

VIREST 200 TABLET

DESCRIPTION

Hexagon-shaped, blue uncoated tablet, bevel-edged with flat faces.

COMPOSITION

Each tablet contains: Aciclovir 200 mg

PHARMACODYNAMICS

Mechanism of Action

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 1 and 2, varicella zoster virus (VZV), Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, aciclovir 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 aciclovir for HSV-1, HSV-2, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non- infected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV 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.

Pharmacodynamic 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.

Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK however, strains with altered viral TK or 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.

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

PHARMACOKINETICS

Absorption

Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C_{ssmax}) following doses of 200 mg administered four-hourly were 3.1 micromolar (0.7micrograms/mL) and equivalent trough plasma levels (C_{ssmin}) were 1.8 micromolar (0.4 micrograms/mL). Corresponding C_{ssmax} levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 micromolar (1.2 micrograms/mL) and 8 micromolar (1.8 micrograms/mL) respectively, and equivalent C_{ssmin} levels were 2.7 micromolar (0.6 micrograms/mL) and 4 micromolar (0.9 micrograms/mL).

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg and 15 mg/kg were 22.7 micromolar (5.1 micrograms/mL), 43.6 micromolar (9.8 micrograms/mL), 92 micromolar (20.7 micrograms/mL) and 105 micromolar (23.6 micrograms/mL) respectively. The corresponding trough levels (C_{ssmin}) 7 hours later were 2.2 micromolar (0.5 micrograms/mL), 3.1 miromolar (0.7 micrograms/mL), 10.2 micromolar (2.3 micrograms/mL) and 8.8 micromolar (2.0 micrograms/mL), respectively. In children over 1 year of age similar mean peak (C_{ssmax}) and through (C_{ssmin}) levels were observed when a dose of 250 mg/m2 was substituted for 5 mg/kg and a dose of 500 mg/m2 was substituted for 10 mg/kg. In neonates (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_{ssmax} was found to be 61.2 micromolar (13.8 micrograms/mL) and the C_{ssmin} to be 10.1 micromolar (2.3 micrograms/mL). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a C_{max} of 83.5 micromolar (18.8 micrograms/mL) and C_{min} of 14.1 micromolar (3.2 micrograms/mL).

Distribution

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.

Elimination

In adults the terminal plasma half life of aciclovir 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- carboxymethoxy-methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10 to 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.

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In neonates (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 terminal plasma half life was 3.8 hours.

Special Patient Populations

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.

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.

Studies have shown no apparent changes in the pharmacokinetic behaviour of aciclovir or zidovudine when both are administered simultaneously to HIV infected patients.

INDICATIONS

Virest 200 Tablet is indicated for the treatment of Herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.

Virest 200 Tablet is indicated for the suppression (prevention of recurrences) of recurrent Herpes simplex infections in immune-competent patients.

Virest 200 Tablet is indicated for the prophylaxis of Herpes simplex infections in immune-compromised patients.

Virest 200 Tablet is indicated for the treatment of Varicella infections (chicken-pox) and Herpes zoster (shingles). Studies have shown that early treatment of shingles with Virest 200 Tablet has a beneficial effect on pain and can reduce the incidence of post-herpetic neuralgia (zosterassociated pain).

RECOMMENDED DOSE

Virest 200 Tablet may be swallowed whole or with a little water, or dispersed in a minimum of 50 ml of water.

• Adults

Treatment of herpes simplex

For treatment of herpes simplex infections, Virest 200 Tablet should be taken five times daily at approximately four-hourly intervals omitting the night time dose.Treatment should continue for five days but in severe initial infections may have to be extended.

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 400 mg 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 or when lesions first appear.

Suppression of herpes simplex

For suppression of Herpes simplex infections in immune-competent patients, 200 mg Virest 200 Tablet should be taken four times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regimen of 400 mg Virest 200 Tablet taken twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200 mg Virest 200 Tablet taken thrice daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.

Some patients may experience break-through infections on total daily doses of 800 mg Virest 200 Tablet .

Therapy should be interrupted periodically at intervals of six to twelve months in order to observe possible changes in the natural history of the disease.

Prophylaxis of herpes simplex

For prophylaxis of herpes simplex infections in immune-compromised patients, 200 mg Virest 200 Tablet should be taken four times daily at approximately six-hourly intervals.

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 400 mg or, alternatively, intravenous dosing could be considered.

The duration of prophylactic administration is determined by the duration of the period at risk.

Treatment of varicella and herpes zoster

For treatment of varicella and herpes zoster infections, 800 mg Virest 200 Tablet should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.

In severely immune-compromised 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 yields better results if initiated as soon as possible after onset of the rash.

• Infants and children

For treatment of herpes simplex infections, and for prophylaxis of herpes simplex infections in the



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BACK

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immune-compromised, children aged two years and over should be given adult dosages and infants and children below the age of two years should be given half the adult dose.

For treatment of varicella infections in children:

6 years and over : 800 mg Virest 200 Tablet four times daily
2 - < 6 years : 400 mg Virest 200 Tablet four times daily
Under 2 years : 200 mg Virest 200 Tablet four times daily

Dosing may be more accurately calculated as 20 mg Virest 200mg Tablet /kg bodyweight (not to exceed 800 mg) four times daily. Treatment should continue for five days

No specific data are available on the suppression of herpes simplex infections or the treatment of Herpes zoster infections in immune-competent children.

• Elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Renal impairment).

Adequate hydration of elderly patients taking high oral doses of Virest 200 Tablet should be maintained.

• Renal impairment

Caution is advised when administering Virest 200 Tablet oral formulations to patients with impaired renal function. Adequate hydration should be maintained.

In the treatment and prophylaxis of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established safe by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10mL/minute) an adjustment of dosage to 200mg twice daily at approximately twelve-hourly intervals is recommended.

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

CONTRAINDICATIONS

Virest 200 Tablet are contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

WARNINGS AND PRECAUTIONS

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 Dosage and Administration). 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 Adverse Reactions).

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

INTERACTIONS WITH OTHER MEDICAMENTS

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 coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

PREGNANCY AND LACTATION

Pregnancy

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Virest 200 Tablet. The registry findings have not shown an increase in the number of birth defects amongst Virest 200 Tablet exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

Lactation

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 Virest 200 Tablet is to be administered to a nursing woman.

SIDE 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 Warnings and Precautions).

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, abdominal pains

Hepato-biliary disorders

Rare: Reversible rises in bilirubin an 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.

General disorders and administration site conditions

Common: Fatigue, fever.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms & 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 aciclovir from the blood and may therefore be considered a management option in the event of symptomatic overdose.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

The clinical status of the patient and the adverse event profile of Virest 200 Tablet should be borne in mind when considering the patient's ability to drive or operate machinery. They 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.

INSTRUCTIONS FOR USE

Virest 200 Tablet may be swallowed whole or with a little water, or dispersed in a minimum of 50 ml of water.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 25°C. Protect from light.

Presentation/Packing: Blisters of 5 x 5's

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