SCHEDULING STATUS

S4

1. **NAME OF THE MEDICINE:**

   HERPIVA 500 mg (film coated tablet)

   HERPIVA 1 g (film coated tablet)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   HERPIVA 500 mg

   Each **HERPIVA 500 mg** film coated tablet contains 556 mg valaciclovir hydrochloride equivalent to 500 mg valaciclovir.

   HERPIVA 1 g

   Each **HERPIVA 1 g** film coated tablet contains 1112 mg valaciclovir hydrochloride equivalent to 1 g valaciclovir.

   Sugar free

   For the full list of excipients, see **section 6.1.**

3. **PHARMACEUTICAL FORM:**

   Film coated tablets.

   HERPIVA 500 mg: Blue colour, capsule shaped, film coated tablets debossed with “C 324 500” on one side and plain on the other side.

HERPIVA 1 g: Blue colour, capsule shaped, film coated tablets with partial score bar on both sides debossed with “C 325 1000” on one side and plain on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

HERPIVA is indicated for the:

- treatment of herpes zoster (shingles). **HERPIVA** reduces the duration of zoster-associated pain, which includes acute and postherpetic neuralgia, thus accelerating resolution of pain. **HERPIVA** 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, CMV disease and other herpes virus infections following organ transplantation, where a special risk exists.

4.2 Posology and method of administration

<u>Posology</u>

Dosage in adults:

For treatment of herpes zoster: 1 g of **HERPIVA** 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 of **HERPIVA** 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 the daily dose of 500 mg being taken as a divided dose (250 mg twice daily).

Immunocompromised patients: 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease:

Adults and adolescents (from 12 years of age): 2 g 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 renal impairment

below). The duration of treatment will usually be 90 days but may need to be extended in high risk patients.

Special populations

Elderly population:

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.

Renal impairment:

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

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

Therapeutic indication	**Creatinine Clearance**	**HERPIVA Dose**
Herpes zoster	15 - 30 mL/min < 15 mL/min	1 g twice a day 1 g once a day
Recurrent genital herpes	> 15 mL/min 0- 15 mL/min	500 mg twice daily 500 mg once daily
Prevention of recurrences		

Immunocompetent	15 - 30 mL/min	No dosage adjustment
	< 15 mL/min	HERPIVA is not recommended for use, as it does not contain a 250 mg strength in a single dose.
Immunocompromised	15 - 30 mL/min < 15 mL/min	No dosage adjustment 500 mg once daily

CMV prophylaxis:

The dosage of **HERPIVA** should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine Clearance	**HERPIVA Dose**
≥ 75 mL/min	2 g 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 **HERPIVA** dosage 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. **HERPIVA** is not recommended for use, as it does not contain a 250 mg strength in a single dose. The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment. The **HERPIVA** dosage should be adjusted accordingly.

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 (4 g or more) see section 4.8

Paediatric population

No data are available.

4.3 Contraindications

Hypersensitivity to valaciclovir or aciclovir or any of the excipients listed in section 6.1.

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

Hydration status

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

Use for HZV 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. Continuous therapy with HERPIVA in patients with recurrent genital herpes 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 valaciclovir, it is recommended that patients use safer sex practices. As genital herpes is a sexually transmitted infection, patients should, in order to further reduce the risk of infecting partners, avoid contact with lesions, damaged skin/mucosa, and avoid intercourse when lesions and/or symptoms are present. Genital herpes is frequently transmitted in the absence of symptoms through asymptomatic viral shedding; therefore patients should be counselled to use safer sex practices. The effect of HERPIVA on transmission of sexually transmitted infections other than herpes (including HIV, gonorrhoea, syphilis and Chlamydia) is unknown.

The efficacy of HERPIVA for reducing transmission of genital herpes has not been established in individuals with multiple partners, non-heterosexual couples and couples not counselled to use safer sex practises.

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 sufficient.

Use in CMV infections

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) should only use **HERPIVA** when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose **HERPIVA** 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).

Renal impairment and elderly patients

Aciclovir is eliminated by renal clearance, therefore the dose of **HERPIVA** 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. 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 are generally reversible on discontinuation of treatment (see section 4.8)

Use of higher doses of HERPIVA in hepatic impairment and liver transplantation

There are no data available on the use of higher doses of **HERPIVA** (4000 mg or more per day) in patients with liver disease. Caution should be exercised when administering daily doses greater than 4000 mg to these patients.

4.5 Interaction with other medicines and other forms of interaction

Nephrotoxic medicines

The combination of **HERPIVA** with nephrotoxic medicines should be made with caution, especially in patients 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, foscarnet, ciclosporin, and tacrolimus.

Active tubular secretion inhibitors or competitors

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Cimetidine and probenecid taken together with **HERPIVA** increases aciclovir concentrations. Other medicines (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase aciclovir concentrations by this mechanism. Similarly, **HERPIVA** administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving higher aciclovir exposures from **HERPIVA** (e.g. at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with medicines which inhibit active renal tubular secretion.

Immunosuppressant medicines

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.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Following oral administration of a 500 mg dose of HERPIVA, peak acyclovir concentrations (Cmax) in breast milk ranged from 0,5 to 2,3 (median 1,4) times the corresponding maternal acyclovir serum concentrations. Mothers on treatment with HERPIVA should not breastfeed their infants.

Fertility

Aciclovir did not affect fertility in rats dosed by the oral route. At high parenteral doses of aciclovir testicular atrophy and aspermatogenesis have been observed in rats and dogs. No human fertility studies were performed with **HERPIVA**, but there were no changes in sperm count, motility or

morphology in 20 patients after 6 months of daily treatment with 400 to 1 g aciclovir.

4.7 Effects on ~~the~~ ability to drive and use machines

HERPIVA may cause dizziness which may influence the ability to drive and use machines. Patients should not drive or operate machines until they know how **HERPIVA** affects them.

4.8 Undesirable effects

Blood and lymphatic system disorders

***Less frequent*:** Leucopenia, thrombocytopenia

Immune system disorders

Less frequent: Anaphylaxis

Psychiatric and nervous system disorders

***Frequent*:** Dizziness

***Less frequent*:** Confusion, hallucinations, decreased consciousness, tremor, agitation, ataxia, dysarthria, convulsions, encephalopathy, coma, psychotic symptoms, delirium.

Nervous system disorders

Frequent**:** Headache

Respiratory, thoracic, and mediastinal disorders

Less frequent**:** Dyspnoea

Gastrointestinal disorders

Frequent**:** Vomiting, diarrhoea, nausea

Less frequent**:** Abdominal discomfort

Hepato-biliary disorders

Less frequent: Reversible increases in liver function tests (e.g. bilirubin, liver enzymes).

Skin and subcutaneous tissue disorders

Frequent: Rashes including photosensitivity, pruritus

Less frequent: Urticaria, angioedema

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

Renal and urinary disorders

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).

Additional information on special populations

There have been reports of renal insufficiency, microangiopathic hemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised adult patients, particularly those with advanced HIV disease, receiving high doses (8000 mg daily) of valaciclovir for prolonged periods in clinical trials. These findings have also been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

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 valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Class of medicine: J05AB11 antivirals for systemic use. Nucleosides and nucleotides excluding reverse transcriptase inhibitors.

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 patients to aciclovir and valine, probably by the enzyme referred to as 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), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), 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 UL97. This requirement for activation of aciclovir by a virus-specific enzyme largely explains its 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

Resistance to aciclovir is normally due to a thymidine kinase deficient phenotype which results in a virus which is disadvantaged in the natural host. Reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent host and is found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

5.2 Pharmacokinetic properties

Absorption

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

Biotransformation and Distribution

Mean peak acyclovir 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 acyclovir from 1 000 mg valaciclovir is 54 % and is not reduced by food. Mean peak acyclovir 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 acyclovir 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 acyclovir pharmacokinetic profiles are similar after single and repeat dosing.

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

Elimination

The elimination plasma half-life

of acyclovir 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 acyclovir and the known acyclovir metabolite, 9-carboxymethoxymethyl-guanine (CMMG), in the urine.

6. Pharmaceutical particulars

6.1 List of excipients

HERPIVA 500 mg AND 1 g

Crospovidone, FD&C blue #2/indigo carmine aluminum lake, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, polysorbate, purified water, titanium dioxide

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in original container.

6.5 Nature and contents of container

HERPIVA 500 mg

60's: a plain 25-micron hard tempered Al-foil coated with a 7 GSM heat sealable lacquer and a transparent 250-micron PVC base film.

HERPIVA 1 g

10's: a plain 25-micron hard tempered Al-foil coated with a 7 GSM heat sealable lacquer and a transparent 250-micron PVC base film.

6.6 Special precautions for disposal and other handling

No special requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

Contact Information: regulatory@innovata.co.za or +27 86 999 0912

8. Registration numbers

HERPIVA 500 mg: A 55/20.2.8/0734

HERPIVA 1 g: A 55/20.2.8/0735

9. Date of first authorization/Renewal of the authorization

03 October 2023

Final PI: 18/02/2025

10. Date of revision of the text

18/02/2025