PROPOSED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

VALZOST 500 mg TABLETS

VALZOST 1 g TABLETS

COMPOSITION

VALZOST 500 mg

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

VALZOST 1 g

Each film-coated tablet contains valaciclovir hydrochloride equivalent to 1 g valaciclovir.

Inactive ingredients: crospovidone, magnesium stearate, microcrystalline cellulose and povidone.

Opadry blue 13B50578 film coating ingredients: FD&C Blue #2/ indigo carmine aluminium lake (C.I. No.: 73015), hypromellose, macrogol, polysorbate 80 and titanium dioxide (C.I. No.: 77891).

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION

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

Pharmacodynamic properties

Valaciclovir is a nucleoside analogue DNA polymerase inhibitor.

Valaciclovir is rapidly and almost completely converted in man to aciclovir and L-valine probably 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 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 result 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 the human immunodeficiency virus (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.

Pharmacokinetic properties

Absorption

After oral administration valaciclovir is well absorbed from the gastrointestinal tract and almost completely converted to aciclovir and L-valine by first-pass intestinal and / or hepatic metabolism.

Metabolism

Aciclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valaciclovir nor aciclovir is metabolised by cytochrome P450 enzymes. Peak plasma concentrations of unconverted valaciclovir are low and transient, generally becoming non-quantifiable 3 hours after administration.

Peak plasma concentration of valaciclovir occurs at median time of 45 – 60 minutes post dose. Peak plasma valaciclovir concentrations are generally less than 0,5 µg/ mL at all doses. After single-dose administration of 1 gram of valaciclovir, average plasma valaciclovir concentrations observed were 0,5; 0,4 and 0,8 µg/mL in patients with hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant cimetidine and probenecid, respectively.

Distribution

The binding of valaciclovir to human plasma proteins ranges from 13,5 % to 17,9 %. The binding of aciclovir to human plasma proteins ranges from 9 % to 33 %.

Elimination

The elimination plasma half-life of aciclovir after both single and multiple dosing with valaciclovir

averaged 2,5 to 3,3 hours in volunteers with normal renal function.

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.

Renal impairment: Following administration of valaciclovir to patients with renal impairment, the average half-life of aciclovir is approximately 14 hours. During haemodialysis, the aciclovir half-life is approximately 4 hours. Approximately one third of aciclovir in the body is removed by dialysis during a 4 hour haemodialysis session. Apparent plasma clearance of aciclovir in dialysis patients is 86,3 +/- 21,3 mL / min / 1,73 m^2 compared with 679,16 +/- 162,76 mL / min / 1,73 m^2 in healthy volunteers.

Characteristics in patients

Herpes zoster and herpes simplex does not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of **VALZOST**. 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 area under the plasma concentration curves (AUCs) is appreciably greater.

INDICATIONS

VALZOST is indicated for the treatment of herpes zoster (shingles). **VALZOST** reduces the duration of zoster-associated pain, which includes acute and postherpetic neuralgia, thus accelerating resolution of pain. **VALZOST** also reduces the proportion of patients with zoster-associated pain.

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

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

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

CONTRAINDICATIONS

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

Safety in pregnancy and lactation has not been established. (See "**PREGNANCY AND LACTATION").**

WARNINGS AND SPECIAL PRECAUTIONS

Thrombotic, thrombocytopenic purpura/haemolytic uraemic syndrome (TTP / HUS):

TTP / HUS in some cases resulted in death, has been reported in patients with advanced HIV disease and also in bone marrow transplant and renal transplant recipients.

Cases of acute renal failure have been reported in:

- Elderly patients with or without reduced renal function. Caution should be exercised when administering **VALZOST** to elderly patients, and dosage reduction is recommended for those with impaired renal function.
- Patients with underlying renal disease who received higher than recommended doses of **VALZOST** for their level of renal function. Dosage reduction is recommended when administering **VALZOST** to patients with renal impairment.
- Patients receiving other nephrotoxic medicines. Caution should be exercised when administering **VALZOST** to patients receiving potentially nephrotoxic medicines.
- Patients without adequate hydration. Precipitation of aciclovir in renal tubules may occur when solubility (2,5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

In the event of acute renal failure and anuria, the patient may benefit from haemodialysis until renal function is restored.

Central Nervous System (CNS)

CNS adverse reactions, including agitation, hallucinations, confusion, delirium, seizures, and encephalopathy, have been reported in both adult and paediatric patients with or without reduced renal function and in patients with underlying renal disease who received higher than recommended doses of **VALZOST** for their level of renal function. Elderly patients are more likely to have CNS adverse reactions. **VALZOST** should be discontinued if CNS adverse reactions occur.

Effects on ability to drive and use machines

When driving vehicles or using machines it should be taken into account that dizziness, weariness or visual disturbances may occur.

INTERACTIONS

No clinically significant interactions have been identified.

Cimetidine and probenecid increase the area under the plasma concentration time curve of aciclovir by reducing its renal clearance: however no dosage adjustment is necessary because of the wide therapeutic index of aciclovir. Other medicines which affect renal physiology could affect plasma levels of aciclovir.

In patients receiving high-dose **VALZOST** (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 agent used in transplant patients, have been shown when the medicines are co-administered.

Care is also required (with monitoring for changes in renal function) if administering high-dose

VALZOST with medicines which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established (see "**CONTRAINDICATIONS"**).

Teratogenicity

Foetal abnormalities were observed in rats.

DOSAGE AND DIRECTIONS FOR USE

Dosage in adults

For the treatment of Herpes Zoster: 1000 mg of **VALZOST** 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 **VALZOST** 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): 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 **VALZOST** should be modified as follows in patients with significantly impaired renal function:

HERPES ZOSTER **Creatinine Clearance**	**VALZOST** **Dose**
15 - 30 mL/min	1000 mg twice a day
< 15 mL/min	1000 mg once a day
RECURRENT GENITAL HERPES **Creatinine Clearance**	**VALZOST** **Dose**
> 15 mL/min	500 mg twice daily
0 - 15 mL/min	500 mg once daily

PREVENTION OF RECURRENCE **Creatinine Clearance**	**VALZOST** **Dose**	
	Immunocompetent	**Immunocompromised**
15 - 30 mL/min	No dosage adjustment required	No dosage adjustment required

< 15 mL/min	250 mg once a day	500 mg once daily

In patients on haemodialysis, the **VALZOST** 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 **VALZOST** should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine Clearance	**VALZOST** **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 daily

** In patients on haemodialysis, the **VALZOST** 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 **VALZOST** 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 shutting) do not indicate the need for dosage adjustment; however, clinical experience is limited. For higher doses recommended for CMV prophylaxis (see **"WARNINGS AND SPECIAL PRECAUTIONS**")**.**

SIDE EFFECTS

Blood and the lymphatic system disorders

Less Frequent: Aplastic anaemia, thrombocytopenia, haemolytic anaemia, micro-angiopathic, neutropenia, leukocytoclastic vasculitis.

Immune system disorders

Less Frequent: Acute hypersensitivity reactions and anaphylaxis and angioedema.

Nervous system disorders

Frequent: Headache.

Less frequent: Decreased consciousness in patients with renal insufficiency, dizziness, somnolence, convulsions, fatigue, aggressive behaviour, agitation, ataxia, coma, confusion, dysarthria, encephalopathy, seizures and tremors.

Psychiatric disorders

Less Frequent: Mania and psychosis, including auditory and visual hallucinations.

Eye disorders

Less Frequent: Visual abnormalities.

Cardiac disorders

Less Frequent: Tachycardia.

Vascular disorder

Less Frequent: Hypertension.

Gastrointestinal disorders

Frequent: Nausea.

Less frequent: Gastrointestinal disturbances such as constipation, diarrhoea, loss of appetite, stomach pain, vomiting.

Hepato-biliary disorders

Less frequent: Hepatitis with liver function test abnormalities, jaundice.

Skin and subcutaneous tissue disorders

Less Frequent: Facial oedema skin reactions such as erythema multiforme, photosensitivity, or rash (redness of the skin), alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, pruritus.

Musculoskeletal, connective tissue and bone disorders

Less Frequent: Arthralgia.

Renal and urinary disorders

Less Frequent: Renal insufficiency manifested by increased serum creatinine, acute renal failure.

Reproductive system and breast disorders

Less Frequent: Dysmenorrhoea.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms and signs

There are at present no data available on overdose with **VALZOST**.

In animal studies, large doses caused obstructive uropathy and crystalluria.

Management

In the event of asymptomatic **VALZOST** overdose occurring, aciclovir is removable by haemodialysis.

IDENTIFICATION

VALZOST 500 mg

Blue, film coated, capsule shaped tablets with a partial score bar on both sides containing “F” on one side and “9” and “3” on the other side.

VALZOST 1 g

Blue, film coated, capsule shaped tablets with a partial score bar on both sides containing “F” on one side and “8” and “3” on the other side.

PRESENTATION

VALZOST 500 mg

1) Blister Pack

Tablets are packed in Clear 250 µm PVC film coated with 90 g/m^2 PVdC and Printed 25 µm aluminium foil with 7g/m^2 heat seal lacquer.

Pack sizes

10's - Each blister contains 5 tablets. Each carton contains 2 blisters of 5 tablets each.

30's - Each blister contains 5 tablets. Each carton contains 6 blisters of 5 tablets each.

42's - Each blister contains 7 tablets. Each carton contains 6 blisters of 7 tablets each.

2) HDPE Container Pack

Tablets are packed in 60 ml HDPE white opaque colour container of 38 mm neck finish with 38 mm – 400 RS closure with induction sealing wad. Each container contains 42 tablets.

Pack size: 42's - One HDPE container contains 42 tablets.

VALZOST 1 g

1) Blister Pack

Tablets are packed in Clear 250 µm PVC film coated with 90 g/m^2 PVdC and Printed 25 µm aluminium foil with 7 g/m^2 heat seal lacquer.

Pack size: 21's – Each carton contains 3 blisters of 7 tablets each.

2) HDPE Container Pack

Tablets are packed in 60 ml white opaque colour HDPE container of 38 mm neck finish with 38 mm – 400 RS closure with induction sealing wad.

Pack size: 21's - One HDPE container contains 21 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Keep HDPE containers tightly closed.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

VALZOST 500 mg: 45/20.2.8/0588

VALZOST 1 g: 45/20.2.8/0589

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2, 100 Sovereign Drive,

Route 21 Corporate Park,

Nellmapius Drive, Irene,

0157, Pretoria,

South Africa

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