

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellvirax 400mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 400 mg tablet contains 400 mg aciclovir .

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Capsule shaped, biconvex, uncoated white to off-white tablets with '400' embossed on one side and 'ACV' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bellvirax Tablets are indicated for the following:

- treatment of herpes simplex virus infections involving the skin and mucous membranes, including initial and recurrent genital herpes,
- suppression of recurrence of herpes simplex virus infections in immunocompetent patients,
- prophylaxis against herpes simplex virus infections in immunocompromised individuals,
- treatment of herpes zoster (shingles) and varicella (chicken pox) infections.

4.2 Posology and method of administration

Bellvirax Tablets should be dissolved in 100 ml (a glassful) of water immediately before taking, or swallowed whole with water, according to the following dosage schedules:

Adults:

Treatment of herpes simplex virus infections:

200 mg, five times a day at four-hourly intervals, omitting the night time dose. Treatment is usually for 5 days, but can be extended, depending on the severity of the infection.

In patients who are severely immunocompromised or with malabsorption, the dose may be increased to 400 mg.

Treatment should be started as soon as infection is evident; i.e. when lesions first appear, or for recurrent infections, during the prodromal phase.

Suppression of recurrent herpes simplex infections in immunocompetent patients:

200 mg, four times a day at six-hourly intervals or 400 mg twice daily at twelve-hourly intervals.

This dose may be reduced according to progress, to 200 mg, three times daily at eight-hourly intervals or twice daily at twelve-hourly intervals; however it should be remembered that total daily doses of 800 mg or less may be associated with breakthrough viral infection.

Treatment should be stopped temporarily after periods of six to twelve months to assess the status of the patient's disease.

Prophylaxis of herpes simplex virus infections in immunocompromised individuals:

200 mg, taken four times daily at six-hourly intervals. In patients with severe impairment of the immune system, for example after a bone marrow transplant, or in patients with impaired gastrointestinal absorption, the dose can be increased to 400 mg. Intravenous dosing may be considered as an alternative.

The length of treatment is determined by the length of time during which the patient is judged to be at risk of infection.

Treatment of herpes zoster and varicella infections:

800 mg, five times daily at four-hourly intervals for 7 days, omitting the night time dose.

Intravenous dosing may be considered in severely immunocompromised patients or in those with impaired gastrointestinal absorption.

In both diseases, treatment should be started as soon as possible after the onset of a rash or other symptoms are recognised.

Children:**Treatment of herpes simplex virus infections and prophylaxis in the immunocompromised:**

The adult dosages may be used in children two years and older.
Children below two should receive half the adult dose.

Treatment of varicella infections:

Children six years and older: 800 mg, four times a day.

Two to five years: 400 mg, four times a day.

Under two years: 200 mg, four times a day.

These dosages should be continued for 5 days.

If required, doses may be calculated on a 20 mg/kg body weight basis, four times daily. A single dose should not exceed 800 mg.

The elderly:

Dosage should be determined with reference to kidney function, as indicated by creatinine clearance. Doses should be reduced in patients with impaired kidney function (see below).

Efforts should be made to ensure adequate hydration of elderly patients taking high oral doses of aciclovir.

Dosage in renal impairment:

Treatment of herpes simplex virus infections:

Severe renal impairment (creatinine clearance < 10 ml/minute): a maximum dose of 200 mg, twice daily, at twelve-hourly intervals is recommended.

Treatment of herpes zoster and varicella infections:

Severe renal impairment (creatinine clearance < 10 ml/minute): a maximum dose of 800 mg, twice daily at twelve-hourly intervals.

Moderate renal impairment (creatinine clearance between 10 and 25 ml/minute): 800 mg, three times a day at six to eight hourly intervals.

4.3 Contraindications

Hypersensitivity to Aciclovir or valaciclovir or any component of aciclovir tablets.

4.4 Special warnings and precautions for use

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

Total body clearance of aciclovir declines along with creatinine clearance and special attention should be given to dosage reduction in elderly and other patients with impaired creatinine clearance.

Aciclovir has not been shown to reduce the incidence of complications associated with chicken pox in immunocompromised patients.

In severely immunocompromised patients, prolonged or repeated courses of aciclovir may result in the selection of viral strains with reduced sensitivity to the drug; these may not respond to continued use.

Evidence from a wide range of *in vitro* and *in vivo* standard, mutagenicity tests indicate that aciclovir is unlikely to produce genetic abnormalities in man. Longitudinal studies in mice and rats indicated no carcinogenic potential. Reversible effects on spermatogenesis have been observed in rats and dogs, at much higher doses of aciclovir than those recommended for therapeutic purposes in man. Aciclovir has not been shown to produce definitive effects on sperm count, morphology or motility in man.

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 Fertility, pregnancy and lactation

Pregnancy: 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.

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

Teratogenicity: 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.

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 0.3 g/kg/day. Caution is therefore advised if Bellvirax is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of Bellvirax should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of Bellvirax 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.

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 addiction.

The following convention has been used for the classification of undesirable effects in terms of frequency: Very common $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$.

Blood and lymphatic system disorders

Very rare: Anaemia, leucopenia, 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 reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, 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

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

4.9 Overdose

Symptoms and 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, seizure 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC Code: JO5AB

Mode of action

Aciclovir is a synthetic, purine nucleoside analogue, structurally related to guanine, with *in vitro* and *in vivo* activity against herpes simplex virus, types 1 and 2, and varicella-zoster virus. This activity is due to intracellular conversion of aciclovir by thymidine kinase to the monophosphate, which is then converted to the diphosphate and ultimately the active, triphosphate by normal cellular enzymes. This form inhibits viral DNA synthesis and replication by incorporation and also by inhibition of DNA polymerase. The process is highly selective for infected cells; uninfected cells do not use aciclovir as a substrate, therefore toxicity to mammalian host cells is low. Aciclovir triphosphate is formed in virally infected cells in amounts up to 100 times those found in normal uninfected cells. Studies in animals and *in vitro* show various sensitivities, but demonstrate that these viruses are inhibited by concentrations of aciclovir that are easily achieved clinically. Aciclovir is active against DNA viruses, particularly the herpes viruses (simplex and varicella-zoster). It is particularly active against herpes simplex virus types 1 and 2; varicella-zoster virus is less sensitive.

Aciclovir has no activity against latent viruses, but there is some evidence that it inhibits latent herpes simplex virus at an early stage of reactivation.

Clinical isolates from some severely immunocompromised patients who have received long-term therapy or repeated courses of aciclovir have shown reduced sensitivity to the drug. Most of these clinical isolates had reduced levels of thymidine kinase; although isolates with altered thymidine kinase or viral DNA polymerase have been observed. The same phenomenon has been observed after *in vitro* exposure of herpes virus samples to aciclovir.

5.2 Pharmacokinetic properties

Approximately 15-30% of an oral dose of aciclovir is absorbed and the time to reach peak concentration is 1.5 to 2 hours, a dose of 200 mg aciclovir, every four hours by mouth was reported to produce maximum and minimum steady state plasma concentrations of 0.7 and 0.4 µg/ml respectively; equivalent values following 400 mg and 800 mg doses were 1.2 and 0.6 µg/ml and 1.8 and 0.9 µg/ml respectively.

Aciclovir is widely distributed to tissues and body fluids including brain, kidney, lungs, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, the CSF where concentrations of approximately half those in plasma are achieved, and herpetic vesicular fluid. The drug is 9 to 33% bound to plasma proteins. Aciclovir crosses the placenta and is excreted in breast milk at concentrations 3-4 times higher than corresponding values in maternal serum.

After intravenous administration, the majority of a dose is excreted unchanged in the urine with approximately 14% appearing as the inactive metabolite, 9 - carboxymethoxy methylguanine. Faecal excretion may account for about 2% of a dose. Aciclovir is excreted by both tubular secretion and glomerular filtration; therefore aciclovir clearance is approximately three times greater than creatinine clearance. Prior administration of probenecid increases the half life and the area under the plasma-concentration-time curve. The terminal half-life is approximately 2 to 3 hours in adults with normal renal function. As renal function declines, a greater percentage of the drug is eliminated by hepatic metabolism. In chronic renal failure the half-life is prolonged and may reach 19.5 hours in anuric patients. The drug is removed by haemodialysis and the half-life may be reduced to 5.7 hours, with 60% of a dose being removed in 6 hours.

In elderly patients, aciclovir total body clearance falls in line with reduced creatinine clearance, although there appears to be little change in the terminal plasma half life.

5.3 Preclinical safety data

The pharmacological and toxicological properties of aciclovir are well established. There are no additional data from preclinical studies of clinical concern.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium Stearate
Microcrystalline Cellulose
Sodium Starch Glycolate
Pregelatinised Maize Starch
Colloidal Anhydrous Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister comprising plain aluminium foil and PVDC coated PVC film.

Pack sizes: 56 tablets per carton.

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

Ranbaxy Ireland Limited,
Spafield,
Cork Road,
Cashel,
Co. Tipperary.

8 MARKETING AUTHORISATION NUMBER

PA 408/53/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th May 1999

Date of last renewal: 27th May 2009

10 DATE OF REVISION OF THE TEXT

March 2010