For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Valcivir 450 mg Tablet

Valganciclovir 450 mg USP tablets

COMPOSITION

Each film coated tablet contains
Valganciclovir Hydrochloride USP equivalent to
Valganciclovir …… 450 mg
Colour: Titanium Dioxide, Red Oxide of Iron

DOSAGE FORM

Film coated tablet

PRODUCT DESCRIPTION

Pink coloured, capsule shaped biconvex film coated tablet plain on both sides.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Valganciclovir is a L-valyl ester (prodrug) of ganciclovir, which after oral administration is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus-6, 7 and 8 (HHV-6, HHV-7, HHV-8), Epstein-Barr virus (EBV), varicella zoster virus (VZV) and hepatitis B virus.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, UL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. This has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 and between 6 and 24 hours respectively after removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing

termination of, or very limited further viral DNA elongation. Typical anti-viral IC_{50} against CMV *in vitro* is in the range 0.08 µM (0.02 µg/ml) to 14 µM (3.5 µg/ml).

~~The clinical antiviral effect of valganciclovir has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis (clinical trial WV15376). CMV shedding was decreased from 46% (32/69) of patients at study entry to 7% (4/55) of patients following four weeks of valganciclovir treatment.~~

Pediatric use

The safety and efficacy of valganciclovir in pediatric patients have not been established in adequate and well-controlled clinical studies (see section *Dosage and Method of Administration).*

Geriatric use

Safety and efficacy have not been established in this patient population (see section *Dosage and Method of Administration).*

Renal impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections *Dosage and Method of Administration and Pharmacokinetics*).

Hepatic impairment

Safety and efficacy have not been established in this patient population (see sections *Dosage and Method of Administration and Pharmacokinetics*).

Immunogenicity

Not applicable.

Pharmacokinetics

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

The parameters which control the exposure of ganciclovir from valganciclovir are bioavailability and renal function. The bioavailability of ganciclovir from valganciclovir is comparable across all the patient populations studied. The systemic exposure of ganciclovir to heart, kidney and liver transplant recipients was similar after oral administration of valganciclovir according to the renal function dosing algorithm.

Absorption

Valganciclovir is a prodrug of ganciclovir, which is well absorbed from the gastrointestinal tract and rapidly metabolised in the intestinal wall and liver to ganciclovir. The bioavailability

of ganciclovir from oral dosing of valganciclovir is approximately 60%. Systemic exposure to valganciclovir is transient and low, $AUC_0 24_h$ and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively. When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir AUC_{24} ~~(approximately 30%)~~ and mean ganciclovir Cmax values ~~(approximately 14%)~~. Therefore, it is recommended that Valganciclovir be administered with food (see sections *Dosage and Method of Administration*).

Distribution

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir was 1-2% over concentrations of 0.5 and 51 µg/ml. The steady state volume of distribution of ganciclovir after intravenous administration was 0.680 ± 0.161 L/kg.

Metabolism

Valganciclovir is rapidly hydrolysed to ganciclovir; no other metabolites have been detected. Ganciclovir itself is not metabolized to a significant extent

Elimination

Following dosing with valganciclovir, renal excretion as ganciclovir by glomerular filtration and active tubular secretion is the major route of elimination of valganciclovir. Renal clearance accounts for 81.5% ±22% of the systemic clearance of ganciclovir.

Pharmacokinetics in special populations

Geriatric population

~~No investigations on valganciclovir or ganciclovir pharmacokinetics in adults older than 65 years of age have been undertaken. However as~~ Valganciclovir is a pro-drug of ganciclovir and because ganciclovir is mainly renally excreted and since renal clearance decreases with age, a decrease in ganciclovir total body clearance and a prolongation of ganciclovir half-life can be anticipated in elderly (see section *Dosage and Method of Administration*).

Patients with renal impairment

~~The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir were evaluated in 24 otherwise healthy individuals with renal impairment.~~

~~**Table 1: Pharmacokinetic parameters of ganciclovir from a single oral dose of 900 mg valganciclovir tablets in patients with various degrees of renal impairment**~~

~~**Estimated Creatinine Clearance (mL/min)**~~	~~**N**~~	~~**Apparent Clearance (mL/min) Mean ± SD**~~	~~**$AUC_{0-\infty}$ last (µg·h/mL) Mean ±SD**~~	~~**Half-life (hours) Mean ± SD**~~

~~51-70~~	~~6~~	~~249 ±99~~	~~50.5 ±23~~	~~4.9 ±1.4~~
~~21-50~~	~~6~~	~~136 ±64~~	~~100 ±54~~	~~10.2 ±4.4~~
~~11-20~~	~~6~~	~~45 ±11~~	~~252 ±64~~	~~21.8 ±5.2~~
~~≤10~~	~~6~~	~~12.8 ±8~~	~~407 ±83~~	~~68.1 ±35~~

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections *Dosage and Method of Administration and and Warnings and Precautions*).

Patients undergoing hemodialysis

Ganciclovir is readily removable by hemodialysis. ~~Data obtained during intermittent haemodialysis in patients dosed with valganciclovir showed estimated dialysis clearance as 138 mL/min ± 9.1% (N = 3) and intra-dialysis half-life estimated to 3.47 h (N = 6). 55% of ganciclovir was removed during a 3 hour dialysis session.~~

Stable liver transplant patients

The bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions, was approximately 60%,. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg intravenous ganciclovir in liver transplant patients.

Hepatic impairment

No pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment undergoing valganciclovir therapy.

Patients with cystic fibrosis

~~Steady state systemic exposure to ganciclovir was assessed in lung transplant recipients with or without cystic fibrosis (N=31) who were receiving 900 mg/day of Valganciclovir as part of their post transplant prophylaxis. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients.~~ Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

INDICATION

Valcivir is indicated for the treatment of cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS) patients.

Valcivir is indicated for the prevention of CMV disease in CMV-negative patients who have received a solid organ transplant from a CMV-positive donor.

DOSAGE AND METHOD OF ADMINSTRATION

Caution – Strict adherence to dosage recommendations is essential to avoid overdose.

Standard dosage

Valcivir is administered orally, and should be taken with food (see section Pharmacokinetics). Valcivir is rapidly and extensively converted into the active ingredient ganciclovir. The bioavailability of ganciclovir from Valcivir is up to 10-fold higher than from oral ganciclovir. The dosage and administration of Valcivir tablets as described below should be closely followed (see sections Warnings and Precautions, and Overdose).

Treatment of cytomegalovirus (CMV) retinitis

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section *Warnings and Precautions*).

Maintenance treatment of CMV retinitis

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg once daily. Patients whose retinitis worsens may repeat induction treatment (see Induction treatment of CMV retinitis).

The duration of maintenance treatment should be determined on an individual basis.

Prevention of CMV disease in solid organ transplantation

For kidney transplant patients, the recommended dose is 900 mg once daily starting within 10 days of transplantation until 200 days post-transplantation.

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg once daily starting within 10 days of transplantation until 100 days post-transplantation

Special dosage instructions

Geriatric use

Safety and efficacy have not been established in this patient population. No studies have been conducted in adults older than 65 years of age. Since renal clearance decreases with age, valganciclovir should be administered to elderly patients with special consideration of their renal status (see Table 2 and section Pharmacokinetics).

Adult patients with renal impairment

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance as shown in the table below (see sections Pharmacokinetics and Warnings and Precautions).

Table 2: Valganciclovir tablets dose for renally impaired

CrCl (mL/min)	**Induction Dose of valganciclovir tablets**	**Maintenance/Prevention Dose of valganciclovir tablets**
≥ *60*	900 mg twice daily	900 mg twice daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly
< 10	Not recommended	Not recommended

Creatinine clearance is calculated from serum creatinine by the following formulae:

For males: $\frac{(140 - \text{age[years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/L]})}$

For females: 0.85 x male value

Children

Safety and efficacy have not been established in this patient population. The use of valganciclovir in children is not recommended because the pharmacokinetic characteristics of valganciclovir have not been established in this patient population (see section Pharmacokinetics).

CONTRAINDICATIONS

Valganciclovir is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any of the excipients.

WARNINGS AND PRECAUTIONS

General

Cross hypersensitivity

Due to the similarity of the chemical structure of ganciclovir and that of aciclovir and penciclovir, a cross-hypersensitivity reaction between these drugs is possible. Caution should therefore be used when prescribing valganciclovir to patients with known hypersensitivity to aciclovir or penciclovir, (or to their prodrugs, valaciclovir or famciclovir respectively)

Mutagenicity, teratogenicity, carcinogenicity, fertility and contraception

~~In animal studies ganciclovir was found to be mutagenic, teratogenic, carcinogenic.~~ Valganciclovir ~~should therefore be~~is considered a potential teratogen and carcinogen in

humans with the potential to cause birth defects and cancers. Prior to initiation of valganciclovir treatment, patients should be advised of the potential risks to the fetus and to use contraceptive measures. Valganciclovir may cause temporary or permanent inhibition of spermatogenesis (see sections *Fertility, Pregnancy and Lactation, Undesirable effects and Dosage and Method of Administration*).

Myelosuppression

Valganciclovir should be used with caution in patients with pre-existing hematological cytopenia or a history of drug-related hematological cytopenia and in patients receiving radiotherapy. Severe leucopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with valganciclovir (and ganciclovir). Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/µl or the platelet count is less than 25000 / µl or the haemoglobin is less than 8 g/dl (see sections *Dosage and Method of Administration, Warnings and Precautions and Undesirable effects*).

It is recommended that complete blood counts and platelet counts be monitored in all patients during therapy, particularly in patients with renal impairment (see section *Warnings and Precautions*).

In patients with severe leukopenia, neutropenia, anemia and/or thrombocytopenia treatment with hematopoietic growth factors and/or the interruption of therapy is recommended (see *Undesirable Effects*). Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Valganciclovir should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section *Drug Interactions*).

Zidovudine and valganciclovir each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage (see section *Drug Interactions*).

Didanosine plasma concentrations may increase during concomitant use with valganciclovir; therefore patients should be closely monitored for didanosine toxicity (see section *Drug Interactions*).

Concomitant use of other drugs that are known to be myelosuppressive or associated with renal impairment with valganciclovir may result in added toxicity (see section *Drug Interactions*).

The bioavailability of ganciclovir from valganciclovir is 10-fold higher than from ganciclovir capsules. Valganciclovir tablets cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of valganciclovir tablets (see section *Dosage and Method of Administration and Overdose*).

<u>Drug abuse and dependence</u>

No information is available for drug abuse and dependence with valganciclovir.

INTERACTIONS WITH OTHER MEDICAMENTS

Drug interactions with valganciclovir

Valganciclovir is the pro-drug of ganciclovir; therefore, interactions associated with ganciclovir are expected.

Imipenem-cilastatin

Seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly and a pharmacodynamic interaction between these two drugs cannot be discounted. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section Warnings and Precautions).

Potential drug interactions

Toxicity may be enhanced when ganciclovir / valganciclovir is co-administered with other drugs known to be myelosuppressive or associated with renal impairment. This includes nucleoside analogues (e.g. zidovudine, didanosine, stavudine), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and antiinfective
agents (trimethoprim/sulphonamides, dapsone, amphotericin B, flucytosine, pentamidine). Therefore, these drugs should only be considered for concomitant use with valganciclovir if the potential benefits outweigh the potential risks (see section Warnings and Precautions).

Zidovudine

Both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, a pharmacodynamic interaction may occur during concomitant administration of these drugs, some patients may not tolerate concomitant therapy at full dosage (see section Warnings and Precautions).

Didanosine

Didanosine plasma concentrations were found to be consistently raised when given with IV ganciclovir. At intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67% has been observed confirming a pharmacokinetic interaction during the concomitant administration of these drugs. There was no significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (e.g. pancreatitis) (see section Warnings and Precautions).

Probenecid

Probenecid given with oral ganciclovir resulted in statistically significantly decreased renal clearance of ganciclovir (20%) leading to statistically significantly increased exposure (40%). These changes were consistent with a mechanism of interaction involving competition for

renal tubular excretion. Therefore patients taking probenecid and valganciclovir should be closely monitored for ganciclovir toxicity.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of valganciclovir for use in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of Valganciclovir should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus. Reprotoxicity studies have not been repeated with valganciclovir because of the rapid and extensive conversion to ganciclovir. ~~In animal studies ganciclovir *was* associated with reproductive toxicity and teratogenicity.~~ The safe use of Valganciclovir during labor and delivery has not been established

Lactation

Peri- and postnatal development has not been studied with valganciclovir or with ganciclovir but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. ~~Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats.~~ Therefore, a decision should be made to discontinue the drug or discontinue nursing taking into consideration the potential benefit of Valganciclovir to the nursing mother.

Fertility

~~In animal studies ganciclovir was found to impair fertility.In renal transplant patients receiving valganciclovir for CMV prophylaxis for up to 200 days were compared to an untreated control group.~~

Spermatogenesis was inhibited during treatment with Valganciclovir. ~~At follow-up, approximately six months after treatment discontinuation, the mean sperm density in treated patients was comparable to that observed in the untreated control group. In Valganciclovir treated patients, all patients with normal sperm density (n=7) and 8/13 patients with low sperm density at baseline, had normal density after treatment cessation. In the control group, all patients with normal sperm density (n=6) and 2/4 patients with low sperm density at baseline, had normal density at the end of follow-up.~~

Contraception

Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment. Sexually active men are recommended to use condoms during and for at least 90 days after cessation of treatment with valganciclovir, unless it is certain that the female partner is not at risk of becoming pregnant (see section *Warnings and Precautions*).

Women of childbearing potential should be advised to use effective contraception during treatment. Male patients should be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir (see section *Warnings and Precautions*).
The safety of valganciclovir for use in human pregnancy has not been established. The use of valganciclovir should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

UNDESIRABLE EFFECTS

Experience with valganciclovir

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir usage can therefore be expected to occur with Valganciclovir. All of the adverse events observed in valganciclovir with ganciclovir. Therefore, adverse drug reactions reported with IV or oral ganciclovir (no longer available) or with valganciclovir are included in the table of adverse reactions (see Table 3).
Most serious and frequent adverse drug reactions are haematological reactions and include neutropenia, anemia and thrombocytopenia. Frequencies are presented as CIOMS frequency categories defined as very common , common , uncommon , rare and very rare.

The overall safety profile of ganciclovir/valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. Pyrexia, candida infections, depression, severe neutropenia (ANC <500/μL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

Table 3 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy

ADR (MedDRA) System Organ Class	**Frequency Category**
Infections and infestations	
Candida infections including oral candidiasis.	Very Common
Upper respiratory tract infection	
Sepsis	Common
Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders	

Neutropenia	Very common
Anemia	
Thrombocytopenia	Common
Leukcopenia	
Pancytopenia	
Bone marrow failure	Uncommon
Aplastic anaemia	Rare
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders	
Hypersensitivity	Common
Anaphylactic reaction*	Rare
Metabolic and nutrition disorders	
Decreased appetite	Very common
Weight decreased	Common
Psychiatric disorders	
Depression	Common
Confusional state	
Anxiety	
Agitation	Uncommon
Psychotic disorder	
Thinking abnormal	
Hallucinations	
Nervous system disorders	
Headache	Very common
Insomnia	Common
Neuropathy peripheral	
Dizziness	
Paraesthesia	
Hypoaesthesia	
Seizures	
Dysgeusia (taste disturbance)	
Tremor	Uncommon
Eye disorders	
Visual impairment	Common
Retinal detachment**	
Vitreous floaters	
Eye pain	
Conjunctivitis	

Macular oedema	
Ear and labyrinth disorders	
Ear pain	Common
Deafness	Uncommon
Cardiac disorders	
Cardiac Aarrhythmias	Uncommon
Vascular disorders*:*	
Hypotension	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Very common
Dyspnoea	
Gastrointestinal disorders	
Diarrhea	Very common
Nausea	
Vomiting	
Abdominal pain	
Dyspepsia	Common
Flatulence	
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders	
Blood alkaline phosphatase increased	Common
Hepatic function abnormal	
Aspartate aminotransferase increased	
Alanine aminotransferase increased	
Skin and subcutaneous tissues disorders	
Dermatitis	Very common
Night sweats	Common
Pruritus	
Rash	
Alopecia	
Dry skin	Uncommon
Urticaria	
Musculo-skeletal and connective tissue disorders	

Back pain	Common
Myalgia	
Arthralgia	
Muscle spasms	
Renal and urinary disorders	
Renal impairment	Common
Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Uncommon
Hematuria	
Reproductive system and breast disorders	
Infertility male	Uncommon
General disorders and administration site conditions	
Pyrexia	Very common
Fatigue	
Pain	Common
Chills	
Malaise	
Asthenia	
Chest pain	Uncommon

** The frequencies of these adverse reactions are derived from post-marketing experience.*

***Retinal detachment has only been reported in HIV patients treated for CMV retinitis.*

Description of selected adverse reactions

Neutropenia

The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalizes within 2 to 5 days after discontinuation of the drug or dose reduction (see section *Warnings and Precautions*).

Thrombocytopenia

Patients with low baseline platelet counts (< 100,000 / µl) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with HIV (see section *Warnings and Precautions*). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Influence of treatment duration or indication on adverse reactions

Severe neutropenia (ANC <500/µL) is seen more frequently in CMV retinitis patients ~~(16%)~~ undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir.

~~There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV retinitis patients. However, impaired renal function is a feature more frequent in solid organ transplantation patients. The overall safety profile of valganciclovir did not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.~~

~~Laboratory abnormalities~~

~~Laboratory abnormalities reported in adult CMV retinitis patients and SOT patients receiving valganciclovir until Day 100 post transplant are listed in Table 4. The incidence of laboratory abnormalities was comparable with the extension of prophylaxis up to 200 days in high risk kidney transplant patients.~~

~~Table 4: Laboratory abnormalities~~

~~Laboratory abnormalities~~	~~CMV Retinitis Patients~~	~~Solid Organ Transplant Patients (Dosing until Day 100 Post-Transplant)~~	
	~~Valganciclovir (n=370)~~	~~Valganciclovir (n=244)~~	~~Oral ganciclovir (n=126)~~
	~~%~~	~~%~~	~~%~~
~~Neutropenia (ANC/µl) <500~~	~~16~~	~~5~~	~~3~~
~~500 - <750~~	~~17~~	~~3~~	~~2~~
~~750 - <1000~~	~~17~~	~~5~~	~~2~~
~~Anemia (haemoglobin g/dl) <6.5~~	~~7~~	~~1~~	~~2~~
~~6.5 - <8.0~~	~~10~~	~~5~~	~~7~~
~~8.0 - <9.5~~	~~14~~	~~31~~	~~25~~
~~Thrombocytopenia (platelets/µl) <25000~~	~~3~~	~~0~~	~~2~~
~~25000 - <50000~~	~~5~~	~~1~~	~~3~~
~~50000 - <100000~~	~~21~~	~~18~~	~~21~~
~~Serum creatinine (mg/dl) >2.5~~	~~2~~	~~14~~	~~21~~
~~>1.5 - 2.5~~	~~11~~	~~45~~	~~47~~

Postmarketing experience

Safety reports from the postmarketing setting are consistent with safety data with valganciclovir and ganciclovir (see section Undesirable Effects - Table 3).

The most frequently reported adverse reactions, regardless of seriousness that were considered related (remotely, possibly or probably) to valganciclovir ~~by the investigator~~ were neutropenia, anemia, diarrhea and nausea.

Prevention of CMV disease in transplantation

The most frequently reported adverse reactions regardless of seriousness that were considered related (remotely, possibly or probably) to valganciclovir in solid organ transplant patients ~~treated until Day 100 post transplant~~ were leuekopenia, diarrheoa, nausea, and neutropenia and were leukopenia, neutropenia, anaemia and diarrhoea in kidney transplant patients. ~~treated until Day 200 post-transplant~~

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

OVERDOSE

Overdose experience with valganciclovir

It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see section Warnings and Precautions and, Dosage and Method of Administration).

Reports of overdoses with intravenous ganciclovir, some with fatal outcomes, experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

- Hematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leukopenia, neutropenia, granulocytopenia
- Hepatotoxicity: hepatitis, liver function disorder
- Renal toxicity: worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.
- Gastrointestinal toxicity: abdominal pain, diarrhea, vomiting
- Neurotoxicity: generalised tremor, seizure
- Hemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section Pharmacokinetics)

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse reactions such as seizures, dizziness, and confusion have been reported with the use of valganciclovir and/or ganciclovir (see section Undesirable Effects). If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

INCOMPATIBILITY

Not applicable

STORAGE AND HANDLING INSTRUCTION

Store below 30°C.

Special Instructions for Use, Handling and Disposal

Tablets should not be broken or crushed. Since Valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section *Warnings and Precautions*). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water or plain water if sterile water is not available.
This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/ expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available in your location

SHELF LIFE

24 Months

PACKAGING INFORMATION

Cearton containing container pack (HDPE bottle with child-resistant caps) of 60 tablets.

MANUFACTURED BY

Cipla Limited
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DATE OF REVISION

February 2022~~2021~~