PROPOSED PROFESSIONAL INFORMATION – CLEAN COPY

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

VALATREX 250 (film-coated tablets)

VALATREX 500 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Valatrex 250 tablet contains valaciclovir hydrochloride monohydrate equivalent to 250 mg valaciclovir.

Each Valatrex 500 tablet contains valaciclovir hydrochloride monohydrate equivalent to 500 mg valaciclovir.

Sugar free.

3. PHARMACEUTICAL FORM

Valatrex 250: White to off-white capsule shaped film-coated tablets plain on both sides.

Valatrex 500: White to off-white capsule shaped film-coated tablets with “500” debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment to start as soon as possible within 24 hours

VALATREX is indicated for the:

- Treatment of herpes zoster (shingles).

VALATREX reduces the duration of zoster-associated pain, which includes acute and post-herpetic neuralgia, thus accelerating resolution of pain. VALATREX also reduces the proportion of patients with zoster-associated pain.

- Episodic treatment of recurrent genital herpes in immunocompetent adult patients. There is no data on the effectiveness of VALATREX when initiated more than 24 hours after the onset of signs and symptoms.
- 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

Dosage in adults:

For treatment of Herpes zoster:

1000 mg of VALATREX 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 VALATREX when initiated more than 24 hours after the onset of signs and symptoms.

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):

2000 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.

Dosage in children:

No data are available.

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:

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

Herpes Zoster ***Creatinine Clearance***	***VALATREX dose***
15 to 30 mℓ/min	1000 mg twice a day
< 15 mℓ/min	1000 mg once a day
Recurrent Genital Herpes ***Creatinine Clearance***	***VALATREX dose***
> 15 mℓ/min	500 mg twice daily
0 to 15 mℓ/min	500 mg once daily

Prevention of Recurrences ***Creatinine Clearance***	***VALATREX dose***	
	Immunocompetent	*Immunocompromised*
15 to 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 VALATREX 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.

Dosage in CMV prophylaxis:

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

Creatinine Clearance	***VALATREX***
≥ 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 VALATREX 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 VALATREX 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).

4.3 Contraindications

VALATREX is contraindicated in patients known to be hypersensitive to valaciclovir, aciclovir or any component of the formulations.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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. 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).

Use of higher doses of valaciclovir in hepatic impairment and liver transplantation:

There are no data available on the use of higher doses of valaciclovir (4000 mg or more per day) in patients with liver disease. Specific studies of valaciclovir have not been conducted in liver transplantation, and hence caution should be exercised when administering daily doses greater than 4000 mg 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.

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 valaciclovir, 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 sufficient.

Use in CMV infections:

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 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 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).

Skin reactions:

There is a risk of Acute generalized exanthematous pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with the use of acyclovir and valacyclovir containing medicines. DRESS and AGEP are considered serious cutaneous adverse reactions (SCARs) which are unpredictable and present an important risk to patients. Therefore, if a patient develops reactions classified as SCARs during VALATREX use, treatment should be withdrawn immediately, and an alternative treatment considered (as appropriate), and treatment with these medicines must not be restarted for the patient at any time.

4.5 Interaction with other medicines and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products should be made 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, foscarnet, 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 about 25 % and 45 %, respectively, by inhibition of the active renal secretion of aciclovir. Cimetidine and probenecid taken together with valaciclovir increased aciclovir AUC by about 65 %. Other medicinal products (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 higher aciclovir exposures from valaciclovir (e.g., at doses for zoster treatment or CMV prophylaxis), caution is required during concurrent administration with drugs which inhibit active renal tubular secretion.

Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. No changes in peak concentrations or AUCs are observed with co-administration of valaciclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and during lactation has not been established.

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.

Undesirable effects such as lethargy and somnolence are possible after taking VALATREX. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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

Blood and lymphatic system disorders:

Less frequent: Leucopenia, thrombocytopenia.

Immune system disorders:

Less frequent: Anaphylaxis.

Psychiatric and nervous system disorders:

Frequent: Headache.

Less frequent: Dizziness, confusion, hallucinations (particularly in organ transplant patients receiving high doses of VALATREX for CMV prophylaxis), lethargy, somnolence, decreased consciousness, agitation, tremors, ataxia, dysarthria, psychotic symptoms, delirium, convulsions, encephalopathy and coma.

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 (8000 mg daily) of Valatrex 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: Vomiting, diarrhoea.

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: Skin rashes, including photosensitivity, pruritus.

Less frequent: Urticaria, angioedema.

Frequency unknown: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Acute generalized exanthematous pustulosis (AGEP)

Renal and urinary disorders:

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

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 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 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.

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:

A 20.2.8 Antiviral agent

PHARMACOLOGICAL ACTION:

Mechanism of action

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

Valaciclovir is rapidly and almost completely converted in man 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.

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:

Valaciclovir is a prodrug of aciclovir. The bioavailability of aciclovir from valaciclovir is about 3.3 to 5.5-fold greater than that historically observed for oral aciclovir. After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as valaciclovir hydrolase. The bioavailability of aciclovir from 1000 mg valaciclovir is 54 %, and is not reduced by food. Valaciclovir pharmacokinetics is not dose-proportional. The rate and extent of absorption decreases with increasing dose, resulting in a less than proportional increase in Cmax over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Aciclovir pharmacokinetic (PK) parameter estimates following single doses of 250 to 2000 mg valaciclovir to healthy subjects with normal renal function are shown below.

Aciclovir PK Parameter		250 mg (N=15)	500 mg (N=15)	1000 mg (N=15)	2000 mg (N=8)
C_{max}	micrograms/mL	2.20 ± 0.38	3.37 ± 0.95	5.20 ± 1.92	8.30 ± 1.43
T_{max}	hours (h)	0.75 (0.75–1.5)	1.0 (0.75–2.5)	2.0 (0.75–3.0)	2.0 (1.5–3.0)
AUC	h.micrograms/mL	5.50 ± 0.82	11.1 ± 1.75	18.9 ± 4.51	29.5 ± 6.36

C_{max} = peak concentration; T_{max} = time to peak concentration; AUC = area under the concentration-time curve. Values for C_{max} and AUC denote mean ± standard deviation. Values for T_{max} denote median and range.

Peak plasma concentrations of unchanged valaciclovir are only about 4 % of peak aciclovir levels, occur at a median time of 30 to 100 min post-dose, and are at or below the limit of quantification 3 h after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. Herpes zoster, herpes simplex and HIV infection do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir compared with healthy adults. In transplant recipients receiving valaciclovir 2000 mg 4 times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Distribution:

Binding of valaciclovir to plasma proteins is very low (15 %). CSF penetration, determined by CSF/plasma AUC ratio, is independent of renal function and was about 25 % for aciclovir and the metabolite 8-OH-ACV, and about 2.5 % for the metabolite CMMG.

Biotransformation:

After oral administration, valaciclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9(carboxymethoxy)methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88 % of the total combined plasma exposure is attributable to aciclovir, 11 % to CMMG and 1 % to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolized by cytochrome P450 enzymes.

Elimination:

Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80 % of the recovered dose) and the aciclovir metabolite CMMG (about 14 % of the recovered dose). The metabolite 8-OH-ACV is detected only in small amounts in urine (< 2 % of the recovered dose). Less than 1 % of the administered dose of valaciclovir is recovered in the urine as unchanged drug. In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 h.

Special Populations

Renal impairment:

The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average

elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).
Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mℓ /min, range 91 to 144 mℓ /min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CL_{cr} 26 m ℓ /min, range 17 to 31 mℓ/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5 to 6 times higher, respectively, at severe renal impairment compared with normal renal function.

Hepatic impairment:

Pharmacokinetic data indicate that hepatic impairment decreases the rate of conversion of valaciclovir to aciclovir but not the extent of conversion. Aciclovir half-life is not affected.

Pregnant women:

A study of the pharmacokinetics of valaciclovir and aciclovir during late pregnancy indicates that pregnancy does not affect the pharmacokinetics of valaciclovir.

Transfer into breast milk:

Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (Cmax) in breast milk ranged from 0.5 to 2.3 times the corresponding maternal aciclovir serum concentrations. The median aciclovir concentration in breast milk was 2.24 micrograms/mℓ (9.95 micromoles/ℓ). With a maternal valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral aciclovir dosage of about 0.61 mg/kg/day. The elimination half-life of aciclovir from breast milk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breast milk, or infant urine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Valaciclovir did not affect fertility in male or female rats dosed by the oral route.

Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolised to aciclovir.

Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal abnormalities and maternal toxicity were observed at subcutaneous doses that produced plasma aciclovir levels of 100 micrograms/mℓ (>10-fold higher than 2000 mg single dose valaciclovir in humans with normal renal function).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone, microcrystalline cellulose, povidone, magnesium stearate and Opadry white (coating ingredient).

6.2 Incompatibilities

N/A

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C, in the original cardboard carton.

6.5 Nature and contents of container

Valatrex 250: Aluminium foil / trilaminate (PVC/PE/PVDC) blister packs of 60 tablets.

Valatrex 500: Aluminium foil / trilaminate (PVC/PE/PVDC) blister packs of 42, 30 and 10 tablets.

The Alu/trilaminate PVC blister strips are packed into a cardboard carton.

6.6 Special precautions for disposal and other handling

None

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd1

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

Valatrex 250: 42/20.2.8/0340

Valatrex 500: 42/20.2.8/0341

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 June 2014

10. DATE OF REVISION OF THE TEXT

28 July 2023

1Company Reg. No.: 1990/001979/07