qualitative and quantitative composition

Each tablet contains 800mg Aciclovir PhEur.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

White uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications

1) Treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2 Posology and method of administration

Posology

***Adults: Treatment of herpes zoster infections*:** 800mg aciclovir should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.

In severely immunocompromised patients (*eg* after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

Dosing should begin as early as possible after the start of an infection. Treatment of herpes zoster yields better results if initiated as soon as possible after the onset of the rash.

Dosage in the paediatric population: Treatment of varicella infection: Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily).

No specific data are 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 dosing should be considered.

***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).

In the elderly, total aciclovir body clearance declines along with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

***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 800mg aciclovir twice daily at approximately twelve-hourly intervals for patients with severe renal impairment (creatinine clearance less than 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).

In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800mg aciclovir twice daily at approximately twelve-hourly intervals for patients with renal impairment (creatinine clearance less than 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).

Method of Administration

Administration: Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

4.3 Contraindications

• Hypersensitivity to the active substance, valaciclovir or to any of the excipients listed in section 6.1.

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). 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 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).

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

Excipients

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

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

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.

Caution should however be exercised by balancing the potential benefits of treatment against any possible hazard. Findings from reproduction toxicology studies are included in Section 5.3.

Breast-feeding

Following oral administration of 200mg 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 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

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, motility or morphology. See clinical studies in section 5.2.

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. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance, but the adverse event profile 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 ≥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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
Symptoms and signs

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 (*eg* nausea and vomiting) and neurological effects (*eg* 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
Pharmacotherapeutic group:

Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors

ATC code: J05AB01.

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, 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 of 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 immune-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

Absorption

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C^{ss}max) following doses of 200 mg administered four-hourly were 3.1 microMol (0.7 micrograms/ml) and equivalent trough plasma levels (C^{ss}min) were 1.8 microMol (0.4 micrograms/ml). Corresponding C^{ss}max levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 microMol (1.2 micrograms/ml) and 8 microMol (1.8 micrograms/ml) respectively and equivalent C^{ss}min levels were 2.7 microMol (0.6 micrograms/ml) and 4 microMol (0.9 micrograms/ml).

Biotransformation and Elimination

In adults the terminal plasma half-life of aciclovir after administrations 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-carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for approximately 10 - 15% of the administered dose recovered from 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.

Paediatric population

In children over 1 year of age similar 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). The terminal plasma half-life in these patients was 3.8 hours. 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). 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.

Renal impairment

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
Also contains: colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, E460

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage
Store below 25°C in a dry place.

6.5 Nature and contents of container
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on

polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 25s, 28s, 30s, 35s, 56s, 60s, 84s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Special precautions for disposal and other handling
Not applicable.

7. Marketing authorisation holder

Emzor Pharmaceutical Industries Limited

Plot 3c,Blk A,Aswani Market Road,Oshodi-Apapa Expressway, Lagos

8. Marketing authorisation number(s)

N/A

9. Date of first authorisation/renewal of the authorisation

N/A

10. Date of revision of the text

N/A