SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VALACYCLOVIR 500 BIOTECH, 500 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VALACYCLOVIR 500 BIOTECH film-coated tablet contains valacyclovir HCl hydrated equivalent to valacyclovir 500 mg.

For full list of excipients, see section 6.1

Sugar free.

3. PHARMACEUTICAL FORM

White, oblong, biconvex film-coated tablets.

Approximately 19,4 mm long, 7,8 mm wide and 5,3 mm thick.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VALACYCLOVIR 500 BIOTECH is indicated for:

- Treatment of herpes zoster (shingles) caused by Varicella zoster virus in immunocompetent adults. VALACYCLOVIR 500 BIOTECH reduces the duration of zoster-associated pain, which includes acute and postherpetic neuralgia, thus accelerating resolution of pain.

VALACYCLOVIR 500 BIOTECH also reduces the proportion of patients with zoster-associated pain.

- Episodic treatment of recurrent genital herpes in immunocompetent adult patients.
- Prevention (suppression) of recurrent herpes simplex infection of the skin and mucous membrane of the

ano-genital area.

- Prophylaxis of cytomegalovirus (CMV) infection and CMV disease and other herpes virus infections following organ transplantation, where a special risk exists.

4.2 Posology and method of administration

Posology

VALACYCLOVIR 500 BIOTECH may be taken with or without meals.

Usual adult dose

Treatment of Herpes zoster:

- Therapy should be initiated as soon as possible following the onset of signs and symptoms.
- Two tablets (1 gram) three times a day for 7 days.

Treatment of Recurrent genital herpes:

- Therapy should be initiated as soon as possible following the onset of signs and symptoms.
- One tablet (500 mg) twice daily for 5 days.

Prevention (suppression) of recurrences of herpes simplex infection

- Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately the first signs or symptoms appear. There is no data on the effectiveness of VALACYCLOVIR 500 BIOTECH when initiated more than 24 hours after the onset of signs and symptoms.
- Immunocompromised patients: One tablet (500 mg) twice daily.
- Immunocompetent patients: One tablet (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 the daily dose of 500 mg being taken as a divided dose (250 mg) twice daily.

Prophylaxis of CMV infection and CMV disease in organ transplantation:

Adults and adolescents (from 12 years of age):

- A dose of 2000 mg (4 tablets) four times daily is recommended.
- Prophylaxis should begin as early as possible post-transplant and is usually continued for 90 days, but may need to be extended in high risk patients.
- This dose should be reduced according to creatinine clearance (see Administration in renal impairment).

Dosage in the elderly:

Dosage modification is not required unless renal function is impaired (see Dosage in renal impairment). Adequate hydration should be maintained.

Dosage in renal impairment:

Doses of VALACYCLOVIR 500 BIOTECH may need to be reduced in patients with renal impairment. The following dosage reductions are suggested according to the creatinine clearance (CrCl)

HERPES ZOSTER Creatinine Clearance	VALACYCLOVIR 500 BIOTECH Dose
15 - 30 ml/minute	1 000 mg twice daily
< 15 ml/minute	1 000 mg once daily

RECURRENT GENITAL HERPES Creatinine Clearance	VALACYCLOVIR 500 BIOTECH Dose
> 15 ml/minute	500 mg twice daily
0 - 15 ml/minute	500 mg once daily

PREVENTION OF RECURRENCES	VALACYCLOVIR 500 BIOTECH

(Herpes simplex) Creatinine Clearance	Dose	
	Immunocompetent	Immunocompromised
15 - 30 ml/minute	No dosage adjustment required	No dosage adjustment required
< 15 ml/minute	250 mg once daily	500 mg once daily

In patients on haemodialysis, the VALACYCLOVIR 500 BIOTECH dose recommended for patients with a creatinine clearance of less than 15 ml/min should be used, but the dose should be administered after the haemodialysis has been performed.

CMV prophylaxis: The dosage of VALACYCLOVIR 500 BIOTECH should be adjusted in patients with impaired renal function as shown in the table below:

CMV PROPHYLAXIS Creatinine Clearance	VALACYCLOVIR 500 BIOTECH Dose
≥ 75 ml/minute	2000 mg four times daily
50 to < 75 ml/minute	1500 mg four times daily
25 to < 50 ml/minute	1500 mg three times daily
10 to < 25 ml/minute	1500 mg twice daily
< 10 ml/minute or dialysis (**)	1500 mg once daily

(**) In patients on haemodialysis, the VALACYCLOVIR 500 BIOTECH dosage should be administered after the haemodialysis has been performed.

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

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 (see section 4.4).

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to acyclovir, valacyclovir or to any or to any of the excipients lists in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Severe renal impairment - a dose reduction is required in patients with a creatinine clearance of < 30 ml/minute.

Bone marrow transplantation; Advanced Human Immunodeficiency Virus (HIV) infection and renal transplantation:

Thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome (TTP/HUS) has been reported in patients with these conditions who were taking high doses of valacyclovir as in VALACYCLOVIR 500 BIOTECH for prolonged periods of time. In some cases death has occurred. VALACYCLOVIR 500 BIOTECH is therefore not indicated in immunocompromised patients. TTP/HUS has not been seen in immunocompetent patients treated with valacyclovir.

Severe cutaneous adverse reactions (SCARs)

Drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS, which can be life-threatening or fatal, has been reported in associate with valacyclovir 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, valacyclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed DRESS with the use of valacyclovir, treatment with valacyclovir must not be restarted in this patient at any time.

Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to acyclovir and valacyclovir-containing medicines. VALACYCLOVIR 500 BIOTECH should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hydration status

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

Use in patients with renal impairment and in elderly patients:

Care should be taken to maintain adequate hydration in patients receiving high doses of VALACYCLOVIR 500 BIOTECH.

Acyclovir is eliminated by renal clearance, therefore the VALACYCLOVIR 500 BIOTECH dose should be adjusted 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. 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 (see section 4.8).

Hepatic impairment and liver transplantation:

The rate, but not the extent, of conversion of valacyclovir to acyclovir is reduced in patients with moderate

to severe liver disease. The half-life of acyclovir is not affected and dosage modification is not recommended for patients with cirrhosis.

There are no data on the use of high doses of VALACYCLOVIR 500 BIOTECH (8 g/day) in patients with liver disease. Caution should therefore be exercised when administering high doses of VALACYCLOVIR 500 BIOTECH to these patients. Studies of VALACYCLOVIR 500 BIOTECH have not been conducted in liver transplantation.

Use for zoster treatment

Clinical response should be closely monitored, particularly in immunocompromised patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is considered insufficient.

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Moreover, immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes

Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated. During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible. Therefore, in addition to therapy with VALACYCLOVIR 500 BIOTECH, it is recommended that patients use safer sex practices.

Use in CMV infections

Data on the efficacy of valacyclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMV-positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that

VALACYCLOVIR 500 BIOTECH should only be used in these patients when safety concerns preclude the use of valgancyclovir or gancyclovir.

High dose valacyclovir as required for CMV prophylaxis may result in more frequent adverse events, including CNS abnormalities, than observed with lower doses administered for other indications (see section 4.8). Patients should be closely monitored for changes in renal function, and doses adjusted accordingly (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Care is required when administering high doses of VALACYCLOVIR 500 BIOTECH with medicines which affect other aspects of renal physiology, e.g. tacrolimus and ciclosporin.

Other medicinal products (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase acyclovir concentrations by this mechanism. Similarly, valacyclovir administration may increase plasma concentrations of the concurrently administered medicine.

Cimetidine and probenecid

Cimetidine and probenecid have been found to decrease the rate, but not the extent, of conversion of valacyclovir to acyclovir. The renal clearance of acyclovir is decreased by cimetidine and probenecid resulting in an increase of the peak plasma concentration of acyclovir.

In patients receiving high-dose VALACYCLOVIR 500 BIOTECH (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with medicines which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both substances or their metabolites

Mycophenolate mofetil

Increase in the AUC of acyclovir and the inactive metabolite of mycophenolate mofetil have been shown when both medicines were co-administered.

No changes in peak concentrations or AUCs are observed with co-administration of valacyclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established. (See section 4.3.)

Pregnancy

The active metabolite of VALACYCLOVIR 500 BIOTECH, acyclovir, crosses the placenta. There are no adequate or well-controlled studies in pregnant women with the active metabolite, acyclovir, or valacyclovir.

Teratogenicity: Foetal abnormalities were observed in rats.

Breastfeeding

It is not known if valacyclovir is distributed into breast milk. The active metabolite, acyclovir, has been found to pass into breast milk.

4.7 Effects on the ability to drive and use machines:

VALACYCLOVIR 500 BIOTECH is unlikely to impair the ability of patients to drive or operate machinery, but may cause nervous system disorders e.g. dizziness. Do not drive or operate machinery if you are affected by VALACYCLOVIR 500 BIOTECH.

4.8 Undesirable effects

List of adverse reactions

Blood and lymphatic system disorders

Less frequent: Anaemia, leucopenia, thrombocytopenia, neutropenia. Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, sometimes resulting in death, have occurred in immunocompromised patients.

Immune system disorders

Less frequent: Anaphylaxis.

Psychiatric disorders

Frequent: Somnolence

Less frequent: Confusional states, hallucination, psychosis, agitation, convulsion, delirium, coma (especially in patients with renal impairment in whom the dosage was in excess of that recommended).

Nervous system disorders

Frequent: Headaches, dizziness

Less frequent: Fatigue, decreased consciousness, ataxia, dyasthria

Neurological disorders, sometimes severe, may be linked to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8000mg daily) of VALACYCLOVIR 500 BIOTECH for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses used for other indications.

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pains.

Less frequent: Gastrointestinal discomfort.

Hepato-biliary disorders

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

Skin and subcutaneous tissue disorders

Frequent: Rashes including photosensitivity, pruritus

Less frequent: Diffuse hair loss, urticaria, angioedema, skin rash (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Frequency unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Acute generalised exanthematous pustulosis (AGEP).

Renal and urinary disorders

Less frequent: Increases in blood urea and creatinine, renal pain, haematuria (often associated with other renal events), renal impairment, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended doses).

Frequency unknown: Tubulointerstitial nephritis.

Renal pain may be associated with renal failure.

Intratubular precipitation of acyclovir crystals in the kidney has also been reported. Adequate fluid intake should be ensured during treatment (see section 4.4).

General disorders and administrative site conditions

Less frequent: Fever

Other:

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised adult patients, particularly those with advanced HIV disease, and also in bone marrow transplant and renal transplant recipients receiving high doses of valacyclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with valacyclovir who have the same underlying or concurrent conditions.

Reporting of suspecting 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 providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

(See section 4.4)

Symptoms of overdose

VALACYCLOVIR 500 BIOTECH has a wide therapeutic window therefore excessive doses of VALACYCLOVIR 500 BIOTECH are generally well tolerated. Repeated overdoses of oral VALACYCLOVIR 500 BIOTECH 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 acyclovir from the blood.

5. PHARMACOLOGICAL PROPERTIES

A 20.2.8 Antiviral agents

Nucleosides and nucleotides excluding reverse transcriptase inhibitors, ATC code: J05AB11.

5.1 Pharmacodynamic Properties

Valacyclovir is the L-valyl ester prodrug of acyclovir. It is converted rapidly and virtually completely to acyclovir after oral administration.

Acyclovir is a synthetic 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, acyclovir is taken up into the herpes infected cells and converted via phosphorylation to the active compound, acyclovir triphosphate. Acyclovir triphosphate competitively inhibits herpes specified DNA polymerase thus preventing further DNA synthesis without affecting normal cellular DNA polymerase.

5.2 Pharmacokinetic Properties

Valacyclovir is rapidly absorbed in the gastrointestinal tract and is converted to its active compound, acyclovir, and L-valine by first-pass intestinal and hepatic metabolism. Administration of valacyclovir with food was not found to alter the bioavailability of acyclovir. The relative oral bioavailability of acyclovir increases three- to fivefold to approximately 70 % following valacyclovir administration.

Protein binding is low (13 to 18 % for valacyclovir and 9 to 33 % for acyclovir). Peak acyclovir concentrations are achieved within 2 hours of oral administration of valacyclovir. Peak plasma concentrations of valacyclovir are only 4 % of acyclovir levels. The half-life of valacyclovir is approximately 30 minutes. In patients with normal renal function, the half-life of acyclovir is approximately 2,5 to 3,3 hours. The half-life of acyclovir is increased in patients with chronic renal failure.

Less than 1 % of an administered dose of valacyclovir is recovered in the urine, and most is eliminated as acyclovir and its metabolite 9-carboxymethoxymethylguanine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dehydrate

Sodium starch glycolate Type A

Hydroxypropyl cellulose (HPC-L),

Purified talc

Magnesium stearate (vegetable grade)

Opadry white OY-LS-28908

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Store in the original packaging (in the carton) at or below 30 °C.

6.5 Nature and contents of container

Packs of 10, 30 or 42 film-coated tablets packed in white opaque PVC/PE/PVDC/Aluminium blisters in a cardboard carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

400 16th Road, Ground, Floor,

Block K West, Central Park,

Randjespark, Midrand, Gauteng, 1685

+27 (0)11 848 3050

8. REGISTRATION NUMBER:

43/20.2.8/0766

9. DATE OF FIRST AUTHORISATION

11 June 2015

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27 August 2025