Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aciclovir 800mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Aciclovir 800mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet
White oval dispersible tablet with S95 embossed on one side and scored on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Aciclovir Tablets are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2 Posology and method of administration

Treatment of varicella and 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 (e.g. 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. Treatment of chicken pox in immunocompetent patients should begin within 24 hours after onset of the rash.

Children

Treatment of varicella infections

6 years and over

800mg aciclovir four times daily.

2 to five years

400mg aciclovir four times daily.

Under 2 years

200mg aciclovir four times daily.

Treatment should continue for five days.

Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg) aciclovir 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

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

In the treatment of varicella and 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 to 25ml/minute).

Route of Administration: Oral.

Aciclovir Dispersible Tablets may be dispersed in a minimum of 50ml of water or swallowed whole with a little water.

4.3 Contraindications

Aciclovir tablets are contraindicated in patients known to be hypersensitive to aciclovir.

4.4 Special warnings and precautions for use

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

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.

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

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The birth defects described amongst aciclovir exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause.

Caution should however be exercised by balancing the potential benefits of treatment against any possible hazard.

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 nursing women.

4.7 Effects on ability to drive and use machines

Some patients may experience dizziness or drowsiness. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal: nausea, vomiting, diarrhoea and abdominal pains have been reported in some patients receiving aciclovir tablets.

Haematological: very rarely, anaemia, leukopenia and thrombocytopenia.

Hypersensitivity and skin: rashes including photosensitivity, urticaria, pruritis and rarely dyspnoea, angioedema and anaphylaxis. The rashes have resolved on withdrawal of the drug.

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

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

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

Other: Occasional reports of accelerated diffuse hair loss have been received. 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

Aciclovir is only partly absorbed in the gastrointestinal tract. It is unlikely that serious toxic effects would occur if a dose of up to 5g were taken on a single occasion. No data are available on the consequences of the ingestion of higher doses; such an occurrence warrants close observation of the patient.

Single intravenous doses of up to 80mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialysable by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, nucleosides and nucleotides; ATC code: J05A B01.

Aciclovir is a synthetic purine nucleoside analogue structurally related to guanine. It is used for the treatment of viral infections due to herpes simplex virus (types 1 and 2) and varicella-zoster virus (zoster and chickenpox).

Herpes simplex infections including herpes keratitis, herpes labialis, and genital herpes respond to aciclovir given by intravenous, oral, or topical routes as soon as possible after symptoms appear. Both initial and recurrent infections can

be successfully treated. Prolonged treatment can reduce the incidence of recurrence which is important in immunocompromised patients. However, when prolonged treatment is withdrawn infections may recur.

Aciclovir also improves the healing of zoster lesions and reduces acute pain when given intravenously or by mouth, although studies indicate that it has little effect on postherpetic neuralgia. Beneficial effects may be more marked in immunocompromised patients.

5.2 Pharmacokinetic properties

About 15 to 30% of a dose of aciclovir given by mouth is considered to be absorbed from the gastro-intestinal tract. A dose of 200mg aciclovir every 4 hours by mouth is reported to produce maximum and minimum steady-state plasma concentrations 0.56 and 0.29 micrograms per ml respectively; equivalent values following 400mg doses are 1.2 and 0.6 micrograms per ml. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately three times higher than those in maternal serum.

5.3 Preclinical safety data

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. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. 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. Aciclovir tablets have been shown to have no definite effect upon sperm count, morphology or motility in man.

Experience in humans is limited so the use of Aciclovir Tablets should be considered only when the potential benefits outweigh the possibility of unknown risks. 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.

There is no experience of the effect of aciclovir tablets on human female fertility. Two-generation studies in mice did not reveal any effect of aciclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Polysorbate 80
Gelatin
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.

6.5 Nature and contents of container

Aluminium (20µm)/PVC (250 µm) strips of 35 tablets in a carton box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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