PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LOVIRE®200 Tablets

LOVIRE®400 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LOVIRE® 200 Tablets

Each dispersible tablet contains 200 mg aciclovir

LOVIRE® 400 Tablets

Each dispersible tablet contains 400 mg aciclovir

Sugar free.

3 PHARMACEUTICAL FORM

LOVIRE® 200 Tablets

Capsule shaped, biconvex, uncoated white to off-white tablets with ‘200' debossed on one side and ‘ACV' on the other side.

LOVIRE® 400 Tablets

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LOVIRE® Tablets are indicated for:

- Treatment of initial and recurrent *Herpes simplex* infections of the skin and mucous membranes including initial and recurrent genital *Herpes simplex* virus infections in both immunocompetent and immunocompromised patients.
- Suppression of recurrent genital *Herpes simplex* infections in immunocompetent patients.
- Prophylaxis of *Herpes simplex* infections in immunocompromised patients.
- Treatment of *Herpes zoster* (shingles) infections if the lesions are not older than 72 hours.
- Treatment of *Varicella zoster* (chicken pox) infection within 24 hours after appearance of the typical chicken pox lesions.
- Reduction of mortality and risk of developing herpes virus infections in certain severely immunocompromised patients, namely those with advanced HIV disease (CD4+ counts <200/mm^3 including patients with AIDS or ARC) or following bone marrow transplantation. In patients with advanced HIV disease, **LOVIRE® Tablets** has been used in conjunction with oral zidovudine.
- In patients following bone-marrow transplantation oral **LOVIRE® Tablets** must be preceded by one month's intravenous treatment with acyclovir*.

  * The applicant does not have an intravenous dosage form registered nor marketed, another acyclovir brand can be used.

4.2 Posology and method of administration

LOVIRE® Tablets may be taken with or without meals.

The tablets must be dispersed in 50 ml of water or swallowed whole.

Treatment of Herpes simplex infections of the skin and mucous membranes

Adults: 200 mg every four hours, five times a day (omitting the night time dose) for 5 days.

In severe infections, the duration of treatment may be extended.

In severely immunocompromised patients or in patients with impaired gastro-intestinal absorption, the dose may be increased to 400 mg five times per day. Alternatively, intravenous administration may be considered.

Treatment should be initiated as early as possible after the start of an infection, or in the case of recurrent episodes, treatment should be started during the prodromal period or when lesions first appear.

Suppression of recurrent genital *Herpes simplex* infections in immunocompetent adults

Adults: 200 mg four times a day at approximately six-hourly intervals.

Some patients may be adequately treated with 400 mg twice a day at approximately twelve - hourly intervals, while 200 mg three times per day, or even twice daily at approximately twelve-hourly intervals, may be suitable for some patients. Some patients may experience breakthrough infections on total daily doses of 800 mg acyclovir.

Therapy should be periodically interrupted 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 adults

Adults: 200 mg four times per day, at approximately six-hourly intervals.

In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired gastro-intestinal absorption, the dose may be increased to 400 mg four times per day or change to intravenous administration.

The duration of prophylactic administration is determined by the duration of the period at risk.

Treatment of *Herpes zoster* and *Varicella zoster* infections

Adults: 800 mg five times per day (omitting the night time dose) for 7 days.

Intravenous (IV) administration should be considered for severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired gastro-intestinal absorption.

Treatment should be initiated as soon as possible after the rash appears.

Intravenous administration may be considered if necessary.

For treatment of *varicella-zoster* infections in adolescents (12 to 18 years):

A dose of 800 mg oral **LOVIRE® Tablets** should be taken four times daily for five days.

Severely immunocompromised patients

Adults: 800 mg four times per day at six hourly intervals.

Bone marrow recipients should receive intravenous (IV) aciclovir 3 times daily for one month prior to receiving oral therapy. Duration of therapy is 6 months from 1 to 7 months post-transplant) and 12 months in patients with advanced HIV disease.

Special populations

Elderly Population

Adequate hydration must be ensured in patients taking high doses of **LOVIRE® Tablets**. Plasma concentrations of **LOVIRE® Tablets** are higher in geriatric patients compared to younger patients, in part due to age-related changes in renal function. Dose reductions may be necessary in the elderly with impaired renal function (See section 4.4).

Renal function impairment

Caution is advised when administering **LOVIRE® Tablets** to patients with impaired renal function. Adequate hydration should be maintained.

Treatment and prophylaxis of *Herpes simplex* infections

Mild to moderate impairment – No dose adjustment necessary.

Severe impairment (creatinine clearance less than 10 ml/min) – 200 mg every 12 hours.

Treatment of *Varicella* and *Herpes zoster* infections and management of severely immunocompromised patients (usual dose is 800 mg every four hours)

Moderate impairment (creatinine clearance of 10 to 25 ml/min) – 800 mg every 8 hours.

Severe impairment (creatinine clearance less than 10 ml/min) – 800 mg every 12 hours.

			Adjusted Dosage

Normal Dosage (5 times daily)	**Creatinine Clearance (ml/min/1,73 m2)**	**Dose (mg)**	**Dosing Interval (hours)**
200 mg every 4 hours	> 10	200	every 4 hours 5 times daily
	0-10	200	every 12 hours
800 mg every 4 hours	10-25	800	every 8 hours
	0-10	800	every 12 hours

Paediatric population

Treatment of *Herpes simplex infections* and prophylaxis of *Herpes simplex infections* in immunocompromised children:

Two years and older: Adult dosage.

Under two years: Half the adult dose (limited data).

Treatment of Herpes zoster and Varicella zoster infections in children

Two years and older: Adult dosage.

Below two years: Half the adult dosage.

LOVIRE® Tablets in children less than 2 years of age has not been fully studied. Dosing for varicella (chickenpox) may be more accurately calculated as 20 mg **LOVIRE® Tablets** per kilogram bodymass (not to exceed 800 mg) four times daily. Treatment should continue for five days and should start within 24 hours after appearance of typical chickenpox rash. Limited data suggest that for management of severely immunocompromised children, over two years of age, the adult dose may be given.

Method of administration

The tablets must be dispersed in 50 ml of water or swallowed whole with a little water

4.3 Contraindications

Hypersensitivity to aciclovir, valaciclovir or to any components of **LOVIRE® Tablets**

4.4 Special warnings and precautions for use

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS, which can be life-threatening or fatal, has been reported in associate with aciclovir treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, **LOVIRE® Tablets** should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed DRESS with the use of **LOVIRE® Tablet**s, treatment with **LOVIRE® Tablets** must not be restarted in this patient at any time.

There is limited data on the use of **LOVIRE® Tablets** in pregnancy and lactation (see section 4.6).

Care should be taken to maintain adequate hydration in patients receiving high doses of **LOVIRE® Tablets**. **LOVIRE® Tablets** should be administered with caution with renal impairment and doses should be adjusted according to creatinine clearance.

Severe renal impairment – A dose reduction is required in patients with a creatinine clearance of <10 mL/minute (See Section 4.2).

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

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).

4.5 Interaction with other medicines and other forms of interaction

Although no clinically significant interactions have been reported, any medicine which is excreted via renal tubular secretion may compete with and thus interact with **LOVIRE® Tablets**. Probenecid and Cimetidine has been shown to decrease renal excretion of aciclovir and to increase the area under the curve (AUC) of aciclovir.

No significant increase in toxicity was noted when zidovudine was given together with acyclovir.

4.6 Fertility, pregnancy and lactation

There is limited data on the use of **LOVIRE® Tablets** in pregnancy and lactation. The data is insufficient to establish safety. Safety and efficacy in pregnancy and lactation have not been established.

Pregnancy: A post-marketing acyclovir pregnancy registry has documented pregnancy outcomes in women exposed to **LOVIRE® Tablets**. The registry findings have not shown an increase in the number of birth defects amongst acliclovir (as contained in **LOVIRE® Tablets**) exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

Lactation: Following oral administration of 200 mg acyclovir as contained in **LOVIRE®** 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 aciclovir dosages of up to 0,3 mg/kg/day.

Fertility: There is no information on the effect of **LOVIRE®** on human female fertility. In a reported study of 20 male patients with normal sperm count, oral acyclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

4.7 Effects on ability to drive and use machines

LOVIRE® may influence the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment

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 indication.

Table 1: Tabulated List of Undesirable effects

System organ class	Frequent	Less frequent	Frequency Not known
Blood and lymphatic system disorders	-	Anaemia, leucopenia, thrombocytopenia, neutropenia	-
Immune system disorders	-	Hypersensitivity reactions including rash, photosensitivity, urticaria, pruritus, dyspnoea, angioedema, anaphylaxis.	-
Psychiatric disorders	Headache, dizziness		Reversible neurological reactions such as, confusional states, hallucinations, tremors, psychosis, agitation, somnolence, convulsions, coma (especially in patients with renal impairment in whom the dosage was in excess of that recommended.
Nervous system disorders	Headache		Fatigue
Gastro-intestinal disorders	Nausea, vomiting, diarrhoea, Abdominal pain		
Hepato-biliary disorders	-	Reversible increases in bilirubin and liver enzymes, hepatitis, jaundice	-

Skin and subcutaneous tissue disorders	-	Diffuse hair loss	-
Renal and urinary disorders	-	Increases in blood urea and creatinine, acute renal failure	-
General disorders and administration site conditions	Fatigue, fever	-	-

Table 1: Tabulated List of Post marketing undesirable effects		
MedDRA System organ class	**Frequency**	**Adverse reactions**
Skin and subcutaneous tissue disorders	Frequency Unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

4.9 Overdose

See **Undesirable effects**

Symptoms of overdose

LOVIRE® Tablets have a wide therapeutic window and therefore excessive doses of **LOVIRE® Tablets** are generally well tolerated. Repeated overdoses of oral aciclovir have been associated with gastro-intestinal effects (such as nausea and vomiting) and neurological effects (such as headache) and psychiatric effects (such as confusion).

Treatment of overdose

Patients should be observed closely for signs of toxicity. Treatment is symptomatic and supportive. Haemodialysis, if required, significantly enhances the removal of **LOVIRE® Tablets** from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral agents

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

ATC code: J05AB01

Aciclovir (**LOVIRE® Tablets**) is active in vitro against herpes simplex virus (HSV) types I and II and varicella-zoster virus. Acyclovir is phosphorylated after entry into herpes-infected cells to the active compound acyclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase. Acyclovir triphosphate acts as an inhibitor of and substrate for the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes.

5.2 Pharmacokinetic properties

Absorption

Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20 %.

Distribution

The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2,3 to 17,8 L/kg. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid concentration are approximately 50 % of corresponding plasma concentration at steady-state.

Biotransformation

Aciclovir is predominantly excreted unchanged by the kidney. The only significant urinary metabolite is 9- [(carboxymethoxy) methyl] guanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination

In adults mean systemic exposure (AUC0-∞) to aciclovir ranges between 1,9 and 2,2 microgram*h/mL after a 200 mg dose. At this dose, the mean terminal plasma half-life after oral administration has been shown to vary between 2,8 and 4,1 hours. Renal clearance of aciclovir (CLr= 14,3 L/h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

There are no pharmacokinetic data for the oral formulation in neonates.

5.3 Preclinical safety data

Mutagenicity:- The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.

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

Teratogenicity:- Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits 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.

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 aciclovir on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, sodium starch glycollate , pregelatinized maize starch, magnesium stearate, colloidal anhydrous silica

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C, protected from moisture.

Keep out of reach of children

6.5 Nature and contents of container

LOVIRE® Tablets are packed in PVdC/PVC blister strips

LOVIRE® 200 Tablets

Carton containing 25 tablets in blister strips

LOVIRE® 400 Tablets

Carton containing 56 or 70 tablets in blister strips

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road,

Stormill, Ext. 1,

Roodepoort, 1724,

South Africa

8. REGISTRATION NUMBER(S)

LOVIRE®200 Tablets: 32/20.2.8/0017

LOVIRE®400 Tablets: 32/20.2.8/0018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATON

Registration date: 13.01.1998

10. DATE OF REVISION OF THE TEXT

Last approval date: 15 August 2023

Botswana: S2 Reg.No. :

Lovire 200 Tablets - BOT0400704

Lovire 400 Tablets - BOT0400705

Namibia: NS2 Reg.No.:

Lovire 200 Tablets - 04/20.2.8/1285

Lovire 400 Tablets - 04/20.2.8/1286