For the Use Only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

LOVIR TABLETS (400 mg and 800 mg)

LOVIR TABLET 400 MG
Each tablet contains:
Acyclovir ……...400 mg

LOVIR TABLET 800 MG
Each tablet contains:
Acyclovir ……...800 mg

Excipients: Colloidal anhydrous silica, sodium starch glycollate, magnesium stearate, pregelatinised starch, microcrystalline cellulose and purified water.

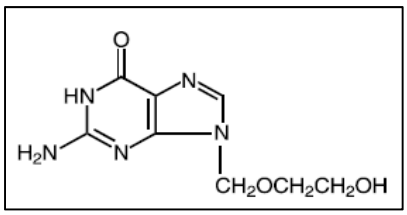
PRODUCT DESCRIPTION

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

LOVIR TABLET 800 MG
Capsule shaped biconvex uncoated white to off-white tablets with '800' embossed on one side and 'ACV' on the other side.

DESCRIPTION

LOVIR TABLETS contain acyclovir, a synthetic nucleoside analogue active against herpes virus. The chemical name of acyclovir is 2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6*H*-purin-6-one. Its molecular formula is $C_{18}H_{11}N_5O_3$ and molecular weight is 225. The structural formula of acyclovir is as given below:



STRUCTURAL FORMULA
ACYCLOVIR

INDICATIONS

LOVIR TABLETS are indicated for:

- The treatment of *Herpes simplex* virus infections of the skin and mucous membranes, including initial and recurrent genital herpes.
- The suppression (prevention of recurrence) of recurrent *Herpes simplex* infections in immune-competent patients.
- The prophylaxis of *Herpes simplex* infections in immune-compromised patients.
- The treatment of *Varicella* (Chickenpox) and *Herpes zoster* (Shingles) infections.

It has been reported 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).

DOSE AND METHOD OF ADMINISTRATION

LOVIRS TABLETS are not suitable for all dosage recommendations given below and therefore, other suitable available strengths and/or dosage forms of acyclovir should be used in such cases.

Dosage for treatment of *Herpes simplex* in adults

For treatment of *Herpes simplex* infections, 200 mg acyclovir 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.

Dosage for suppression of *Herpes simplex* in adults

For suppression of *Herpes simplex* infections in immune-competent patients, 200 mg acyclovir should be taken four times daily at approximately six-hourly intervals. Many patients may be conveniently managed on a regimen of 400 mg acyclovir taken twice daily at approximately twelve-hourly intervals. Dosage titration down to 200 mg acyclovir taken three times 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 acyclovir.

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.

Dosage for prophylaxis of *Herpes simplex* in adults

For prophylaxis of *Herpes simplex* infections in immune-compromised patients, 200 mg acyclovir 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.

Dosage for treatment of *Varicella* and *Herpes zoster* in adults

For treatment of *Varicella* and *Herpes zoster* infections, 800 mg acyclovir 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.

Dosage in children

LOVIR TABLETS are not suitable for children who cannot swallow tablets. Other appropriate dosage forms and/or strengths may be used in such cases.

For treatment of *Herpes simplex* infections, and for prophylaxis of *Herpes simplex* infections in the immune-compromised 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.

For treatment of *Varicella* infections, children over the age of six years can be given 800 mg acyclovir four times daily and children between the ages of two and six years can be given 400 mg acyclovir four times daily.

Children below the age of two years can be given 200 mg acyclovir four times daily. Dosing may be more accurately calculated as 20 mg acyclovir per kg of 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 immunocompetent children.

Dosage in the elderly

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

Dosage in renal impairment

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. However, for patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg 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).

ROUTE OF ADMINISTRATION : ORAL

USE IN SPECIAL POPULATIONS Pregnancy

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.

Lactation

Following oral administration of 200 mg acyclovir five times a day, acyclovir 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 acyclovir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if acyclovir is to be administered to a nursing woman.

CONTRAINDICATIONS

LOVIR TABLETS are contraindicated in patients with hypersensitivity to acyclovir or to any other component/excipient of the product.

WARNINGS AND PRECAUTIONS

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

Acyclovir tablets are intended for oral ingestion only. Renal failure, in some cases resulting in death, has been reported with acyclovir therapy. Thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), which has resulted in death, has been reported to occur in immunocompromised patients receiving acyclovir therapy.

Acyclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see DOSE AND METHOD OF ADMINISTRATION). 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.

Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents, since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

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: Adequate hydration should be maintained. Particularly, 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.

The data currently available from clinical studies is not sufficient to conclude that treatment with acyclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.

Effects on 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. A detrimental effect on such activities cannot be predicted from the pharmacology of the active substance, but the adverse event profile should be borne in mind.

Information for patients

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir or they have any other questions.

Patients should be advised to maintain adequate hydration.

Herpes Zoster: There are no reported data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital herpes infections: Acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox: Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was reported to be initiated within 24 hours of the typical chickenpox rash, and there was no information regarding the effects of treatment begun later in the disease course.

Preclinical safety

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that acyclovir is unlikely to pose a genetic risk to man. Acyclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Systemic administration of acyclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, fetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of acyclovir on fertility. There is no experience of the effect of acyclovir tablets on human female fertility. Acyclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

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. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of acyclovir. Probenecid and cimetidine increase the AUC of acyclovir by this mechanism and reduce acyclovir renal clearance. Probenecid also increases the acyclovir mean half life. Similarly increases in plasma AUCs of acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppresant agent used in transplant patients have been reported when the drugs were coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of acyclovir.

It was reported 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.

UNDESIRABLE EFFECTS

Below given is the summary of adverse events reported with acyclovir:

Blood and lymphatic system disorders
Very rare: Anaemia, leukopenia, thrombocytopenia, small decreases in haematological indices.

Immune system disorders
Rare: Anaphylaxis.

Psychiatric and nervous system disorders
Common: Headache, dizziness.
Very rare: Reversible neurological reactions, agitation, confusion/ confusional states, tremor, ataxia, dysarthria, hallucinations, psychosis/psychotic symptoms, convulsions/seizures, 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 (hyperbilirubinemia) and liver related enzymes/ elevated liver function tests.
Very rare: Hepatitis, jaundice.

Skin and subcutaneous tissue disorders
Common: Pruritus, rashes (including photosensitivity / photosensitivity rash).
Uncommon: Urticaria. Accelerated diffuse hair loss / alopecia. Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to acyclovir therapy is uncertain.
Rare: Angioedema.

Renal and urinary disorders
Rare: Increases in blood urea / blood urea nitrogen 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.

Other reported adverse events are: pain, peripheral oedema, malaise, aggressive behavior, decreased consciousness, delirium, paraesthesia, gastrointestinal distress, leukocytoclastic vasculitis, lymphadenopathy, myalgia, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, visual abnormalities, and haematuria.

In patients receiving anti-retroviral therapy (mainly oral zidovudine), no significant increase in toxicity was associated with the addition of acyclovir.

OVERDOSE

Acyclovir is only partly absorbed in the gastrointestinal tract. It is unlikely that serious toxic effects would occur if a dose of up to 5g were taken on a single occasion. No data are available on the consequences of the ingestion of higher doses. Single intravenous doses of up to 80mg/kg have been inadvertently administered without adverse effects.

Treatment
Ingestion of doses of acyclovir in excess of 5g warrants close observation of the patient. Acyclovir is dialysable by haemodialysis.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES Pharmacodynamic properties

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, *Varicella zoster* virus (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. The enzyme thymidine kinase (TK) of normal, non-infected cells does 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 interferes with the viral DNA polymerase and inhibits viral DNA replication with the resultant chain termination following its incorporation into the viral DNA.

Prolonged or repeated course of acyclovir in severely immunocompromised 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 DNA polymerase have also been reported. *In vitro* exposure of HSV isolates to acyclovir can also lead to 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 200 mg administered four-hourly were 3.1 µmol (0.7 mcg/ml) and equivalent trough plasma levels ($C_{ss,min}$) were 1.8 µmol (0.4 mcg/ml). Corresponding $C_{ss,max}$ levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 µmol (1.2 mcg/ml) and 8 µmol (1.8 mcg/ml) respectively, and equivalent $C_{ss,min}$ levels were 2.7 µmol (0.6 mcg/ml) and 4 µmol (0.9 mcg/ml).

In adults, the terminal plasma half life of acyclovir after administration 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-carboxymethoxy methylguanine is the only significant metabolite of acyclovir and accounts for approximately 10 to 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% or 40% respectively. In adults, mean $C_{ss,max}$ levels following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 µmol (5.1 mcg/ml), 43.6 µmol (9.8 mcg/ml), 92 µmol (20.7 mcg/ml), respectively. The corresponding C_{ssmin} levels 7 hours later were 2.2 µmol (0.5 mcg/ml), 3.1 µmol (0.7 mcg/ml) and 10.2 µmol (2.3 mcg/ml), respectively. In children over 1 year of age, similar mean $C_{ss,max}$ and $C_{ss,min}$ levels were reported 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 reported to be 61.2 µmol (13.8 mcg/ml) and the $C_{ss,min}$ to be 10.1 µmol (2.3 mcg/ml). The terminal plasma half-life in these patients was 3.8 hours. 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 reported 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.

STORAGE
Store below 30°C, protected from moisture

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

SUPPLY
LOVIR TABLET 400 MG: Blister packs of 14 x 5 tablets
LOVIR TABLET 800 MG: Blister packs of 7 x 5 tablets

Date of Revision: July 2018

Product Registration Holder & Manufactured by:
RANBAXY (MALAYSIA) SDN. BHD.
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah,
Malaysia