1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYLAN VALACICLOVIR 250 mg (film-coated tablet)

MYLAN VALACICLOVIR 500 mg (film-coated tablet)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each MYLAN VALACICLOVIR 250 mg film-coated tablet contains valaciclovir hydrochloride monohydrate equivalent to 250 mg valaciclovir.

Each MYLAN VALACICLOVIR 500 mg film-coated tablet contains valaciclovir hydrochloride monohydrate equivalent to 500 mg valaciclovir.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MYLAN VALACICLOVIR 250 mg: White coloured, oval shaped, biconvex film-coated tablet.

MYLAN VALACICLOVIR 500 mg: White coloured, oval shaped, biconvex film-coated tablet with breakline on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLAN VALACICLOVIR is used in the treatment of:

- Herpes Zoster (shingles) infections. It reduces the duration of zoster-associated pain, which includes acute and post-herpetic neuralgia, thus accelerating resolution of pain.
- Episodic treatment of recurrent genital herpes in immunocompetent adult patients.
- Prevention/suppression of recurrent herpes simplex infections of the skin and mucous membranes of the ano-genital area.
- Prophylaxis of cytomegalovirus (CMV) infection.
- Prophylaxis of cytomegalovirus (CMV) and other herpes infections following organ transplant where a special risk exists.

4.2 Posology and method of administration

Posology

Treatment of Herpes Zoster infections:

Adults: 1000 mg three times a day for 7 days

Recurrent genital herpes:

Immunocompetent patients:

500 mg twice daily for 5 days beginning as early as possible.

For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately when the first symptoms appear. There are not data on efficacy when treatment was initiated after 24 hours after the onset of symptoms.

Prevention or suppression of recurrent Herpes simplex infections:

Immunocompetent patients:

500 mg once daily. If more than 10 episodes occur per year, administer 250 mg twice daily.

Immunocompromised patients:

500 mg twice daily.

CMV infection prophylaxis:

Adults and adolescents 12 years and older: Initiate therapy as soon as possible.

Post-transplant:

2000 mg four times daily for usually 90 days. The duration of treatment may have to be extended in high-risk patients. Modify the dosage in significant renal impairment.

Special populations

Elderly population:

Dose modification is not required unless renal function is impaired. Adequate hydration must be ensured.

Renal impairment:

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

Herpes Zoster **Creatinine clearance**	**MYLAN VALACICLOVIR dose**
15-30 ml/min	1000 mg twice daily
< 15 ml/min	1000 mg once a day
Recurrent Genital herpes **Creatinine clearance**	**MYLAN VALACICLOVIR dose**
> 15 ml/min	500 mg twice daily
0 - 15 ml/min	500 mg once daily

Prevention of recurrences **Creatinine clearance**	**MYLAN VALACICLOVIR dose**	
	Immunocompetent	Immunocompromised
15 – 30 ml/min	No dosage adjustment required	
< 15 ml/min	250 mg once daily	500 mg once daily

In patients on haemodialysis, the MYLAN VALACICLOVIR 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 have been performed.

CMV prophylaxis **Creatinine clearance**	**MYLAN VALACICLOVIR dose**
> 75 ml/min	2000 mg four times daily
50 to 75 ml/min	1500 mg four times daily
25 to 50 ml/min	1500 mg three times daily
10 to 25 ml/min	1500 mg twice daily
< 10 ml/min or dialysis*	1500 mg once a day

* In patients on haemodialysis, the MYLAN VALACICLOVIR dose should be administered after the haemodialysis have 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 MYLAN VALACICLOVIR dose should be adjusted accordingly.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to valaciclovir, aciclovir or any of the other ingredients.
- Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

Thrombotic, thrombocytopenic purpura/haemolytic uraemic syndrome, in some cases resulting in death, has been reported in patients with advanced HIV disease and also in bone marrow transplant and renal transplant patients.

Central nervous system (CNS) adverse reactions including agitation, hallucinations, confusion, delirium, seizures, and encephalopathy have been reported. Elderly patients are more likely to be prone to these adverse reactions. MYLAN VALACICLOVIR should be discontinued if CNS adverse reactions occur.

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.

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

Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir 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. Cases of acute renal failure have been reported in elderly patients, with or without reduced renal function, patients with underlying renal disease receiving higher than recommended doses, patients receiving other nephrotoxic medicines and patients without adequate hydration. All patients should be adequately hydrated.
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 (see section 4.8).

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.
However, 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 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

Published data on the efficacy of valaciclovir 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 valaciclovir, as contained in MYLAN VALACICLOVIR should only be used in these patients when safety concerns preclude the use of valganciclovir or ganciclovir.

High dose valaciclovir as required for CMV prophylaxis may result in more frequent adverse events, including central nervous system 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

- The combination of valaciclovir, as contained in MYLAN VALACICLOVIR with nephrotoxic medicines should be used 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.
- Although no clinically significant interactions have been reported, any medicine which is excreted via renal tubular secretion may compete, and thus interact, with MYLAN VALACICLOVIR.
- Cimetidine and probenecid have been shown to decrease the 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 aciclovir.
- In patients receiving higher aciclovir exposures from valaciclovir, as contained in MYLAN VALACICLOVIR (e.g., at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with medicines which inhibit active renal tubular secretion.

- Increases in plasma AUC's of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant medicine used in transplant patients, have been shown when co-administered.
- Care should be taken when high-dose MYLAN VALACICLOVIR is administered with other medicines that affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).
- 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.
- 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 medicine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Foetal abnormalities were observed in rats.

Breastfeeding

Safety in lactation has not been established.

Fertility

No data.

4.7 Effects on ability to drive and use machines

MYLAN VALACICLOVIR has been reported to cause dizziness and confusion. Patients should be cautioned against driving or operating machinery until it is established how they react to MYLAN VALACICLOVIR.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (ARs) reported are headache and nausea. For more information on serious side effects such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure, neurological disorders and DRESS, see section 4.4.

Tabulated list of adverse reactions

Body System	Undesirable effect		
	Frequent	Less frequent	Frequency not known
Blood and the lymphatic system disorders:		Aplastic anaemia, thrombocytopenia, leukopenia, neutropenia, leukocytoclastic vasculitis.	
Immune system disorders:		Hypersensitivity reactions, angioedema, anaphylaxis.	
Psychiatric disorders:		Mania, psychosis including auditory and visual hallucinations, aggressive behaviour, delirium, psychotic symptoms.	
Nervous system disorders:	Headache. In patients treated with high doses for CMV prophylaxis,	Reversible neurological reactions (confusion, fatigue and	

	confusion and hallucinations occur frequently.	dizziness) may occur in patients with renal impairment. Dizziness, agitation, ataxia, coma, confusion, decreased consciousness, tremor, dysarthria, convulsions, encephalopathy.	
Eye disorders:		Visual abnormalities.	
Cardiac disorders:		Tachycardia.	
Vascular disorders:		Hypertension.	
Respiratory, thoracic and mediastinal disorders:		Dyspnoea.	
Gastrointestinal disorders:	Nausea, diarrhoea.	Gastro-intestinal disturbances, vomiting, abdominal discomfort.	
Hepato-biliary disorders:		Hepatitis, jaundice, abnormal liver function tests.	
Skin and subcutaneous tissue disorders:		Rash, erythema multiforme, photosensitivity, alopecia, Stevens-Johnson syndrome, toxic epidermal necrosis, urticaria, pruritus, angioedema.	Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Musculoskeletal, connective tissue and bone disorders:		Arthralgia.	
Renal and urinary disorders:		Renal pain, haematuria, renal impairment, renal insufficiency,	Tubulointerstitial nephritis.

		increased serum creatinine, acute renal failure (especially in elderly patients or in patients with renal impairment receiving higher than the recommended doses).	
Reproductive system and breast disorders:		Dysmenorrhoea.	

Description of selected adverse reactions

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

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 on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311

4.9 Overdose

- In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.
- There are no data available on overdosage.

- In animals, large doses caused obstructive uropathy and crystalluria.
- Treatment is symptomatic and supportive.
- Haemodialysis, if required, enhances the removal of MYLAN VALACICLOVIR.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use

ATC code: J05AB11

Valaciclovir is the L-valine ester of aciclovir. Aciclovir is a purine nucleoside analogue. Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine 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), cytomegalovirus (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.

The requirement of 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.

Extensive monitoring of clinical isolates from patients receiving aciclovir therapy or prophylaxis, has revealed that herpes simplex virus and varicella zoster virus with reduced sensitivity to aciclovir is rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. solid organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with HIV.

Resistance is normally due to a thymidine kinase 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 thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

5.2 Pharmacokinetic properties

Absorption:

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.

Metabolism and Distribution:

Mean peak aciclovir concentrations are 25 µM (5,7 µg/ml) following a single 1000 mg dose of valaciclovir and occur at a median time of 1,75 h post dose. The bioavailability of aciclovir 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 mg – 1000 mg valaciclovir, and occur at a median time of 1,5 h 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 %).

Elimination:

The elimination 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 metabolite, 9-carboxymethoxymethyl-guanine (CMMG), in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Magnesium stearate, microcrystalline cellulose (Avicel PH 101) {coating: Opadry white OY-58900 - composition: HPMC 2910/Hypromellose 5cp (E484), macrogol/PEG 400, titanium dioxide (E171)}.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

- Store at or below 25 ºC, protected from light and moisture.

- The bottles must be kept tightly closed.
- Do not remove from the carton until required for use.

6.5 Nature and contents of container

The tablets are packed in a PVC High density polyethylene (HDPE) bottle pack (marketable pack) that comprises of a round, wide-mouth white HDPE bottle with a white, opaque polypropylene (PP) screw closure with an aluminium induction sealing liner and is packed in a cardboard carton (100's).

Cold form blister pack (marketable pack) comprises cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on the other side i.e. OPA/Al/PVC) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side (blisters of 10's), packed into a carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Not applicable.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street, Isando,

Johannesburg

1600, Gauteng, South Africa

8 REGISTRATION NUMBER(S)

MYLAN VALACICLOVIR 250 mg: 45/20.2.8/0604

MYLAN VALACICLOVIR 500 mg: 45/20.2.8/0605

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 October 2014

10 DATE OF REVISION OF TEXT

16 August 2023