Professional Information for JUBITREX

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

JUBITREX 500 mg film coated tablets

JUBITREX 1 000 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

JUBITREX 1 000: Each film coated tablet contains valaciclovir hydrochloride equivalent to 1 000 mg valaciclovir.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

JUBITREX 500: Blue, capsule shaped, film coated tablets, debossed with 'C324 500' on one side and plain on the other side.

JUBITREX 1 000: Blue, capsule shaped, film coated tablets, debossed with 'C325 1 000' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

JUBITREX is indicated for the 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 the treatment of herpes zoster: 1 000 mg to be taken three times per day for 7 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 when the first signs or symptoms appear. There are no data on the effectiveness of JUBITREX 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.

Immunocompromised patients: 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease:

Adults andadolescents (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 JUBITREX to patients with impaired renal function.

Adequate hydration should be maintained

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

Therapeutic indication	**Creatinine clearance**	**JUBITREX 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 < 15 mL/min	No dosage adjustment 500 mg once daily

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

Creatinine clearance	**JUBITREX 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 JUBITREX 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 JUBITREX 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 section 4.4.

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

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 patients participating in clinical trials of valaciclovir as contained in JUBITREX. This syndrome has not been observed in immunocompetent patients in valaciclovir clinical trials.

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 JUBITREX 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, as contained in JUBITREX (4 000 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 4 000 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.

Use in 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 JUBITREX 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 JUBITREX on transmission of sexually transmitted infections other than herpes (including HIV, gonorrhoea, syphilis and Chlamydia) is unknown.

The efficacy of JUBITREX 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 CMV infections:

Data on the efficacy of valaciclovir from transplant patients (~200) at high risk of CMV disease (e.g. donor CMVpositive/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 central nervous system (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).

4.5 Interaction with other medicines and other forms of interaction

The combination of valaciclovir with nephrotoxic medicines 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 1 000 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 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 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 medicines which inhibit active renal tubular secretion.
Co-administration of JUBITREX and medicine that compete with aciclovir for elimination, may cause a potential increase in plasma levels of both medicine and/or their metabolites.
Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate motefil, an immunosuppressant medicine used in transplant patients, have been shown when the medicines 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

Pregnancy:

Safety in pregnancy has not been established.

Breastfeeding:

Aciclovir, the principle metabolite of valaciclovir, is excreted in breastmilk. Mothers on treatment with JUBITREX should not breastfeed their infants.

Fertility:

No human fertility studies were performed with valaciclovir.

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. The clinical status of the patient and the adverse reaction profile of JUBITREX should be borne in mind when considering the patient`s ability to drive or operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Clinical trial data:

Nervous system disorders

Frequent: headache

Gastrointestinal disorders

Frequent: nausea

Post-marketing data:

Blood and the lymphatic system disorders

Less frequent: leucopenia, thrombocytopenia

Leucopenia is mainly reported in immunocompromised patients.

Immune system disorders

Less frequent: anaphylaxis

Psychiatric disorders

Less frequent: hallucinations, psychotic symptoms, delirium

Nervous system disorders

Frequent: dizziness

Less frequent: confusion, decreased consciousness, tremor, agitation, ataxia, dysarthria, convulsions, encephalopathy, 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 (8 000 mg daily) of JUBITREX 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), sometimes referred to as hepatitis

Skin and subcutaneous tissue disorders

Frequent: rashes including photosensitivity, pruritus

Less frequent: urticaria, angioedema

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Renal and urinary disorders

Frequent: renal pain, haematuria (often associated with other renal events)

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 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 human immunodeficiency virus (HIV) disease, receiving high doses (8 000 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 JUBITREX is important. It allows continued monitoring of the benefit/risk balance of JUBITREX. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who- umc.org) found on the SAHPRA website. By reporting side effects, you can help provide more information on the safety of JUBITREX.

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. In the event of a symptomatic JUBITREX overdose occurring, aciclovir is removable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.8 Antivirals agents.

Pharmacotherapeutic group: Nucleosides and nucleotides excluding reverse transcriptase inhibitors.

ATC code: J05AB11.

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 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.

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 aciclovir and valine.

This conversion is probably mediated by valaciclovir hydrolase, an enzyme isolated from human liver. Mean peak aciclovir 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 aciclovir from 1 000 mg valaciclovir 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 – 1 000 mg valaciclovir and occur at a median time of 1,50 hours post dose 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 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.

Distribution:

Binding of valaciclovir to plasma proteins is very low (15 %). Cerebrospinal fluid (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 9-carboxymethoxymethylguanine (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 metabolite 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 metabolised 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 medicine. 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 – 144 mL/min) receiving 2 000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17 – 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 – 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 breastmilk:

Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations

(Cmax) in breastmilk ranged from 0,5 to 2,3 times the corresponding maternal aciclovir serum concentrations. The median aciclovir concentration in breastmilk 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 breastmilk was similar to that for serum. Unchanged valaciclovir was not detected in maternal serum, breastmilk, or infant urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Crospovidone

Hypromellose (E464)

Magnesium stearate

Microcrystalline cellulose (E460(i)).

Film coating:

Opadry Blue (containing FD&C Blue No. 2 (E132), hypromellose (E464), macrogol, polysorbate 80 (E433), and 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 °C.

Protect from light.

Keep in the outer carton until required for use.

6.5 Nature and contents of container

JUBITREX 500: PVC/aluminium blister strips packed in an outer carton, containing 10, 30, 60 or 100 tablets.

JUBITREX 1 000: PVC/aluminium blister strips packed in an outer carton, containing 10, 30, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Jubilant Pharma SA (Pty) Ltd

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Lenasia

Johannesburg 1820

Contact Details: g-rp.sa@jubl.com

8. REGISTRATION NUMBERS

JUBITREX 500: 49/20.2.8/0546

JUBITREX 1 000: 49/20.2.8/0547

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 March 2022

10. DATE OF REVISION OF THE TEXT

20 November 2024