PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

VALACICLOVIR 500 UNICORN

VALACICLOVIR 1000 UNICORN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALACICLOVIR 500 UNICORN

film coated tablets contain:

valaciclovir hydrochloride equivalent to 500 mg valaciclovir per tablet

VALACICLOVIR 1000 UNICORN

film coated tablets contain:

valaciclovir hydrochloride equivalent to 1000 mg valaciclovir per tablet

VALACICLOVIR UNICORN is sugar free. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VALACICLOVIR 500 UNICORN:

Blue colored, capsule shaped, film coated tablets debossed with '324 500' on one side and plain on the other side.

VALACICLOVIR 1000 UNICORN:

Blue colored, capsule shaped, film coated tablets, with partial score bar on both sides and debossed with '325 1000' on one side and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VALACICLOVIR UNICORN is indicated for the treatment of herpes zoster (shingles).

VALACICLOVIR UNICORN reduces the duration of zoster-associated pain, which includes acute and postherpetic neuralgia, thereby accelerating resolution of pain.

VALACICLOVIR UNICORN also reduces the proportion of patients with zoster-associated pain.

VALACICLOVIR UNICORN is indicated for the episodic treatment of recurrent genital herpes in immunocompetent adult patients.

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

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

4.2 Posology and method of administration

Dosage in adults

For treatment of herpes zoster

1 000 mg of **VALACICLOVIR UNICORN** to be taken three times per day for seven 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 the first signs or symptoms appear. There are no data on the effectiveness when treatment is 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.

Immunocompromised patients

500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease

Adults and adolescents (from 12 years of age)

2 000 mg to be taken four 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). The 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.

Dosage in renal impairment

Caution is advised when administering **VALACICLOVIR UNICORN** to patients with impaired renal function. Adequate hydration should be maintained.

The dose of **VALACICLOVIR UNICORN** should be adjusted as follows in patients with

significantly impaired renal function:

Therapeutic indication	**Creatinine Clearance**	**VALACICLOVIR UNICORN Dose**
Herpes zoster	15-30 ml/min	1 000 mg twice a day
	< 15 ml/min	1 000 mg once a day
Recurrent genital herpes	> 15 ml/min	500 mg twice daily
Prevention of recurrences	0-15 ml/min	500 mg once daily
Immunocompetent	15-30 ml/min	No dosage adjustment
	< 15 ml/min	250 mg* once daily
Immunocompromised	15-30 ml/min	No dosage adjustment
	< 15 ml/min	500 mg once daily

*__VALACICLOVIR UNICORN 500__ is not a scored tablet.

In patients on haemodialysis the **VALACICLOVIR UNICORN** 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

In patients with impaired renal function, the dosage of **VALACICLOVIR UNICORN** should be adjusted as shown in the table below:

Creatinine Clearance	**VALACICLOVIR UNICORN 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 on haemodialysis, the **VALACICLOVIR UNICORN** dosage should be administered after the 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 dosage of **VALACICLOVIR UNICORN** should be adjusted accordingly.

Dosage in hepatic impairment

In patients with mild or moderate cirrhosis (hepatic synthetic function maintained) dose modification is not required. 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 (4 g or more) see section 4.8.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In patients with advanced HIV disease and also in bone marrow transplant and renal transplant recipients' 'thrombotic, thrombocytopenic purpura/haemolytic uremic syndrome' (in some cases fatal) has been reported. This syndrome has not been observed in immunocompetent patients.

Hydration status

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

Use in patients with renal impairment and in elderly patients

The dose of **VALACICLOVIR UNICORN** should be adjusted in patients with renal

impairment as aciclovir is eliminated by renal clearance (see section 4.2: Dosage in renal impairment).

Dose reduction must be considered in the elderly as they are likely to have reduced renal function.

Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored. It has been reported that these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Uses of higher doses of VALACICLOVIR UNICORN in hepatic impairment and liver transplantation

There are no data available on the use of high doses of **VALACICLOVIR UNICORN** (4 g or more per day) in patients with liver disease. Caution should therefore be exercised when administering high doses of **VALACICLOVIR UNICORN** to these patients.

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.

Use in genital herpes

Suppressive treatment with **VALACICLOVIR UNICORN** reduces the risk of

transmitting genital herpes. It does not cure genital herpes. The frequency of viral shedding is significantly reduced. However, the risk of transmission is still possible.
In addition to therapy with **VALACICLOVIR UNICORN**, it is recommended that patients use safer sex practices.

Use in ocular HSV infections

Clinical response should be closely monitored in these patients. Consideration should be given to intravenous antiviral therapy when response to oral therapy is unlikely to be adequate.

Use in CMV infections

Data on the efficacy of valaciclovir from transplant patients at high risk of CMV disease (e.g. donor CMV-positive/recipient CMV negative or use of anti-thymocyte globulin induction therapy) indicate that valaciclovir should only be used in these patients when safety concerns prohibit the use of valganciclovir or ganciclovir. High dose valaciclovir 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 medicinal products and other forms of interaction

The combination of valaciclovir with nephrotoxic medicines should be used with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function. This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscamet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion.

Following 1000 mg valaciclovir, cimetidine and probenecid reduce aciclovir renal clearance and increase the AUC of aciclovir by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC; however no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Other medicines (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase aciclovir concentrations by this mechanism. Similarly, valaciclovir administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving high doses of **VALACICLOVIR UNICORN** (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 the inactive metabolite of mycophenolate mofetil (an immunosuppressant medicine used in transplant patients) have been shown when the medicines are co-administered. There is limited clinical experience with the use of this combination.

No significant increase in toxicity was noted when zidovudine and aciclovir is administered concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Lactation

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk.

Mothers on treatment with **VALACICLOVIR UNICORN** should not breastfeed their infants.

Fertility

No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 to 1000 mg aciclovir.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

The clinical status of the patient and the undesirable effects of **VALACICLOVIR UNICORN** should be borne in mind when considering the patient's ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Adverse reactions reported from clinical trials

Nervous system disorders:

Frequent: Headache

Gastrointestinal disorders:

Frequent: Nausea

Tabulated summary of adverse reactions reported post-marketing

System Organ Class	Frequency	Side effect
Blood and the lymphatic system disorders	Less frequent	Aplastic anaemia, thrombocytopenia, thrombotic

	Frequency unknown	thrombocytopenia, purpura, haemolytic uraemic syndrome, and leukopenia (mainly reported in immunocompromised patients). Microangiopathic haemolytic anaemia.
Immune system disorders	Less frequent	Anaphylaxis.
Psychiatric disorders	Less frequent Frequency unknown	Agitation, somnolence, psychotic symptoms, delirium and hallucinations. Aggressive behaviour
Nervous system disorders[1]	Frequent Less frequent	Dizziness. Confusion, decreased consciousness, tremor, convulsions, ataxia, dysarthria, convulsions, encephalopathy and coma.
Cardiac disorders	Frequency unknown	Tachycardia
Vascular disorders	Frequency unknown	Hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea

Gastrointestinal disorders	Frequent Less frequent	Vomiting and diarrhoea. Abdominal discomfort.
Hepato-biliary disorders	Less frequent	Reversible increases in liver function tests (e.g. bilirubin, liver enzymes), occasionally described as hepatitis.
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rashes including photosensitivity and pruritus. Urticaria and angioedema.
Musculoskeletal and connective tissue disorders	Frequency unknown	Arthralgia
Renal and urinary disorders[2]	Less frequent	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).

[1] Neurological disorders (sometimes severe) may be related to encephalopathy and include confusion, agitation, convulsions, hallucinations, coma. These adverse 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 (8 g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower

doses used for other indications.

[2] Renal pain may be associated with renal failure.

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

Additional information on special populations

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

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

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

4.9 Overdose

Symptoms and signs

There have been reported cases of acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma. Nausea and vomiting may also occur. Many of these reported cases involved renally

impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Management of overdose

Treatment is symptomatic and supportive. Patients should be observed closely for signs of toxicity.

In the event of a symptomatic **VALACICLOVIR UNICORN** overdose occurring, aciclovir is removable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 20.2.8 Antiviral agent(s)

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors.

ATC code: J05AB11.

5.1 Pharmacodynamic properties

Mechanism of action

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue. Valaciclovir is rapidly and almost completely converted in humans to Aciclovir and valine in all probability by the enzyme valaciclovir hydrolase.

aciclovir is a specific inhibitor of the herpes viruses with *in vitro* activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), CMV and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of the UL97 gene of CMV. This

gene encodes for the viral kinase which facilitates the intracellular anabolism of aciclovir. This requirement for activation of aciclovir by a virus specific enzyme largely explains its unique selectivity.

The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects

Extensive monitoring of clinical isolates from patients receiving aciclovir therapy or prophylaxis has revealed that HSV and VZV with reduced sensitivity to aciclovir is extremely rare in immunocompetent patients and is only found infrequently in severely immunocompromised patients e.g. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV). Resistance is normally due to a TK deficient phenotype which results in a virus which is profoundly disadvantaged in the natural host. Infrequently, reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus TK or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

5.2 Pharmacokinetic properties

After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to 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 µg/ml) following a single 1 000 mg dose of valaciclovir and occur at a median time of 1,75 hours post dose. The bioavailability of aciclovir from 1 000 mg valaciclovir is 54 % and is not reduced by food. Mean peak aciclovir concentrations are 15-25 µm (3,3-5,7 µg/ml) following single doses of 500-1 000 mg valaciclovir, and occur

at a median time of 1,50 hours post dose.

Peak plasma concentrations of valaciclovir are only 4 % of aciclovir levels, occur at a median time of 45 to 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. Binding of aciclovir to plasma proteins is very low (15 %). The elimination plasma half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1 % of the administered dose of valaciclovir is recovered in the urine. Valaciclovir is eliminated principally as aciclovir and the known aciclovir metabolite, 9-carboxymethoxymethyl-guanine (CMMG), in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Microcrystalline cellulose, crospovidone, hypromellose and magnesium stearate.

Coating

VALACICLOVIR UNICORN: Opadry blue which contains hypromellose, titanium dioxide, macrogol, indigo carmine aluminium lake and polysorbate 80.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blisters in outer carton until required for use.

Protect from light. Keep dry.

Do not use the tablets after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

VALACICLOVIR UNICORN are packed in blister packs. The blister packs are thermo formable blisters consisting of a lidding foil, which is a plain, aluminium foil coated with heat sealable lacquer, and base film (forming) comprising of a transparent PVC film.

Pack sizes

VALACICLOVIR UNICORN:

Blister of 10 tablets. Pack size: 10, 30, 60 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets,

Cape Town,

South Africa, 8001

8. REGISTRATION NUMBER(S)

VALACICLOVIR 500 UNICORN: 49/20.2.8/0443

VALACICLOVIR 1000 UNICORN: 49/20.2.8/0444

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 May 2021

10. DATE OF REVISION OF THE TEXT

Not applicable