

New Zealand Data Sheet



1. PRODUCT NAME

LOVIR® Dispersible tablet, 200 mg
LOVIR® Dispersible tablet, 400 mg
LOVIR® Dispersible tablet, 800 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LOVIR 200 mg Dispersible tablet contains aciclovir 200 mg.
Each LOVIR 400 mg Dispersible tablet contains aciclovir 400 mg.
Each LOVIR 800 mg Dispersible tablet contains aciclovir 800 mg.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LOVIR 200 mg: White to off-white capsule shaped, biconvex uncoated tablet with “200” embossed on one side and “ACV” on the other side.

LOVIR 400 mg: White to off-white capsule shaped, biconvex uncoated tablet with “400” embossed on one side and “ACV” on the other side.

LOVIR 800 mg: White to off-white capsule shaped, biconvex uncoated tablet with “800” embossed on one side and “ACV” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LOVIR Dispersible tablets are indicated for:

- Treatment of Herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.
- Suppression (prevention of recurrences) of recurrent Herpes simplex infections in immune-competent patients.
- Prophylaxis of Herpes simplex infections in immune-compromised patients.
- Treatment of acute Herpes zoster (shingles) infections, for the reduction of the duration and severity of acute symptoms and rash, for the reduction of all zoster-associated pain and for the reduction of the incidence and duration of post-herpetic neuralgia.

- Management of patients with severe AIDS who have a CD4 count of less than 50/ μ L. Studies have shown that oral aciclovir given in conjunction with anti-retroviral therapy reduced mortality in patients with advanced HIV disease.
- Patients undergoing allogenic bone marrow transplantation who are at risk of developing CMV infection while immunosuppressed (preceded by one month's treatment with intravenous aciclovir). Studies have shown that oral aciclovir reduced mortality in allogenic bone marrow transplant recipients. In addition oral aciclovir provided effective prophylaxis for herpes virus disease.

4.2. Dose and method of administration

Dose

Adults

Dosage for treatment of First Episode Herpes simplex

For treatment of Herpes simplex infections one 400 mg LOVIR tablet should be taken three times daily at approximately eight-hourly intervals. Treatment should continue for 7 days, but in severe initial infections may have to be extended.

Alternatively one 200 mg LOVIR tablet can be taken five times daily at approximately four-hourly intervals for five days. In severe initial infections may have to be extended.

Dosing should begin as early as possible after the start of an infection.

In severely immunocompromised patients (e.g. after bone marrow transplant) or in patients with impaired absorption from the gut, one 400 mg LOVIR tablet can be taken five times daily at approximately four-hourly intervals for five days or intravenous administration should be considered.

Episodic Treatment for recurrent Herpes Simplex

Oral aciclovir 800 mg (2 x 400mg) three times daily for two days.

Alternatively one 400 mg LOVIR tablet can be taken three times daily for 3 – 5 days or one 200 mg Lovir tablet five times a day for five days.

For recurrent episodes treatment should preferably start during the prodromal period or when the lesions first appear. It is recommended that a prescription be given to patients who experience recurrences so they can self-initiate treatment at symptom onset.

Dosage for Suppression of Herpes simplex in Adults

For suppression of Herpes simplex infections in immune-competent patients, one 400 mg LOVIR tablet should be taken twice daily.

Alternatively one 200 mg LOVIR tablet should be taken four times daily at approximately six-hourly intervals.

Dosage titration down to one 200 mg LOVIR 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 breakthrough infections on total daily doses of 800 mg aciclovir.

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 immunocompromised

For prophylaxis of Herpes simplex infections in immunocompromised patients, 200 mg aciclovir should be taken four times daily at approximately six-hourly intervals.

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 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 Herpes zoster

For treatment of Herpes zoster infections, 800 mg aciclovir should be taken five times daily at approximately four-hourly intervals. Treatment should continue for seven days.

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 yields better results if initiated as soon as possible after onset of the rash, ideally within 48 hours, but up to 72 hours being acceptable.

Special populations

Paediatric population

For treatment of Herpes simplex infections and for prophylaxis of Herpes simplex infections in the immunocompromised, children over the age of 2 years should be given adult doses and children below the age of 2 years should be given half the adult dose. No specific data are available on the suppression of Herpes simplex infections or the treatment of Herpes zoster infections in immunocompetent children.

Elderly population

In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

Special attention should be given to dosage reduction in elderly patients with impaired renal function.

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 aciclovir beyond 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 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 or four times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25 mL/minute).

Method of Administration

LOVIR tablets may be swallowed whole with a little water or dispersed in a minimum of 50 mL of water.

4.3. Contraindications

LOVIR tablets are contraindicated in patients known to be hypersensitive to aciclovir.

4.4. Special warnings and precautions for use

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients.

4.5. Interaction with other medicines and other forms of interaction

Probenecid increases the aciclovir mean half-life and area under the plasma concentration/time curve. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of aciclovir. However, clinical experience has not identified other drug interactions with aciclovir.

4.6. Fertility, pregnancy and lactation

Pregnancy

Category B3.

Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450 mg/kg/day orally), rabbit (50 mg/kg/day subcutaneously and intravenously) or rat (50 mg/kg/day subcutaneously) when dosed throughout the period of major organogenesis. This exposure in the rat resulted in plasma levels 11-fold the mean steady state peak

concentration in human doses of 800 mg every four hours. In additional studies in which rats were given three subcutaneous doses of aciclovir 100 mg/kg on gestation day 10, foetal abnormalities, e.g. head and tail anomalies, were reported (exposure was 62-fold human levels after 800 mg every four hours).

There have been no adequate and well controlled studies concerning the safety of aciclovir in pregnant women. It should not be used during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the foetus. If suppressive therapy is used in the perinatal period, it should not be assumed that viral shedding has ceased, or that the risk to fetus/neonate has decreased. Pregnancy should be managed according to considerations normally applicable to patients with genital herpes.

Breast-feeding

Limited human data show that the drug does pass into breast milk.

Fertility

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically.

Two-generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.

There is no experience of the effect of aciclovir tablets on human female fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

4.7. Effects on ability to drive and use machines

Aciclovir is presumed to be safe or unlikely to produce an effect on the ability of the patient to drive or use machinery.

4.8. Undesirable effects

Skin rashes have been reported in a few patients receiving aciclovir tablets; the rashes have resolved on withdrawal of the drug.

Gastrointestinal effects, including nausea, vomiting, diarrhoea and abdominal pains, have been reported in some patients receiving aciclovir tablets. In double-blind placebo controlled trials, the incidence of gastrointestinal events has not been found to differ between placebo and aciclovir recipients.

Other events reported rarely in patients receiving oral formulations of aciclovir include mild, transient rises in bilirubin and liver related enzymes, small increases in blood urea and

creatinine, small decreases in haematological indices, headaches, mild reversible neurological reactions and fatigue.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Aciclovir is only partly absorbed in the gastrointestinal tract. It is unlikely that serious toxic effects would occur if a dose of up to 5 g 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 80 mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialysable.

Ingestion of doses of aciclovir in excess of 5 g warrants close observation of the patient.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors

ATC code: J05AB01.

Mechanism of action

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) Types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes-infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the viral-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, thus preventing further viral DNA synthesis without affecting normal cellular processes.

5.2. Pharmacokinetic properties

Aciclovir 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 0.68 µg/mL and the

equivalent trough plasma levels ($C_{ss\min}$) were 0.36 µg/mL. Corresponding steady-state plasma concentrations following doses of 800 mg administered four hourly were 1.56 µg/mL and 0.79 µg/mL respectively.

From the studies with intravenous aciclovir the terminal plasma half-life has been determined at 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 10-15 % of the dose excreted in the urine. 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.

5.3. Preclinical safety data

Mutagenicity

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man.

Carcinogenicity

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized maize starch, purified water, sodium starch glycolate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

6.5. Nature and contents of container

LOVIR 200 mg Tablets: PVC/PVDC blister packs of 25 or 90 tablets.

LOVIR 400 mg Tablets: PVC/PVDC blister packs of 56 tablets.
LOVIR 800 mg Tablets: PVC/PVDC blister packs of 35 tablets.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

25 June 1998

10. DATE OF REVISION OF THE TEXT

21 December 2018

Summary table of changes

Section Changed	Summary of new information
All	SPC format