VICLORIX®

Acyclovir

FORMS AND PRESENTATION
viclorix® 400: Tablets: Box of 40.
viclorix® 800: Tablets: Box of 40.
COMPOSITION
viclorix®400: Each tablet contains Acyclovir 400mg.
Viclorix® 800: Each tablet contains Acyclovir 800mg.
Excipients: Microcrystalline Cellulose, Sodium Starch Gycollate, Colloidal Silicon dioxide, povidone (K30), Magnesium Stearate, Ferric Oxide (Acivir 400), FD & C ble lake #2 Indigo carmine AL 30%-36% (Acivir 800).
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: antiviral.
ATC code: S01AD03
Acyclovir 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 Acyclovir for HSV I and HSV II and VZV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use Acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV and VZV 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 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 Acyclovir in severely immuno-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued Acyclovir 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 Acyclovir 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 Acyclovir therapy is not clear.
Pharmacokinetic properties
Acyclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C^{ss}max) following doses of 800 mg administered four-hourly were 8 microMol (1.8 µg/ml) and equivalent trough plasma levels (C^{ss}min) were 4 microMol (0.9 µg/ml). Corresponding C^{ss}max levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 microMol (1.2 µg/ml) and 8 microMol (1.8 µg/ml) respectively and equivalent C^{ss}min levels were 2.7 microMol (0.6 µg/ml) and 4 microMol (0.9 µg/ml).
In adults the terminal plasma half-life of acyclovir after administrations of intravenous acyclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of acyclovir 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 acyclovir, and accounts for approximately 10 - 15% of the administered dose recovered from the urine. When acyclovir 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 µg/ml), 43.6 microMol (9.8 µg/ml) and 92 microMol (20.7 µg/ml), respectively. The corresponding trough levels (C^{ss}min) 7 hours later were 2.2 microMol (0.5 µg/ml), 3.1 microMol (0.7 µg/ml), and 10.2 microMol (2.3 µg/ml), respectively.
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 µg/ml) and C^{ss}min to be 10.1 microMol (2.3 µg/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 C_{max} of 83.5 micromolar (18.8 µg/ml) and Cmin of 14.1 micromolar (3.2 µg/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.
In patients with chronic renal failure the mean terminal half-life was found to be 19.5 hours. The mean acyclovir half-life during haemodialysis was 5.7 hours. Plasma acyclovir 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.
INDICATIONS
Viclorix® 400 is indicated for:
- The treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).
- The suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
- The prophylaxis of herpes simplex infections in immunocompromised patients.
- The treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

Viclorix® 800 tablets are used to:
- treat chicken pox (varicella infection)
- treat shingles (herpes zoster infection).

CONTRAINDICATIONS
Viclorix® is contra-indicated in patients known to be hypersensitive to acyclovir or valacyclovir, or to any of the excipients.
PRECAUTIONS
Use in patients with renal impairment and in elderly patients:
Acyclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment. 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. Prolonged or repeated courses of acyclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued acyclovir treatment.
Hydration status: Care should be taken to maintain adequate hydration in patients receiving high doses of acyclovir.
The risk of renal impairment is increased by use with other nephrotoxic drugs.
Ability to drive and use machines
There have been no studies to investigate the effect of acyclovir on driving performance or the ability to operate machinery
PREGNANCY AND LACTATION
Pregnancy
The use of acyclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.
A post-marketing acyclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Viclorix® The registry findings have not shown an increase in the number of birth defects amongst Viclorix® 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 acyclovir 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.
Breast-feeding:
Caution is therefore advised if Viclorix® is to be administered to a nursing woman.
DRUG INTERACTIONS
Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increase the AUC of acyclovir by this mechanism, and reduce acyclovir renal clearance. Similarly increases in plasma AUCs of acyclovir 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 acyclovir.
An experimental study on five male subjects indicates that concomitant therapy with acyclovir increases AUC of totally administered theophylline with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with acyclovir.
ADVERSE EFFECTS
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.
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.
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
DOSAGE AND ADMINISTRATION
Viclorix® tablets may be dispersed in a minimum of 50 ml of water or swallowed whole with a little water. Ensure that patients on high doses of acyclovir are adequately hydrated.
Dosage in adults
Herpes simplex infection:
-Treatment of herpes simplex infections: 200mg 5 times a day at 4 hourly intervals for 5 days.
-Prevention of herpes simplex infection: 200mg 4 times a day at 6 hourly intervals for 6-12 months.
-Prevention in immunocompromised patients: 200mg 4 times a day at 6 hourly intervals for the period that the patient is at risk.
-In severely impaired Kidney function: 200mg twice a day at 12 hourly intervals.
-In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be increased 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 infections in immunocompetent patients: Many patients may be conveniently managed on a regimen of 400 mg Viclorix® twice daily at approximately 12 hourly intervals.
Dosage titration down to 200 mg Viclorix® 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 infection on total daily doses of 800 mg Viclorix® 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 infections in immunocompromised patients: In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg Viclorix®, or alternatively, intravenous dosing could be considered.
The duration of prophylactic administration is determined by the duration of the period at risk.
Herpes zoster infections:
-Treatment: 800 mg Viclorix® should be taken 5 times daily at approximately 4 hourly intervals, omitting the night time dose, for 7 days.
-Treatment in patients with moderately impaired Kidney function: 800mg 3 times a day at 6-8 hourly intervals.
-Treatment in patients with severely impaired Kidney function: 800mg twice a day at 12 hourly intervals.
-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.
Varicella infection (chicken pox):
-Treatment of chickenpox in immunocompetent patients should begin within 24 hours after onset of the rash.
Dosage in children
Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: Children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.
Treatment of varicella infection (chicken pox):
6 years and over : 800 mg Viclorix® 4 times daily.
2 - 5 years : 400mg Viclorix®4 times daily.
Under 2 years : 200mg Viclorix® 4 times daily.

Treatment should continue for 5 days.
Dosing may be more accurately calculated as 20 mg/kg bodyweight (not to exceed 800 mg) Viclorix® 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.
Dosage in the elderly:
Dosage may be reduced in the elderly, especially in those kidneys are not working properly.
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 acyclovir should be maintained.
Dosage in renal impairment:
Caution is advised when administering acyclovir to patients with impaired renal function. Adequate hydration should be maintained.
In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of acyclovir above levels that have been established safe by intravenous infusion.
In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800 mg acyclovir twice daily at approximately twelve - hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800 mg acyclovir three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10 – 25 ml/minute).

OVERDOSAGE
Acyclovir is only partly absorbed in the gastrointestinal tract.
Patients have ingested overdoses of up to 20g acyclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral acyclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).
Overdosage of intravenous acyclovir 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.

STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

Date de revision:
September 2014.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
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