PACKAGE INSERT

ZELITREX® Tablets

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZELITREX® 250 Tablets

ZELITREX® 500 Tablets

COMPOSITION:

ZELITREX 250 Tablets contain: valaciclovir hydrochloride equivalent to 250 mg valaciclovir per tablet

ZELITREX 500 Tablets contain: valaciclovir hydrochloride equivalent to 500 mg valaciclovir per tablet

Excipients:

The tablet core also contains microcrystalline cellulose, crospovidone, povidone K90, magnesium stearate and colloidal anhydrous silica.

The film-coat contains hydroxypropylmethylcellulose titanium dioxide, polyethylene glycol 400. The 500 mg film-coat also contains polysorbate and blue printing ink.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agent(s)

PHARMACOLOGICAL ACTION:

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

Mode of Action:

Valaciclovir is rapidly and almost completely converted in man to acyclovir and valine probably by the enzyme valaciclovir hydrolase.

Acyclovir 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). Acyclovir 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 acyclovir.

The requirement for activation of acyclovir by a virus specific enzyme largely explains its unique selectivity. The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases.

Acyclovir 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 acyclovir therapy or prophylaxis has revealed that herpes simplex virus and varicella zoster virus with reduced sensitivity to acyclovir is extremely 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 acyclovir 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:

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. 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. Binding of acyclovir to plasma proteins is very low (15 %). 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.

INDICATIONS:

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

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

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

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

CONTRA-INDICATIONS:

ZELITREX is contra-indicated in patients known to be hypersensitive to valaciclovir, acyclovir or any component of their formulations.

WARNINGS AND SPECIAL PRECAUTIONS:

Thrombotic, thrombocytopenic purpura/haemolytic uremic 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 recipients participating in clinical trials of ZELITREX. This syndrome has not been observed in immunocompetent patients treated with ZELITREX in clinical trials.

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:

Acyclovir is eliminated by renal clearance, therefore the ZELITREX dose should be adjusted in patients with renal impairment (see DOSAGE AND DIRECTIONS FOR USE: Dosage in renal impairment). 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 SIDE EFFECTS).

Effects on ability to drive and use machines:

The clinical status of the patient and the adverse event profile of valaciclovir should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of ZELITREX on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

INTERACTIONS:

No clinically significant interactions have been identified.

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

In patients receiving high-dose ZELITREX (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with medicines which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites.

Increases in plasma AUCs of acyclovir 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 ZELITREX with medicines which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

PREGNANCY AND LACTATION:

Pregnancy: Safety in pregnancy has not been established.

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

DOSAGE AND DIRECTIONS FOR USE:

Dosage in adults:

For treatment of herpes zoster: 1 000 mg of ZELITREX 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 ZELITREX 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): 2 000 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.

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 ZELITREX to patients with impaired renal function. Adequate hydration should be maintained.

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

Therapeutic indication	Creatinine Clearance	ZELITREX 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

	0-15 ml/min	500 mg once daily
Prevention of recurrences		
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

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

Creatinine Clearance	**ZELITREX 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 ZELITREX 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 ZELITREX 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 (4 g or more) see SIDE EFFECTS.

SIDE EFFECTS:

Adverse reactions are listed below by body system organ class and by frequency. The frequency categories used are: very common ≥ 1 in 10, common ≥ 1 in 100 and < 1 in 10, uncommon ≥ 1 in 1 000 and < 1 in 100, rare ≥ 1 in 10 000 and < 1 in 1 000, very rare < 1 in 10 000.

Clinical trial data have been used to assign frequency categories to adverse reactions if, in the trials, there was evidence of an association with valaciclovir (i.e. there was a statistically significant difference between the incidence in patients taking valaciclovir and placebo).

Clinical Trial Data:

Nervous system disorders:

Common: Headache

Gastrointestinal disorders:

Common: Nausea

Post-marketing Data:

Blood and lymphatic system disorders: Leukopenia, thrombocytopenia. Leukopenia is mainly reported in immunocompromised patients.

Immune system disorders: Anaphylaxis

Psychiatric and nervous system disorders: Dizziness, confusion, hallucinations, decreased consciousness, agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma.

The above events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see WARNINGS AND SPECIAL PRECAUTIONS). In organ transplant patients receiving high doses ZELITREX for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Respiratory, thoracic and mediastinal disorders: Dyspnoea.

Gastrointestinal disorders: Abdominal discomfort, vomiting, diarrhoea.

Hepato-biliary disorders: Reversible increases in liver function tests. These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders: Rashes including photosensitivity, pruritus, urticaria, angioedema.

Renal and urinary disorders: Renal impairment, acute renal failure, renal pain.

Other: 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 of ZELITREX for prolonged periods in clinical trials. These findings have also been observed in patients not treated with ZELITREX who have the same underlying or concurrent conditions.

Uses of higher doses of ZELITREX in Hepatic Impairment and Liver Transplantation:

There are no data available on the use of high doses of ZELITREX (4 g or more per day) in patients with liver disease. Caution should therefore be exercised when administering high doses of ZELITREX to these patients. Studies of ZELITREX have not been conducted in liver transplantation; however high dose acyclovir prophylaxis has been shown to reduce CMV infection and disease.

Use in genital herpes: Suppressive therapy with ZELITREX 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 ZELITREX, it is recommended that patients use safer sex practices.

Teratogenicity: Foetal abnormalities were observed in rats. The therapeutic peak is 5,7 µg/ml after 1 000 mg.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Management:

In the event of a symptomatic ZELITREX overdose occurring, acyclovir is removable by haemodialysis.

IDENTIFICATION:

ZELITREX 250: Biconvex, elongated, white film-coated tablet with a white to off-white core. Unscored and branded GXCE7 by engraving.

ZELITREX 500: Biconvex, elongated, white film-coated tablet with a white to off-white core. Unscored and branded GXCF1 and printed with blue-green or blue ink.

PRESENTATION:

ZELITREX 250: Blister pack of 60 tablets

ZELITREX 500: Blister packs of 42 tablets

Blister packs of 30 tablets

Blister packs of 10 tablets

STORAGE INSTRUCTIONS:

Keep out of reach of children.

Store at or below 30 °C.

Protect from light. Keep dry.

REGISTRATION NUMBER:

ZELITREX 250: 32/20.2.8/0465

ZELITREX 500: 29/20.2.8/0442

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

LITHA PHARMA (PTY) LTD

106 16th Road

Midrand

1685

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

6 December 2013

GDS 015

History:

Amended: 16 March 2001
Amended: 17 February 2011 (To include new safety info GDS Versions 7 – 20)
Compliant response to CCC recommendation dated 8 April 2013.
Final Proposed Package Insert 8 August 2013
Approved by MCC 2013 12 06
25.06.2015 – Notification of implementation of Reg 9 & 10