For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZIMIVIR

1. GENERIC NAME

Valacyclovir Tablets USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZIMIVIR 500

Each film coated tablet contains:

Valacyclovir Hydrochloride USP equivalent to Valacyclovir 500 mg
Colours: Lake Indigo Carmine & Titanium Dioxide IP

ZIMIVIR 1000

Each film coated tablet contains:

Valacyclovir Hydrochloride USP equivalent to Valacyclovir 1000 mg
Colour: Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- *ZIMIVIR* is indicated for the treatment of herpes zoster (shingles). *ZIMIVIR* accelerates the resolution of pain: it reduces the duration of and the proportion of patients with zoster-associated pain, which includes acute and post-herpetic neuralgia.
- *ZIMIVIR* is indicated for the treatment of initial and recurrent genital herpes.
- *ZIMIVIR* is indicated for the prevention (suppression) of recurrent genital herpes.
- *ZIMIVIR* can reduce transmission of genital herpes when taken as suppressive therapy and combined with safer sex practices.

4.2 Posology and Method of Administration

Adults

Treatment of herpes zoster (shingles) including ophthalmic zoster

The dosage is 1000 mg of *ZIMIVIR* to be taken three times daily for seven days.

Treatment of genital herpes

Immunocompetent adults and adolescents (12 years and older)~~)~~

The dosage is 500 mg of *ZIMIVIR* to be taken twice daily.

For recurrent episodes, treatment should be for three or five days. For initial episodes, which can be more severe, treatment may have to be extended from five days to ten days. Dosing should begin as early as possible. For recurrent episodes, this should ideally be during the prodromal period or immediately as the first signs or symptoms appear. *ZIMIVIR* can prevent lesion development when taken at the first signs and symptoms of a recurrence.

Prevention (suppression) of recurrences of genital herpes

Immunocompetent adults and adolescents (12 years and older)

In immunocompetent patients, 500 mg of *ZIMIVIR* 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 adults

For immunocompromised patients the dose is 500 mg twice daily.

Reduction of transmission of genital herpes

In immunocompetent heterosexual adults with 9 or fewer recurrences per year, 500 mg of *ZIMIVIR* to be taken once daily by the infected partner.

There are no data on the reduction of transmission in other patient populations.

Children

There are no data available on the use of *ZIMIVIR* in children.

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.

Renal Impairment

Caution is advised when administering valacyclovir to patients with impaired renal function. Adequate hydration should be maintained.

The dosage of *ZIMIVIR* should be reduced in patients with significantly impaired renal function as shown in the table below:

Therapeutic indication	***Creatinine clearance mL/min***	***ZIMIVIR* dosage**
Herpes zoster (treatment) in immunocompetent and immunocompromised adults	at least 50 30 to 49 10 to 29 less than 10	1 g three times a day 1 g twice a day 1 g once a day 500 mg once a day
Genital herpes (treatment)		
- immunocompetent adults and adolescents	at least 30 less than 30	500 mg twice a day 500 mg once a day
Genital herpes prevention (suppression):		
- immunocompetent adults and adolescents	at least 30 less than 30	500 mg once a day 250 mg once a day
- immunocompromised adults	at least 30 less than 30	500 mg twice a day 500 mg once a day

In patients on intermittent haemodialysis, the *ZIMIVIR* dosage recommended for patients with a creatinine clearance of less than 15 mL/min should be used. This should be administered after the haemodialysis has been performed.

Hepatic impairment

Studies with a 1 g unit dose of *ZIMIVIR* show that 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/day), see *4.4 Special Warnings and Precautions for Use.*

4.3 Contraindications

ZIMIVIR is contraindicated in patients known to be hypersensitive to valacyclovir or acyclovir or any components of formulations of *ZIMIVIR.*

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: Acyclovir is eliminated by renal clearance; therefore the dose of valacyclovir must be reduced in patients with renal impairment (see *4.2 Posology and Method of Administration*). 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 *4.8 Undesirable Effects*).

Use of higher doses of ZIMIVIR in hepatic impairment: There are no data available on the use of higher doses of *ZIMIVIR* (4 g or more/day) in patients with liver disease. Caution should therefore be exercised when administering higher doses of *ZIMIVIR* to these patients.

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

4.5 Drug Interactions

No clinically significant interactions have been identified.

Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations following *ZIMIVIR* administration.

Following 1g valacyclovir, cimetidine and probenecid increase the AUC of acyclovir by this mechanism, and reduce acyclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of acyclovir.

In patients receiving higher doses of *ZIMIVIR* (4 g or more/day), caution is required during concurrent administration with drugs which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both drugs or their metabolites.

Care is also required (with monitoring for changes in renal function) if administering higher doses of *ZIMIVIR* (4 g or more/day) with drugs which affect other aspects of renal physiology (*e.g.* cyclosporin, tacrolimus).

4.6 Use in Special Population

Fertility

In animal studies, *ZIMIVIR* did not affect fertility. However, high parental doses of acyclovir caused testicular effects in rats and dogs (see *6 Nonclinical Properties*).

No human fertility studies were performed with *ZIMIVIR*, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 mg to 1 g acyclovir.

Pregnancy

There are limited data on the use of *ZIMIVIR* in pregnancy. *ZIMIVIR* should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Pregnancy registries have documented the pregnancy outcomes in women exposed to *ZIMIVIR* or to any formulation of acyclovir, the active metabolite of *ZIMIVIR*; 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. The findings of the acyclovir pregnancy registry have not shown an increase in the number of birth defects amongst acyclovir-exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern

to suggest a common cause. Given the small number of women enrolled into the valacyclovir pregnancy registry, reliable and definitive conclusions could not be reached regarding the safety of *ZIMIVIR* in pregnancy (see *5.3 Pharmacokinetic Properties*).

Lactation

Acyclovir, the principle metabolite of *ZIMIVIR*, is excreted in breast milk. Following oral administration of a 500 mg dose of *ZIMIVIR*, 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. The acyclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2). The median acyclovir concentration in breast milk was 2.24 micrograms/m*L* (9.95 micromoles). With a maternal *ZIMIVIR* 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 maternal serum, breast milk, or infant urine.

Caution is advised if *ZIMIVIR* is to be administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machines

The clinical status of the patient and the adverse event profile of *ZIMIVIR* 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 valacyclovir 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.

4.8 Undesirable Effects

Adverse reactions are listed below by MedDRA 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 *ZIMIVIR* (i.e. there was a statistically significant difference between the incidence in patients taking *ZIMIVIR* and placebo). For all other adverse events, spontaneous post-marketing data have been used as a basis for allocating frequency.

Clinical Trial Data

Nervous system disorders

Common: Headache.

Gastrointestinal disorders

Common: Nausea.

Post Marketing Data

Blood and lymphatic system disorders

Very rare: Leukopenia, thrombocytopenia

Leukopenia is mainly reported in immunocompromised patients.

Immune system disorders

Very rare: Anaphylaxis.

Psychiatric and nervous system disorders

Rare: Dizziness, confusion, hallucinations, decreased consciousness.

Very rare: 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 *4.4 Special Warnings and Precautions for Use).*

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea.

Gastrointestinal disorders

Rare: Abdominal discomfort, vomiting, diarrhoea.

Hepatobiliary disorders

Very rare: Reversible increases in liver function tests.

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders

Uncommon: Rashes including photosensitivity.

Rare: Pruritus.

Very rare: Urticaria, angioedema.

Renal and urinary disorders

Rare: Renal impairment.

Very rare: Acute renal failure, renal pain.

Renal pain may be associated with renal failure.

Other: 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 (8 g daily) of *ZIMIVIR* for prolonged periods in clinical trials. These findings have been observed in patients not treated with *ZIMIVIR* who have the same underlying or concurrent conditions.

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 (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 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 result in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

5.2 Pharmacodynamic Properties

ATC code
J05A B11

Pharmacodynamic effects

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.

Extensive 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 and is only 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).

5.3 Pharmacokinetic Properties

Absorption

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 from 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 are not dose-proportional. The rate and extent of absorption decrease with increasing dose, resulting in a less than proportional increase in C_{max} over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Mean peak acyclovir concentrations are 10 to 37 micromoles (2.2 to 8.3 micrograms/m*L*) following single doses of 250 to 2000 mg valacyclovir to healthy subjects with normal renal function, and occur at a median time of 1 to 2 h post dose.

Peak plasma concentrations of valacyclovir are only 4% of 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 and herpes simplex do not significantly alter the pharmacokinetics of valacyclovir and acyclovir after oral administration of valacyclovir.

Distribution

Binding of valacyclovir to plasma proteins is very low (15%). CSF penetration, determined by CSF/plasma AUC ratio, is about 25% for acyclovir and the metabolite 8-hydroxy-acyclovir (8-OH-ACV), and about 2.5% for the metabolite 9-(carboxymethoxy)methylguanine (CMMG) (see *Pharmacokinetic Properties: Special Patient Populations*)

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 9-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 *ZIMIVIR* nor acyclovir is metabolized by cytochrome P450 enzymes.

Elimination

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. Less than 1% of the administered dose of valacyclovir is recovered in the urine as unchanged drug. Valacyclovir is eliminated in the urine principally as acyclovir (greater than 80% of the recovered dose) and the known acyclovir metabolite, 9-(carboxymethoxy) methylguanine (CMMG).

Special Patient Populations

Renal impairment

The elimination of acyclovir is co-related 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 *ZIMIVR* administration is approximately 14 hours, compared with about 3 hours for normal renal function (see *4.2 Posology and Method of Administration*).

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 *ZIMIVIR* administration in 6 subjects with normal renal function (mean creatinine clearance 111mL/min, range 91-144 mL/min) receiving 2000 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 acyclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, in severe renal impairment compared with normal renal function. There was no difference in extent of CSF penetration (as determined by CSF/plasma AUC ratio) for acyclovir, CMMG or 8-OH-acyclovir between the two populations (see *Pharmacokinetic Properties: Distribution*).

Hepatic impairment

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

Pregnant women

In a study of the pharmacokinetics of *ZIMIVIR* and acyclovir during late pregnancy, the steady-state daily acyclovir AUC following *ZIMIVIR* 1000 mg daily was approximately 2 times greater than that observed with oral acyclovir at 1200 mg daily.

For information on transfer into breast milk - see *4.6 Use in Special Population - Lactation section.*

HIV infection

In patients with HIV infection, the disposition and pharmacokinetic characteristics of acyclovir after oral administration of single or multiple doses of 1000 mg or 2000 mg *ZIMIVIR* are unaltered compared with healthy subjects.

6. NONCLINICAL PROPERTIES

The results of mutagenicity tests *in vitro* and *in vivo* indicate that *ZIMIVIR* is unlikely to pose a genetic risk to humans.

Valacyclovir was not carcinogenic in bio-assays performed in mice and rats.

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

At high parental doses of acyclovir testicular atrophy and aspermatogenesis have been observed in rats and dogs.

Valacyclovir was not teratogenic in rats or rabbits. Valacyclovir is almost completely metabolised to acyclovir. Subcutaneous administration of acyclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal abnormalities were observed at subcutaneous doses that produced plasma levels of 100 micrograms/mL-and maternal toxicity.

7. DESCRIPTION

ZIMIVIR 500

Each film coated tablet contains:

Valacyclovir Hydrochloride USP equivalent to Valacyclovir 500 mg
Colours: Lake Indigo Carmine & Titanium Dioxide IP

ZIMIVIR 1000

Each film coated tablet contains:

Valacyclovir Hydrochloride USP equivalent to Valacyclovir 1000 mg
Colour: Titanium Dioxide IP

8. PHARMACEUTICAL PARTICULARS

List of Excipients

ZIMIVIR 500

Microcrystalline Cellulose, Polyvinyl Pyrrolidine K-90, Polyvinyl Pyrrolidine K-30, Crospovidone. Magnesium Stearate, Opadry Blue 13B50578, Purified Water

ZIMIVIR 1000

Microcrystalline Cellulose, Polyvinyl Pyrrolidine K-90, Polyvinyl Pyrrolidine K-30, Crospovidone. Magnesium Stearate, Opadry White YS-1-7003, Purified Water

8.1 Incompatibilities

No data available.

8.2 Shelf Life

The expiry date is indicated on the packaging.

8.3 Packaging Information

Blister strips of tablets in a carton

8.4 Storage and Handling Information

Store at temperature not exceeding 30^{o}C.

Keep out of reach of children.

No special instructions for use.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *ZIMIVIR*. Patients may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information please contact:

GlaxoSmithKline Pharmaceuticals Limited
Registered office:
Dr.Annie Besant Road, Worli,

Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

12-JUN-2020

Trade marks are owned by or licensed to the GSK group of companies.

Version: ZMV/PI/IN/2020/01

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