1.16.2	Patient Information Leaflet

PACKAGE LEAFLET:

INFORMATION FOR THE USER

VACIVOX-500 &VACIVOX-1000

Valacyclovir Tablets USP 500 mg / 1000 mg

DOSAGE FORMS:

Film coated tablets.

COMPOSITION:

VACIVOX-500

Each film coated tablet contains:

Valacyclovir Hydrochloride USP eqv. to

Valacyclovir ……. 500 mg

Excipients ……. Q.S.

VACIVOX-1000

Each film coated tablet contains:

Valacyclovir Hydrochloride eqv. to

Valacyclovir USP……. 1000 mg

Excipients ……. Q.S.

DESCRIPION:

A blue coloured, capsule shaped, film coated tablets with break line on one side and plain on other side.

PHARMACOTHERAPEUTIC GROUP:

Pharmacotherapeutic group: Nucleosides and nucleotides excl. reverse transcriptase inhibitors

ATC Code: J05AB11

INDICATIONS:

VACIVOX is indicated for

Varicella zoster virus (VZV) infections-herpes zoster.

OXFORD LABORATORIES PVT. LTD. MUMBAI

- The treatment of herpes zoster (shingles) and ophthalmic zoster in immunocompetent adults.
- The treatment of herpes zoster in adult patients with mild or moderate immunosuppression.

Herpes simplex virus (HSV) infections.

- The treatment and suppression of HSV infections of the skin and mucous membranes including:
- The treatment of first-episode of genital herpes in immunocompetent adults and adolescents and in immunocompromised adults.
- The treatment of recurrences of genital herpes in immunocompetent adults and adolescents, and in immunocompromised adults.
- Suppression ofrecurrent genital herpes in immunocompetent adults and adolescents and in immunocompromised adults.
- Treatment and suppression of recurrent ocular HSV infections in immunocompetent adults and adolescents and in immunocompromised adults.

Cytomegalovirus (CMV) infections:

- The prophylaxis of CMV infection and disease following solid organ transplantation in adults and adolescents.

PHARMACOLOGICAL PROPERTY:

Pharmacodynamics:

Mechanism of Action

Valacyclovir, an antiviral, is the L-valine ester of acyclovir. Acyclovir is a purine (guanine) nucleoside analogue. Valacyclovir is rapidly and almost completely converted in man to acyclovir and valine, probably by the enzyme referred to as Valacyclovir 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), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV6). 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 UL97. This requirement for activation of acyclovir by a virus specific enzyme largely explains its 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.

OXFORD LABORATORIES PVT. LTD. MUMBAI

Pharmacodynamic effects:

Resistance to acyclovir is normally due to a thymidine kinase deficient phenotype which results in a virus which is disadvantaged in the natural host. 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 wildtype virus. Monitoring of clinical HSV and VZV Isolates from patients receiving acyclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to acyclovir 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).

Pharmacokinetics:

Absorption:

Valacyclovir is a prodrug of acyclovir. The bioavailability of acyclovir from valacyclovir is about 3.3 to 5.5-fold greater than that historically observed for oral acyclovir. After oral administration valacyclovir is well absorbed and rapidly and almost completely converted to acyclovir and valine. This conversion is probably mediated by an enzyme isolated kom human liver referred to as valacyclovir hydrolase. The bioavailability of acyclovir from 1000 mg valacyclovir is 54 %, and is not reduced by food. Valacyclovir 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. Acyclovir pharmacokinetic (PK) parameter estimates following single doses of 250 to 2000 mg valacyclovir to healthy subjects with normal renal function are shown below.

Acyclovir PK Parameter		**250mg(N=15)**	**500mg(N=15)**	**1000mg(N=15)**	**2000mg(N=8)**
Cmax	Micrograms/mL	2.20 ± 0.38	3.37 ± 0.95	5.20 ± 1.92	8.30 ± 1.43
Tmax	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

Cmax = peak concentration; Tmax=time to peak concentration; AUC = area under the concentration time curve. Values for Cmax and AUC denote mean ± standard deviation. Values for Tmax denote median and range.

Peak plasma concentrations of unchanged valacyclovir are only about 4 % of peak acyclovir 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 valacyclovir and acyclovir pharmacokinetic profiles are similar after single and repeat dosing. Herpes zoster, herpes simplex and HIV infection do not significantly alter the pharmacokinetics of valacyclovir and acyclovir after oral administration of valacyclovir compared with

healthy adults. In transplant recipients receiving valacyclovir 2000 mg 4 times daily, acyclovir 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 valacyclovir 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 acyclovir and the metabolite 8-OH-ACV, and about 2.5 % for the metabolite CMMG.

Metabolism:

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

Elimination

Valacyclovir is eliminated in the urine principally as acyclovir (greater than 80% of the recovered dose) and the acyclovir 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 valacyclovir is recovered in the urine as unchanged drug. In patients with normal renal function the plasma elimination half-life of acyclovir after both single and multiple dosing with valacyclovir is approximately 3 h.

Special Populations:

1. Renal impairment

The elimination of acyclovir is correlated to renal function, and exposure to acyclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of acyclovir after valacyclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function.

Exposure to acyclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valacyclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mt/min) receiving 2000mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 ml/min, range 17 31ml/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of acyclovir, 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.

2. Hepatic impairment

Pharmacokinetic data indicate that hepatic impairment decreases the rate of conversion of Valacyclovir to acyclovir but not the extent of conversion. Acyclovir half-life is not affected.

3. Pregnant women

A study of the pharmacokinetics of valacyclovir and acyclovir during late pregnancy indicates that pregnancy does not affect the pharmacokinetics of valacyclovir.

4. Transfer into breast milk

Following oral administration of a 500 mg dose of valacyclovir, peak acyclovir concentrations (Cmax) in breast milk ranged from 0.5 to 2.3 times the corresponding maternal acyclovir serum concentrations.

The median acyclovir concentration in breast milk was 2.24 micrograms/ml (9.95 micromoles/L). With a maternal valacyclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral acyclovir dosage of about 0.61 mg/kg/day. The elimination half-life of acyclovir from breast milk was similar to that for serum. Unchanged valacyclovir was not detected in maternaliserum, breast milk, or infant urine.

DOSAGE AND ADMINISTRATION:

Varicella zoster virus (VZV) infections-herpes zoster and ophthalmiczoster.

Patients should be advised to start treatment as soon as possible after a diagnosis of herpes zoster. There are no data on treatment started more than 72 hours after onset of the zoster rash.

Immunocompetent Adults

The dose in immunocompetent patients is 1000 mg three times daily for seven days (3000 mg total daily dose this dose should be reduced according to creatinine clearance (see Renal impairment below).

Immunocompromised Adults

The dose in immunocompromised patients is 1000 mg three times daily for at least seven days (3000 mg total daily dose) and for 2 days following crusting of lesions. This dose should be reduced according to creatinine clearance (see Renal impairment below).

In immunocompromised patients, antiviral treatment is suggested for patients presenting within one week of vesicle formation or at any time before full crusting of lesions.

Treatment of herpes simplex virus (HSV) infections in adults and adolescents (≥12 years)

OXFORD LABORATORIES PVT. LTD. MUMBAI

Immunocompetent Adults and Adolescents (≥12 years). The dose is 500 mg of VACIVOX to be taken twice daily (1000 mg total daily dose). This dose should be reduced according to creatinine clearance (see Renal impairment below).

For recurrent episodes, treatment should be for three to five days. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms. VACIVOX can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.

Herpes labialis

For herpes labialcold sores), valacyclovir 2000 mg twice daily for one day is effective treatment in adults and adolescents. The second dose should be taken about 12 h (no sooner than 6 h) after the first dose. This dose should be reduced according to creatinine clearance (see Renal impairment below). When using this dosing regimen, treatment should not exceed one day, since this has been shown not to provide additional clinical benefit. Therapy should be initiated at the earliest symptom of a cold sore (e.g. tingling, itching or burning).

Immunocompromised Adults

For the treatment of HSV in immunocompromised adults, the dosage is 1000 mg twice daily for at least 5 days, following assessment of the severity of the clinical condition and immunological status of the patient. For initial episodes, which can be more severe, treatment may have to be extended to ten days. Dosing should begin as early as possible. This dose should be reduced according to creatinine clearance (see Renal impairment below). For maximum clinical benefit, the treatment should be arted within 48 hours. A strict monitoring of the evolution of lesions is advised.

Suppression of recurrences of herpes simplex virus (HSV) infections in adults and adolescents (>12 years)

Immunocompetent Adults and Adolescents (2-12 years)

The dose is 500 mg of VACIVOX to be taken once daily. Some patients with very frequent recurrences (210/year in absence of therapy) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily). This dose should be reduced according to creatinine clearance (see Renal impairment below). Treatment should be re-evaluated after 6 to 12 months of therapy.

Immunocompromised Adults

The dose is 500 mg of VACIVOX twice daily. This dose should be reduced according to creatinine clearance (see Renal impairment below). Treatment should be re-evaluated after 6 to 12 months of therapy.

Prophylaxis of cytomegalovirus (CMV) infection and disease in adults and adolescents (≥12 years)

OXFORD LABORATORIES PVT. LTD. MUMBAI

The dosage of VACIVOX is 2000 mg four times a day, to be initiated as early as possile post-transplant. This dose should be reduced according to creatinine clearance (see Renal impairment below). The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.

Special populations

1. Children

The efficacy of YASWOX in children below the age of 12 years has not been evaluated.

2. Elderly

The possibility of renal impairment in the elderly must be considered and the dose should be adjusted accordingly (see Renal impairment below). Adequate hydration should be maintained.

3. Renal impairment

Caution is advised when administering VACIVOX to patients with impaired renal function. Adequate hydration should be maintained. The dose of VACIVOX should be reduced in patients with impaired renal function as shown in Table 1 below.

In patients on intermittent haemodialysis, the VACIVOX dose 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 renal transplantation or engraftment. The VACIVOX dosage should be adjusted accordingly.

4. Hepatic impairment

Studies with a 1000 mg dose of valacyclovir in adult patients show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in adult patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portalsystemic shunting) do not indicate the need for dose adjustment; however, clinical experience is limited. For higher doses (4000 mg or more per day), refer Special warnings and precautions for use.

Therapeutic Indication	Creatinine Clearance (mL/min)	Valacyclovir Dosage (a)
Varicella-Zoster Virus (VZV) Infections		
Treatment of herpes zoster (shingles)	≥50	1000 mg three times daily
in immunocompetent and immunocompromised adults	30 to 49	1000 mg twice daily
	10 to 29	1000 mg once daily

	10	500 mg once daily
Herpes Simplex Virus (HSV) Infections		
Treatment of HSV infections		
- immunocompetent adults and adolescents	≥30	500 mg twice daily
	<30	500 mg once daily
- immunocompromised adults	≥30	1000 mg twice daily
	<30	1000 mg once daily
Treatment of herpes labialis (cold sores) in immunocompetent adults and adolescents (alternative 1-day regimen)	≥50	2000mg twice in one day
	30 to 49	1000 mg twice in one day
	10 to 29	500 mg twice in one day
	<10	500 mg single dose
Suppression of HSV infections		
- immunocompetent adults and adolescents	≥30	500 mg once daily (b)
	<30	250 mg once daily
- immunocompromised adults	≥30	500 mg twice daily
	<30	500 mg once daily
Cytomegalovirus (CMV) Infections		
CMV prophylaxis in solid organ transplant recipients in adults and adolescents	≥75	2000 mg four times daily
	50 to <75	1500 mg four times daily
	25 to <50	1500 mg three times daily
	10 to <25	1500 mg twice daily
	<10 or on dialysis	1500 mg once daily

a - For patients on intermittent haemodialysis, the dose should be given after dialysis on dialysis days.

b - For HSV suppression in immunocompetent subjects with a history of 210 recurrences/year, better results may be obtained with 250 mg twice daily.

Method of administration:

VACIVOX is for Oral use only. Swallow the tablets whole with a drink of water. Take VACIVOX at the same time each day. Take VACIVOX according to instructions from your doctor or pharmacist.

UNDESIRABLE EFFECTS:

The most common adverse reactions (ARS) reported in at least one indication by patients treated with Valacyclovir in clinical trials were headache and nausea. More serious ARs such as thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, acute renal failure and neurological disorders are discussed in greater detail

OXFORD LABORATORIES PVT. LTD. MUMBAI

in other sections of the label. Undesirable effects are listed below by body system organ class and by frequency.

The following frequency categories are used for classification of adverse effects:

Very common ≥1/10,

Common 21/100 to <1/10,

Uncommon 21/1,000 to <1/100,

Rare 21/10,000 to <1/1000,

Very rare < 1/10,000

USE IN SPECIFIC POPULATIONS

Pregnancy

A limited amount of data on the use of Valacyclovir and a moderate amount of data on the use of acyclovir in pregnancy is available from pregnancy registries (which have documented the pregnancy outcomes in women exposed to Valacyclovir or to oral or intravenous acyclovir (the active metabolite of Valacyclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy, respectively) and postmarketing experience indicate no malformative or foeto/neonatal toxicity. Animal studies do not show reproductive toxicity for Valacyclovir. Valacyclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Breast-feeding:

Acyclovir, the principle metabolite of Valacyclovir, is excreted in breast milk. However, at therapeutic doses of Valacyclovir, no effects on the breastfed newkorns/infants are anticipated since the dose ingested by the child is less than 2 % of the therapeutic dose of intravenous acyclovir for treatment of neonatal herpes. Valacyclovir should be used with caution during breast feeding and only when clinically indicated.

Fertility:

Valacyclovir did not affect fertility in rats dosed by the oral route. At high parenteral doses of acyclovir testicular atrophy and as permatogenesis have been observed in rats and dogs. No human-fertility studies were performed with Valacyclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 to 1000 mg acyclovir.

FORMS OF INTERACTION

The combination of valacyclovir 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.

OXFORD LABORATORIES PVT. LTD. MUMBAI

Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Following 1000 mg valacyclovir, cimetidine and probenecid reduce acyclovir renal clearance and increase the AUC of acyclovir by about 25 % and 45 %, respectively, by inhibition of the active renal secretion of acyclovir. Cimetidine and probenecid taken together with valacyclovir increased acyclovir AUC by about 65 %. Other medicinal products (including e.g. tenofovir) administered concurrently that compete with or inhibit active tubular secretion may increase acyclovir concentrations by this mechanism.

Similarly, valacyclovir administration may increase plasma concentrations of the concurrently administered substance.

In patients receiving higher acyclovir exposures from valacyclovir (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 acyclovir and of the inactive metabolite of mycophenolate motefil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are coadministered. No changes in peak concentrations on ALICs are observed with coadministration of valacyclovir and mycophenolate mofetil in healthy volunteers. There is limited clinical experience with the use of this combination.

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 valacyclovir. 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 acyclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

STORAGE INSTRUCTIONS

Store at temperature not more than 25°C in a cool dry place, protected from light. Keep away from children.

PRESENTATION

VACIVOX-500

(3's pack) 1 x 3 Tablets in a Blister Strip packed in carton with pack insert.

(6's pack) 2 x 3 Tablets in a Blister Strip packed in carton with pack insert.

OXFORD LABORATORIES PVT. LTD. MUMBAI

(10's pack) 1 x 10 Tablets in a Blister Strip packed in carton with pack insert.

(20's pack) 2 x 10 Tablets in a Blister Strip packed in carton with pack insert.

(30's pack) 3 x 10 Tablets in a Blister Strip packed in carton with pack insert.

VACIVOX-1000

(3's pack) 1 x 3 Tablets in a Blister Strip packed in carton with pack insert.

(6's pack) 2 x 3 Tablets in a Blister Strip packed in carton with pack insert.

(10's pack) 1 x 10 Tablets in a Blister Strip packed in carton with pack insert.

(20's pack) 2 x 10 Tablets in a Blister Strip packed in carton with pack insert.

(30's pack) 3 x 10 Tablets in a Blister Strip packed in carton with pack insert.

SHELF LIFE

3 years from the date of manufacture.

PRESCRIBING CONDITIONS

To be sold only on doctor's prescription only.

MANUFACTURER

Oxford Laboratories Pvt. Ltd.

B/306, Crystal Plaza, New Link Road.

Andheri (West), Mumbai - 400 053, India.

OXFORD LABORATORIES PVT. LTD. MUMBAI