PACKAGE INSERT FOR ANVIRO 500 TABLETS

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ANVIRO 500 TABLETS

COMPOSITION

Each film coated tablet contains valaciclovir hydrochloride monohydrate equivalent to 500 mg valaciclovir.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Valaciclovir is the L-valine ester of aciclovir, a purine nucleoside analogue used in the treatment of viral infections caused by Herpes simplex virus (HSV) types I and II as well as Varicella zoster virus (Herpes zoster and chickenpox). With the aid of HSV thymidine kinase, aciclovir is taken up into the herpes infected cells and converted via phosphorylation to the active compound, aciclovir triphosphate. Aciclovir triphosphate competitively inhibits herpes specified DNA polymerase once it has been phosphorylated to the active triphosphate form, thus preventing further DNA synthesis without affecting normal cellular DNA polymerase.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of the UL97 gene of CMV. This gene encodes for the viral kinase which facilitates the intracellular anabolism of aciclovir.

Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this

nucleoside analogue results in obligatory chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacokinetics:

Valaciclovir is readily absorbed from the gastrointestinal tract after oral doses, and is rapidly converted to aciclovir and valine by first-pass intestinal or hepatic metabolism. The bioavailability of aciclovir after valaciclovir administration is reported to be 54 % and peak plasma concentrations of 5,7 µg/ml aciclovir are achieved after 1,75 hours following a single dose of 1000 mg. Peak plasma concentrations of valaciclovir are only 4 % of aciclovir levels, occur at a median time of 45 to 60 minutes post dose, and are below measurable concentrations 3 hours after dosing.
Valaciclovir is eliminated mainly as aciclovir and its metabolite 9-carboxymethoxymethyl-guanine.
Less than 1 % of a dose of valaciclovir is excreted unchanged in the urine.
Binding of aciclovir to plasma proteins is very low (15 %).

INDICATIONS

ANVIRO 500 TABLETS is indicated for:

- Treatment of Herpes zoster (shingles).
- Treatment of recurrent genital Herpes simplex infections in immunocompetent patients.
- Prevention of Herpes simplex infections of the skin and mucous membranes on the ano-genital area.
- Prophylaxis of cytomegalovirus (CMV) infection or disease after organ transplant.

CONTRAINDICATIONS

Hypersensitivity to valaciclovir, aciclovir or to any components of the formulation.
Safety in pregnancy and lactation has not been established (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

In patients with advanced HIV disease, after bone marrow transplant or renal transplant,

thrombocytopenic purpura/haemolytic uremic syndrome has been reported, with some cases being fatal. This syndrome has not been observed in immunocompetent patients.

Care should be taken to maintain adequate hydration in patients receiving high doses of **ANVIRO 500 TABLETS**. **ANVIRO 500 TABLETS** should be administered with caution with renal impairment and doses should be adjusted according to creatinine clearance (see **DOSAGE AND DIRECTIONS FOR USE**).

INTERACTIONS

Although no clinically significant interactions have been reported, any medicine which is excreted via renal tubular secretion may compete with and thus interact with **ANVIRO 500 TABLETS**. Caution should be taken with such medicines.

Cimetidine and probenecid have been shown to decrease the renal excretion of aciclovir and to increase the area under the curve (AUC) of aciclovir. With co-administration of aciclovir and mycophenolate mofetil (immunosuppressant agent used during organ transplant), increases in plasma AUCs of both medicines have been shown.

No significant increase in toxicity was noted when zidovudine and aciclovir was given concomitantly.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. Caution should be exercised by balancing the potential benefits of treatment against risk when **ANVIRO 500 TABLETS** is used in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

ANVIRO 500 TABLETS may be taken with or without meals.

Normal renal function:

Herpes zoster:

Adults: 1000 mg (two tablets) to be taken three times a day.

Recurrent genital herpes:

Adults: 500 mg (one tablet) twice a day for 5 days. Start as soon as possible, within 24 hours when signs and symptoms appear.

Prevention of recurrent Herpes simplex:

Immunocompromised adults: 500 mg (one tablet) twice a day.

Prevention of cytomegalovirus (CMV) infection and disease:

Adults: 2000 mg (four tablets) four times a day. Should be initiated as soon as possible after transplant. Creatinine clearance should be monitored and dosing should be reduced accordingly. Treatment is usually 90 days, but may be extended for high risk patients.

Children:

Safety in children has not been established.

Elderly:

Dose reductions may be necessary in the elderly with impaired renal function (see **Renal function impairment** below).

Adequate hydration must be ensured in patients taking high doses of **ANVIRO 500 TABLETS**.

Renal function impairment:

Herpes zoster:

Moderate impairment (creatinine clearance of 15 to 30 ml/min): 1000 mg twice a day.

Severe impairment (creatinine clearance of less than 15 ml/min): 1000 mg once a day.

Recurrent genital herpes:

Moderate impairment (creatinine clearance of more than 15 ml/min): 500 mg twice a day.

Severe impairment (creatinine clearance of 0 to 15 ml/min): 500 mg once a day.

Prevention of recurrent Herpes simplex:

Immunocompetent adults:

Moderate impairment (creatinine clearance of 15 to 30 ml/min): No dosage adjustment required.

Severe impairment (creatinine clearance of less than 15 ml/min): 250 mg once a day.

Immunocompromised adults:

Moderate impairment (creatinine clearance of 15 to 30 ml/min): No dosage adjustment required.

Severe impairment (creatinine clearance of less than 15 ml/min): 500 mg once a day.

Prevention of cytomegalovirus (CMV) infection and disease:

Creatinine clearance of ≥ 75 ml/min: 2000 mg four times a day.

Creatinine clearance of 50 to < 75 ml/min: 1500 mg four times a day.

Creatinine clearance of 25 to < 50 ml/min: 1500 mg three times a day.

Creatinine clearance of 10 to < 25 ml/min: 1500 mg twice a day.

Creatinine clearance of < 10 ml/min or dialysis: 1000 mg once a day.

Patients on haemodialysis should receive **ANVIRO 500 TABLETS** after haemodialysis has been completed.

Creatinine clearance should be monitored frequently.

Hepatic impairment:

Dose adjustment for hepatic impairment is not necessary.

SIDE EFFECTS

Gastrointestinal:

Frequent: Nausea, vomiting, diarrhoea, abdominal pain.

Neurological:

Frequent: Headache.

Less frequent: Fatigue, reversible neurological reactions such as dizziness, confusional states, hallucinations, tremors, psychosis, agitation, somnolence, convulsions, coma.

Haematological:

Less frequent: Aplastic anaemia, leucopenia, thrombocytopenia, neutropenia.

Kidney/Genitourinary:

Less frequent: Increases in blood urea and creatinine, acute renal failure, dysmenorrhoea.

Liver:

Less frequent: Reversible increases in bilirubin and liver enzymes, hepatitis and jaundice.

Skin:

Less frequent: Diffuse hair loss.

Other:

Less frequent: Hypersensitivity reactions including rash, photosensitivity, urticaria, pruritus, dyspnoea, angioedema and anaphylaxis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **SIDE EFFECTS**)

Symptoms of overdose:

ANVIRO 500 TABLETS has a wide therapeutic window therefore excessive doses of **ANVIRO 500 TABLETS** are generally well tolerated. Repeated overdoses of oral **ANVIRO 500 TABLETS** have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (such as headache and confusion).

Treatment of overdose:

Treatment is symptomatic and supportive. Haemodialysis, if required, significantly enhances the removal of **ANVIRO 500 TABLETS** from the blood.

IDENTIFICATION

ANVIRO 500 TABLETS: White to off white, capsule shaped, biconvex, film coated tablets, debossed with “500” on one side and median line on the other side. Tablet should be free of all physical defects.

PRESENTATION

ANVIRO 500 TABLETS are packed into plain silver aluminium/transparent PVC/PVDC foil blisters.

ANVIRO 500 TABLETS are available in blister strips containing 10 tablets. 1 or 3 blister strips are packed into a carton box with the PI.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light and moisture.

Do not remove from the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

42/20.2.8/0820

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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