APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZELIVIRE 500 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Blue coloured, capsule shaped, biconvex, film coated, tablets, debossed with 'V' and '5' on either side of the breakline on one side, notched on either side along with the breakline and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZELIVIRE 500 is indicated for the treatment of herpes zoster (shingles). ZELIVIRE 500 reduces the duration of zoster associated pain, which includes acute and post-herpetic neuralgia, thus accelerating resolution of pain. ZELIVIRE 500 also reduces the proportion of patients with zoster associated pain.

ZELIVIRE 500 is indicated for the episodic treatment of recurrent genital herpes in immunocompetent adult patients.

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ZELIVIRE 500 is indicated for prevention (suppression) of recurrent herpes simplex infection of the skin and mucous membrane of the ano-genital area.

ZELIVIRE 500 is indicated for the prophylaxis of cytomegalovirus (CMV) infection, CMV disease and other herpes virus infections following organ transplantation, where a special risk exists.

Treatment should be initiated as soon as possible following the onset of signs and symptoms. In the treatment of recurrent genital herpes there are no data on effectiveness of ZELIVIRE 500 when initiated more than 24 hours after the onset of signs and symptoms.

4.2 Posology and method of administration

Posology

For the treatment of herpes zoster:

1 000 mg of ZELIVIRE 500 to be taken 3 times per day for 7 days.

Recurrent genital herpes:

The recommended dosage for the treatment of recurrent genital herpes is

500 mg twice daily for 5 days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately on first signs or symptoms appearance.

There are no data on effectiveness of ZELIVIRE 500 when initiated more than 24 hours after the onset of signs and symptoms.

For the prevention (suppression) of recurrences of herpes simplex infection

Immunocompetent patients: 500 mg to be taken once daily. Some patients with very frequent recurrences (e.g. 10 or more per year) may gain additional benefit from daily dose of 500 mg being taken as divided dose (250 mg twice daily).

Immunocompromised patients: 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease

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Adults and adolescents (from 12 years of age): 2 000 mg to be taken 4 times a day. Dosing should be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance (see dosage in renal impairment). Duration of treatment will usually be 90 days but may need to be extended in high risk patients.

Special populations

Dosage in children

No data are available.

Dosage in the elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see renal impairment below). Adequate hydration should be maintained.

Dosing in high-risk individuals

Dosage in renal impairment

Caution is advised when administering ZELIVIRE 500 to patients with impaired renal function. Adequate hydration should be maintained.

The dose of ZELIVIRE 500 should be modified as follows in patients with significantly impaired renal function:

HERPES ZOSTER	
Creatinine Clearance	ZELIVIRE 500 dose
15 – 30 mL/min	1 000 mg twice daily
<15 mL/min	1 000 mg once daily
RECURRENT GENITAL HERPES	
Creatinine Clearance	ZELIVIRE 500 dose
>15 mL/min	500 mg twice daily
0 - 15 mL/min	500 mg once daily
PREVENTION OF RECURRENCES	

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Creatinine Clearance	ZELIVIRE 500 dose	
	Immunocompetent	Immunocompromised
15 – 30 mL/min	No dosage adjustment required	No dosage adjustment required
<15 mL/min	250 mg once daily	500 mg once daily

In patients on haemodialysis, the ZELIVIRE 500 dose recommended for patients with a creatinine clearance of <15 mL/min should be used, but the dose should be administered after the haemodialysis has been performed.

CMV Prophylaxis:

Dosage of ZELIVIRE 500 should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine Clearance	ZELIVIRE 500 dose
> 75 mL/min	2 000 mg four times daily
50 to < 75 mL/min	1 500 mg four times daily
25 to < 50 mL/min	1 500 mg three times daily
10 to < 25 mL/min	1 500 mg twice daily
< 10 mL/min or dialysis**	1 500 mg once daily

** In patients with haemodialysis, the ZELIVIRE 500 dosage should be administered after haemodialysis has been performed.

Creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment. The ZELIVIRE 500 dosage should be adjusted accordingly.

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Dosage in hepatic impairment

Dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal systemic shunting) do not indicate the need for dosage adjustment; however, clinical experience is limited. For higher doses recommended for CMV prophylaxis (4 g or more) see section 4.8**.**

4.3 Contraindications

ZELIVIRE 500 is contraindicated in patients known to be hypersensitive to valaciclovir, aciclovir or to any of the excipients listed in section 6.1.

Safety in pregnancy and lactation has not been established (see section 4.6).

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 valaciclovir 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, valaciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed DRESS with the use of valaciclovir, treatment with valaciclovir must not be restarted in this patient at any time.

Thrombotic, thrombocytopenic uraemic syndrome, in some cases resulting in death, have been reported in patients with advanced HIV disease and also in bone marrow transplant and renal transplant recipients participating in clinical trials of valaciclovir. This syndrome has not been observed in immunocompetent patients treated with valaciclovir in clinical trials.

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Hydration status: Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

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.

These reactions were generally reversible on discontinuation of treatment (see section 4.8).

Uses of higher doses of ZELIVIRE 500 in Hepatic impairment and liver transplantation:

There are no data available on the use of high doses of ZELIVIRE 500 (4 g/day) in patients with liver disease. Caution should therefore be exercised when administering high doses of ZELIVIRE 500 to these patients. Studies of ZELIVIRE 500 have not been conducted in liver transplantation; however high dose acyclovir prophylaxis has been shown to reduce CMV infection and disease.

In organ transplant patients receiving high doses ZELIVIRE 500 for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Use in genital herpes: Suppressive therapy with ZELIVIRE 500 reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with ZELIVIRE 500, it is recommended that patients use safer sex practices.

Patients should avoid sexual intercourse and contact with lesions and damaged skin.

Genital herpes may be transmitted in the absence of symptoms and patients should be counselled to use safer sex practices.

Teratogenicity

Foetal abnormalities were observed in rats. The therapeutic peak is 5,7 mcg/mL after 1 000 mg.

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4.5 Interaction with other medicines and other forms of interaction

No clinically significant interactions have been identified.

Cimetidine and probenecid increase the area under the plasma concentration time curve of aciclovir by reducing its renal clearance; however no dosage adjustment is necessary because of the wide therapeutic index of aciclovir. Other medicines which affect renal physiology could affect plasma levels of aciclovir.

Concomitant use which requires some care

In patients receiving high dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites.

Increases in plasma AUCs of aciclovir and of inactive metabolites of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when these medicines are co-administered.

Care is also required (with monitoring for changes in renal function) if administering high dose valaciclovir with medicines which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

Breastfeeding

Safety in lactation has not been established (see section 4.3).

Following oral administration of a 500 mg dose of ZELIVIRE 500, peak acyclovir concentrations (Cmax) in breast milk ranged from 0,5 to 2,3 (median 1,4) times the

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corresponding maternal acyclovir serum concentrations. Mothers on treatment with ZELIVIRE 500 should not breastfeed their infants.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of valaciclovir 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 ZELIVIRE 500 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

Valaciclovir was well tolerated when used for the treatment of herpes zoster or herpes simplex in clinical trials.

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, anaemia.
	Frequency Unknown	Leucopenia, neutropenia
Immune system disorders	Frequency Unknown	Hypersensitivity reactions including rash,

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		photosensitivity, urticaria, pruritus, dyspnoea, angioedema, anaphylaxis.
Psychiatric and Nervous system disorders	Frequent	Headaches
	Less frequent	Fatigue, reversible neurological reactions such as dizziness.
	Frequency Unknown	Reversible neurological reactions such as agitation, aggressive behaviour, confusional states, delirium, decreased consciousness, hallucinations, tremors, ataxia, dysarthria, psychosis, somnolence, convulsions, encephalopathy, coma (especially in patients with renal impairment in whom the dosage was in excess of that recommended).
Gastrointestinal disorders	Frequent	Nausea.
	Less frequent	Vomiting, diarrhoea,

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		abdominal pains.
Hepato-biliary disorders	Less frequent	Hepatitis
	Frequency Unknown	Reversible increases in bilirubin and liver enzymes, jaundice.
Renal and urinary disorders	Frequency Unknown	Increases in blood urea and creatinine, acute renal failure.

Post marketing adverse reactions

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) aggressive behaviour, delirium,

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 adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12 643 2000.

4.9 Overdose

Symptoms and signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of ZELIVIRE 500. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of these reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Management:

In the event of a symptomatic ZELIVIRE 500 overdose occurring, aciclovir is removable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue.

5.1 Pharmacodynamic properties

A.20.2.8 Antiviral agents

Mode of action

Valaciclovir is rapidly and completely converted in man to aciclovir and valine probably by the enzyme, valaciclovir hydrolase. Aciclovir triphosphate competitively inhibits the

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virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Monitoring of clinical isolates from immunocompromised patients e.g. solid organ or bone marrow transplant recipients receiving aciclovir therapy or prophylaxis has revealed that herpes simplex virus and varicella zoster virus have reduced sensitivity to aciclovir.

5.2 Pharmacokinetic properties

Absorption

After oral administration valaciclovir is well absorbed and rapidly and almost completely converted into aciclovir and valine. This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from human liver.

Mean peak aciclovir concentrations are 25 µM (5,7 mcg/ mL) following a single 1 000 mg dose of valaciclovir and occur at a median time of 1,75 hours post dose.

Distribution

Bioavailability of aciclovir from 1 000 mg valaciclovir is 54 % and is not reduced by food.

Binding of aciclovir to plasma proteins is very low (15 %).

Mean peak aciclovir concentrations are 15-25 µM (3,3-5,7 mcg/ml) following single dose of 500-1 000 mg valaciclovir and occur at a median time of 1,5 hours post dose.

Peak plasma concentrations of valaciclovir are only 4 % of aciclovir levels, occur at a median time of 45 – 60 minutes post dose, and are below measurable concentrations 3 hours after dosing.

The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing.

Elimination

The elimination plasma half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1 % of administered dose of valaciclovir

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is recovered in the urine. Valaciclovir is eliminated principally as aciclovir and the known aciclovir metabolite, 9-carboxymethoxymethyl-guanine (CMMG) in the urine.

Characteristics in patients:

Herpes zoster and herpes simplex do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir. In transplant recipients receiving valaciclovir 2 000 mg four times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily area under the plasma concentration curves (AUCs) is appreciably greater.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Crospovidone

FD & C Blue No. 2 Aluminium Lake

Povidone

Magnesium stearate

Film-coat

Aluminium lake

Hypromellose

Macrogol

Polysorbate

Polyethylene glycol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from light and moisture. Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

Cartons contain 30 tablets packed in PVdC coated PVC blister strips.

PVdC coated PVC blister strips comprises of clear transparent PVC film, coated uniformly with PVdC on inner side with a backing of aluminium foil coated with heat seal lacquer on inner side.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

a Sun Pharma company

14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

42/20.2.8/0476

Signed:

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 April 2010

10. DATE OF REVISION OF THE TEXT

14 August 2025

Botswana: S2 Reg. no.: BOT 0801269

Namibia: NS2 Reg. no.: 10/20.2.8/0358

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