SM PHARMACEUTICALS SDN BHD

VIROX (ACYCLOVIR) TABLET 200MG AND 400MG

DESCRIPTION:
200 mg: Blue, round, flat faced, bevelled edged tablet with breakline on one side.
400 mg: Pink, round, flat faced, bevelled edged tablet with breakline on one side.

COMPOSITION:
Each tablet contains Acyclovir 200 mg or 400 mg

ACTIONS AND MODE OR MECHANISMS OF ACTION:
Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activities against human herpes viruses, including Herpes simplex virus (HSX) types 1 and 2, Varicella zoster viruses (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture, acyclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV and CMV.
The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, EBV and CMV is highly selective. Acyclovir is 300 to 3000 times more effective against viral enzymes compaired with mammalian enzymes, particularly thymidine kinase (TK). The enzyme TK of normal, non-infected cells do not use acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir triphosphate is formed in virally infected cells in amounts 40 to 100 times greater than in normal uninfected cells. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):
Absorption:
Acyclovir is slowly and poorly absorbed from the gastrointestinal tract.
Bioavailability 20% (range 10 to 30%). Bioavailability decreases with increasing dose.

Distribution
Widely distributed to tissues and body fluids including brain, kidneys, lungs, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid (CSF), and herpetic vesicular fluid. Highest concentrations are found in kidneys, liver, and intestines. CSF concentrations are approximately 50% of plasma concentrations. Crosses the placenta and is excreted in breast milk in concentrations approximately 3 – 4 times higher than those in maternal serum.

Protein binding
Low (9 to 33%).

Biotransformation
Hepatic; only major metabolite found in urine is 9-carboxymethoxymethylguanine, which accounts for approximately 9 to 14% of the dose. This metabolite has no known antiviral activity.

Half-life
Oral – 3.3 hours (2 to 3 hours for adults without renal impairment). In chronic renal failure this value is increased, and may be up to 19.5 hours in anuric patients. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of acyclovir being removed in 6 hours.

Time to peak serum concentration
Oral – 1.7 hours (1.5 – 2 hours).

Mean peak serum concentration (steady-state)
Oral – Adults –
200 mg every 4 hours: 0.6 mcg/mL (2.5 micromoles/L).

Elimination
Renal – Excreted by both glomerular filtration and tubular secretion. Approximately 14% of total dose excreted unchanged in urine. Fecal – Insignificant amounts (<2%).

INDICATIONS:
Herpes simplex virus infections
Treatment of herpes simplex virus infections of the skin and mucous membranes, including initial and recurrent genital herpes. Suppression (prevention of recurrence) of recurrent herpes simplex infections in immunocompetent patients. Prophylaxis of herpes simplex infections in immune-compromised patients.

Varicella (Chickenpox) and herpes zoster infections
Treatment of varicella (chickenpox) and herpes zoster (shingles) infections in immunocompromised and normally immune individuals. Studies have shown that early treatment of shingles with Acyclovir has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zoster-associated pain).

CONTRAINDICATIONS:
Patients known to be hypersensitive to acyclovir.

SIDE EFFECTS / ADVERSE REACTIONS:

Acyclovir is generally well tolerated. Skin rashes have been reported in a few patients receiving the tablets, the rashes have resolved on withdrawal of the drug. Gastrointestinal effects including nausea, vomiting, diarrhoea and abdominal pains have been reported in some patients receiving the tablets. In double blind, placebo-controlled trials the incidence of gastrointestinal events has not been found to differ between placebo and acyclovir recipients.

Reversible neurological reactions, notably dizziness, confusional states, hallucinations and somnolence, have occasionally been reported, usually in patients with renal impairment or other predisposing factors.

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 acyclovir therapy is uncertain.

Other events reported rarely in patients receiving oral formulations of acyclovir include mild, transient rises in bilirubin and liver related enzymes, small increases in blood urea and creatinine, small decreases in haematological indices, headaches, lightheadedness and fatigue.

PRECAUTIONS / WARNINGS:

All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Use in pregnancy and lactation:

Limited data are available on the use of acyclovir in pregnancy. Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard.

Following oral administration of 200mg acyclovir 5 times a day, acyclovir has been detected in breast milk at concentrations ranging from 0.6 – 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to acyclovir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if Virox is to be administered to a nursing woman.

Use in the elderly:

Studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of acyclovir in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

Pediatric use:

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied. However, no usual toxicity or pediatrics-specific problems have

been observed in studies done in children using doses of up to 3000 mg/m² of body surface area and 80 mg/kg per day.

DRUG INTERACTIONS:
Excretion of the drug through the kidney is retarded by probenecid. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of acyclovir. However, clinical experience has not identified other drug interactions with acyclovir.
Overwhelming fatigue has been associated with the use of acyclovir and zidovudine. When each agent was given alone there was no such effect.

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:
Adults:
Treatment of herpes simplex infections:
One 200-mg tablet should be taken 5 times daily at approximately 4-hourly intervals, omitting the night-time dose. Treatment should continue for 5 days, but in severe initial infections may have to be extended up to 10 days. In severely immune-compromised patients (e.g., after marrow transplant) or in-patients with impaired absorption from the gut the dose can be doubled to 400mg. Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.
Suppression of herpes simplex infections in immunocompetent patients:
200 mg 4 times daily at approximately 6-hourly intervals.
Many patients may be conveniently managed on a regimen of 400mg taken twice daily at approximately 12-hourly intervals. Dosage titration down to 200mg taken 3 times daily at approximately 8-hourly intervals or even twice daily, may prove effective. Some patients may experience breakthrough infections on total daily doses of 800mg. Therapy should be interrupted periodically at intervals of 6-12 months in order to observe possible changes in the natural history of the disease.
Prophylaxis of herpes simplex infections in immune-compromised patients:
200 mg 4 times daily (every 6 hours). In severely immune-compromised patients or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg 4 times daily. The duration of prophylactic administration is determined by the duration of the period at risk.
Treatment of varicella and herpes zoster infections:
800 mg 5 times daily (every 4 hours), omitting the night-time dose. Treatment should continue for 7 to 10 days. Dosing should begin as early as possible after the start of an infection; treatment yields better results if initiated as soon as possible after rash onset.
Children:
For treatment of herpes simplex infections, and for prophylaxis of herpes simplex infections in the immune-compromised, children 2 years and over should be given adult dosages and children <2 years should be given ½ adult dose.

For treatment of varicella infections, children > 6 years (over 40 kg): 800 mg 4 times daily; 2-6 years: 400 mg 4 times daily; below 2 years: 200mg 4 times daily. Dosing may be more accurately calculated as 20 mg/kg body weight (not to exceed 800 mg) 4 times daily. Treatment should continue for 5 days. No specific data are available on the suppression of Herpes simplex infections or the treatment of Herpes zoster infections in immune-competent children.

Dosage in renal impairment:

In the management of herpes simplex infections, for patients with severe renal impairment (creatinine clearance <10mL / min) an adjustment of dosage to 200mg twice daily (every 12 hours) is recommended. In the treatment of varicella and herpes zoster infections it is recommended to adjust the dosage to 800 mg twice daily (every 12 hours), for patients with severe renal impairment, and to 800 mg 3 times daily (every 8 hours) for patients with moderate renal impairment (creatinine clearance in the range 10-25mL/min).

Use in the elderly:

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

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):

Symptoms

Acyclovir is only partly absorbed in the gastrointestinal tract. It is unlikely that serious toxic effects would occur if a dose of up to 5 g were taken on a single occasion. Patients have ingested intentional overdoses of up to 100 capsules (20g) of acyclovir, with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid.

Treatment:

Ingestion of doses of acyclovir in excess of 5 g warrants close observation of the patient. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored. Adequate hydration should be maintained to prevent precipitation of acyclovir in the renal tubules.

PACKING / PACK SIZES:

Blister pack of 10 x 5's/box

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.
Store in a dry place, below 30°C .
Protect from light.

SHELF LIFE: 3 Years

NAME AND ADDRESS OF MANUFACTURER AND DISTRIBUTOR IN MALAYSIA:

SM PHARMACEUTICALS SDN BHD (218620-M)
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