For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

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Valganciclovir Tablets USP 450mg

CYMGAL® सिमगल

WARNING
- **THE CLINICAL TOXICITY OF VALGANCICLOVIR, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA.**
- **IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.**

Composition:
Each film coated tablet contains :
Valganciclovir Hydrochloride USP
Eq. to Valganciclovir 450mg
Excipients q.s.
Colours: Ferric Oxide USP-NF Red & Titanium Dioxide IP

ATC code: J05AB14

DOSAGE FORM
Tablets

DESCRIPTION
Valganciclovir tablets contain Valganciclovir Hydrochloride (Valganciclovir HCl), a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of two diastereomers. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

PHARMACOLOGY
Pharmacodynamics
Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of two diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits replication of cytomegalovirus *in vitro* and *in vivo*.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly (half-life 18 hours). 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 ganciclovir triphosphate.

Pharmacokinetics
Because the major elimination pathway for ganciclovir is renal, dosage reductions according to creatinine clearance are required.

Absorption
Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from Valganciclovir tablets following administration with food was approximately 60%. Systemic exposure to the prodrug, Valganciclovir, is transient and low, and the AUC_{24} and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects
When Valganciclovir tablets were administered with a high fat meal containing approximately 600 total calories at a dose of 875 mg once daily to 16 HIVpositive subjects, the steady-state ganciclovir AUC increased by 30%, and the C_{max} increased by 14%, without any prolongation in time to peak plasma concentrations (T_{max}).

Valganciclovir tablets should be administered with food.

Distribution
Due to the rapid conversion of Valganciclovir to ganciclovir, plasma protein binding of Valganciclovir was not determined. Plasma protein binding of ganciclovir is 1% to 2% over concentrations of 0.5 and 51 µg/mL. When ganciclovir was administered intravenously, the steady-state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=69).

After administration of Valganciclovir tablets, no correlation was observed between ganciclovir AUC and reciprocal weight; oral dosing of Valganciclovir tablets according to weight is not required.

Metabolism
Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabeled ganciclovir (1000 mg single dose) accounted for more than 1% to 2% of the radioactivity recovered in the feces or urine.

Elimination
The major route of elimination of Valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.07 ± 0.64 mL/min/kg (n=68) while renal clearance was 2.99 ± 0.67 mL/min/kg (n=16).

The terminal half-life ($t_{1/2}$) of ganciclovir following oral administration of Valganciclovir tablets to either healthy or HIV-positive/CMV-positive subjects was 4.08 ± 0.76 hours (n=73), and that following administration of intravenous ganciclovir was 3.81 ± 0.71 hours (n=69). In heart, kidney, kidney-pancreas, and liver transplant patients, the terminal elimination half-life of ganciclovir following oral administration of Valganciclovir was 6.48 ± 1.38 hours, and following oral administration of ganciclovir capsules was 8.56 ± 3.62 hours.

INDICATIONS
Adult Patients
Treatment of Cytomegalovirus (CMV) Retinitis: CYMGAL® tablets are indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Prevention of CMV Disease: CYMGAL® tablets are indicated for the prevention of CMV disease in kidney, heart, or kidney-pancreas transplant patients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])

Limitations of Use
CYMGAL® is not indicated for use in liver transplant patients
The safety and efficacy of Valganciclovir have not been established for:
- Prevention of CMV disease in solid organ transplants other than those indicated
- Treatment of congenital CMV disease

DOSAGE AND ADMINISTRATION
- CYMGAL® should be taken with food
- The bioavailability of ganciclovir from Valganciclovir is significantly higher than from ganciclovir capsules. Therefore, Valganciclovir tablets cannot be substituted for ganciclovir capsules on a one-to-one basis.

Adult Patients With Normal Renal Function
Treatment of CMV Retinitis:
- Induction: The recommended dose is 900 mg (two 450 mg tablets) twice a day for 21 days.
- Maintenance: Following induction treatment, or in adult patients with inactive CMV retinitis, the recommended dose is 900 mg (two 450 mg tablets) once a day.

Prevention of CMV Disease:
- For adult patients who have received a heart or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once a day starting within 10 days of transplantation until 100 days post transplantation
- For adult patients who have received a kidney transplant, the recommended dose is 900 mg (two 450 mg tablets) once a day starting within 10 days of transplantation until 200 days post-transplantation

Renal impairment
Dosage recommendations for adult patients with reduced renal function are provided below:

*An estimated creatinine clearance is calculated from serum creatinine by the following formulas:

$$\text{For males} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (\text{serum creatinine [mg/dL]})}$$

$$\text{For females} = 0.85 \times \text{male value}$$

CrCl* (mL/min)	Induction Dose	Maintenance / Prevention Dose
≥ 60	900 mg twice daily	900 mg once daily
40 - 59	450 mg twice daily	450 mg once daily
25 - 39	450 mg once daily	450 mg every 2 daily
10 - 24	450 mg every 2 days	450 mg twice weekly
< 10 (on hemodialysis)	not recommended	not recommended

For adult patients on hemodialysis (CrCl <10 mL/min), a dose recommendation for CYMGAL® cannot be given.

CONTRAINDICATIONS
CYMGAL® is contraindicated in patients who have had a demonstrated clinically significant hypersensitivity reaction (e.g., anaphylaxis) to Valganciclovir, ganciclovir, or any component of the formulation.

WARNINGS AND PRECAUTIONS
Haematologic effects
Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow aplasia, and aplastic anemia have been reported in patients treated with Valganciclovir or ganciclovir. CYMGAL® should not be administered if the absolute neutrophil count is less than 500 cells/µL, the platelet count is less than 25,000/µL, or the hemoglobin is less than 8 g/dL. CYMGAL® should also be used with caution in patients with pre-existing cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may worsen with continued dosing. Cell counts usually begin to recover within 3 to 7 days after discontinuing drug. Due to the frequency of neutropenia, anemia, and thrombocytopenia in patients receiving CYMGAL®, complete blood counts with differential and platelet counts should be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µL at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to CYMGAL® because of increased plasma concentration of ganciclovir after CYMGAL® administration.

Impairment of fertility
Animal data indicate administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses but irreversible at higher doses. In men, Valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate suppression of fertility in females may occur.

Teratogenesis and Mutagenesis
Animal data indicate ganciclovir is teratogenic and mutagenic. Therefore, Valganciclovir should be considered to have the potential to cause birth defects and cancers in humans. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with Valganciclovir. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with Valganciclovir.

Carcinogenesis
Animal data indicate that administration of ganciclovir is carcinogenic. Valganciclovir should therefore be considered a potential carcinogen in humans.

Acute Renal Failure
Acute renal failure may occur in:
- Elderly patients with or without reduced renal function. Caution should be exercised when administering CYMGAL® to geriatric patients, and dosage reduction is recommended for those with impaired renal function
- Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering CYMGAL® to patients receiving potential nephrotoxic drugs
- Patients without adequate hydration. Adequate hydration should be maintained for all patients.

Drug Interactions
In vivo drug-drug interaction studies were not conducted with Valganciclovir. However, because Valganciclovir is rapidly and extensively converted to ganciclovir, drug-drug interactions associated with ganciclovir will be expected for Valganciclovir. Established and other potentially significant drug interactions conducted with ganciclovir are listed in Table 1.

Table 1: Established and Other Potentially Significant Drug Interactions with Ganciclovir

Name of the Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Clinical Comment
Zidovudine	↓ Ganciclovir ↑ Zidovudine	Zidovudine and Valganciclovir each have the potential to cause neutropenia and anemia
Probenecid	↑ Ganciclovir	Patients taking probenecid and Valganciclovir should be monitored for evidence of ganciclovir toxicity
Mycophenolate Mofetil (MMF)	↔ Ganciclovir (in patients with normal renal function) ↔ MMF (in patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of MMF metabolites and ganciclovir may increase
Didanosine	↓ Ganciclovir ↑ Didanosine	Patients should be closely monitored for didanosine toxicity

Pregnancy
After oral administration, Valganciclovir (prodrug) is converted to ganciclovir (active drug) and, therefore, is expected to have reproductive toxicity effects similar to ganciclovir. There are no adequate and well-controlled studies of Valganciclovir or ganciclovir use in pregnant women. In animal studies of ganciclovir, embryo-fetal toxicity and structural malformations occurred. Valganciclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
It is not known whether Valganciclovir (prodrug) or ganciclovir (active drug) are excreted in human milk. Because Valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, serious adverse events may occur from ganciclovir exposure in nursing infants. Because of the potential for serious adverse events in nursing infants, a decision should be made whether to discontinue nursing or discontinue drug, taking into consideration the importance of the drug to the mother.

Renal Impairment
Dose reduction is recommended when administering CYMGAL® to patients with renal impairment.

For adult patients on hemodialysis (CrCl <10 mL/min) CYMGAL® tablets should not be used. Adult hemodialysis patients should use ganciclovir in accordance with the dose reduction algorithm cited in ganciclovir complete product information.

Hepatic Impairment
The safety and efficacy of Valganciclovir tablets have not been studied in patients with hepatic impairment.

Paediatric Use
Valganciclovir can be used for the prevention of CMV disease in kidney or heart transplant pediatric patients 4 months to 16 years of age at risk for developing CMV disease, using an appropriate formulation.

Geriatric Use
Studies on Valganciclovir have not been conducted in adults older than 65 years of age. Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valganciclovir is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly.

UNDESIRABLE EFFECTS
The following serious adverse events are discussed in greater detail in other sections of the labeling:
- Hematologic adverse events [see Warnings and Precautions]
- Acute renal failure [see Warnings and Precautions]

The most common adverse events and laboratory abnormalities reported in at least one indication by ≥20% of adult patients treated with Valganciclovir tablets are diarrhea, pyrexia, nausea, tremor, neutropenia, anemia, graft rejection, thrombocytopenia, and vomiting.

Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with Valganciclovir tablets.

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Treatment of CMV retinitis in AIDS patients
In a clinical study for the treatment of CMV retinitis in HIV-infected patients, the adverse events reported by patients receiving Valganciclovir tablets (n=79) or intravenous ganciclovir (n=79) for 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose), respectively, included diarrhea (16%, 10%), nausea (8%, 14%), headache (9%, 5%), and catheter-related infections (3%, 11%). The incidence of adverse events was similar between the group who received Valganciclovir tablets and the group who received intravenous ganciclovir, with the exception of catheter-related infections, which occurred with greater frequency in patients randomized to receive intravenous ganciclovir. The frequencies of neutropenia (ANC < 500/µL) were 11% for patients receiving Valganciclovir tablets compared with 13% for patients receiving intravenous ganciclovir. Anemia (Hgb < 8 g/dL) occurred in 8% of patients in each group. Other laboratory abnormalities occurred with similar frequencies in the two groups.

Adverse events and abnormal laboratory values data are available for 370 patients who received maintenance therapy with Valganciclovir tablets 900 mg once daily in two open-label clinical trials. Approximately 252 (68%) of these patients received Valganciclovir tablets for more than nine months (maximum duration was 36 months).

Table 2 and Table 3 show the pooled adverse event data and abnormal laboratory values from these patients.

Table 2: Pooled selected adverse events reported in ≥5% of patients who received Valganciclovir tablets maintenance therapy for CMV retinitis

	Patients with CMV Retinitis
Adverse Events According to Body System	**Valganciclovir Tablets (N=370) %**
Gastrointestinal system	
Diarrhea	41
Nausea	30
Vomiting	21
Abdominal pain	15
Body as a whole	
Pyrexia	31
Headache	22
Central and peripheral nervous system	
Insomnia	16
Peripheral neuropathy	9
Paresthesia	8
Special senses	
Retinal detachment	15

Table 3: Pooled Laboratory Abnormalities Reported in Patients Who Received Valganciclovir Tablets Maintenance Therapy for the Treatment of CMV Retinitis

	Patients with CMV Retinitis
Laboratory Abnormalities	**Valganciclovir Tablets (N=370) %**
Neutropenia: ANC/µL	
< 500	19
500 – < 750	17
750 – < 1000	17
Anemia: Hemoglobin g/dL	
< 6.5	7
6.5 – < 8.0	13
8.0 – < 9.5	16
Thrombocytopenia: Platelets/µL	
< 25000	4
25000 – < 50000	6
50000 – < 100000	22
Serum Creatinine: mg/dL	
> 2.5	3
> 1.5 – 2.5	12

Prevention of CMV Disease in Selected Solid Organ Transplantation
Table 4 shows selected adverse events regardless of severity and drug relationship with an incidence of ≥5% from a clinical trial (up to 28 days after study treatment) where heart, kidney, kidney-pancreas and liver transplant patients received Valganciclovir tablets (N=244) or oral ganciclovir (N=126) until Day 100 post-transplant. The majority of the adverse events were of mild or moderate intensity.

Table 4: Percentage of selected grades 1-4 adverse events reported in ≥ 5% of patients from a study of selected solid organ transplant patients

Adverse Event	Valganciclovir Tablets (N=244) %	Oral Ganciclovir (N=126) %
Diarrhea	30	29
Tremors	28	25
Graft rejection	24	30
Nausea	23	23
Headache	22	27
Insomnia	20	16
Hypertension	18	15
Vomiting	16	14
Pyrexia	13	14

The overall safety profile of Valganciclovir did not change with the extension of prophylaxis until Day 200 post-transplant in high risk kidney transplant patients (see Table 5).
Table 5: Percentage of Selected Grades 1-4 Adverse Events reported in ≥5% of Patients from a Study of Kidney Transplant Patients

Adverse Event	Valganciclovir Tablets Day 100 Post-transplant (N=164) %	Valganciclovir Tablets Day 200 Post-transplant (N=156) %
Diarrhea	26	31
Tremors	12	17
Hypertension	13	12
Nausea	11	11
Pyrexia	12	9
Transplant rejection	9	6
Headache	10	6
Insomnia	7	6
Vomiting	3	6

Adverse events not included in Table 4 and Table 5, which either occurred at a frequency of ≥ 5% in clinical studies with solid organ transplant patients, or were selected serious adverse events reported in studies with patients with CMV retinitis or in studies with solid organ transplant patients with a frequency of < 5% are listed below.

Allergic reactions: Valganciclovir hypersensitivity
Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia
Central and peripheral nervous system: paresthesia, dizziness (excluding vertigo), convulsion
Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, abdominal distention, ascites
General disorders and administration site disorders: fatigue, pain, edema, peripheral edema, weakness
Hemic system: anemia, neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, aplastic anemia
Hepatobiliary disorders: abnormal hepatic function
Infections and infestations: pharyngitis/nasopharyngitis, upper respiratory tract infection, urinary tract infection, local and systemic infections and sepsis, postoperative wound infection
Injury, poisoning, and procedural complications: postoperative complications, postoperative pain, increased wound drainage, wound dehiscence
Metabolism and nutrition disorders: hyperkalemia, hypokalemia, hypomagnesemia, hyperglycemia, appetite decreased, dehydration, hypophosphatemia, hypocalcemia
Musculoskeletal and connective tissue disorders: back pain, arthralgia, muscle cramps, limb pain
Psychiatric disorders: depression, psychosis, hallucinations, confusion, agitation
Renal and urinary disorders: renal impairment, dysuria, decreased creatinine clearance
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, rhinorrhea, pleural effusion
Skin and subcutaneous tissue disorders: dermatitis, pruritus, acne
Vascular disorders: hypotension

Table 6: Laboratory abnormalities reported in a study of kidney transplant patients*

patients* Laboratory Abnormalities	Valganciclovir Tablets Day 100 Post-transplant (N=164) %	Valganciclovir Tablets Day 200 Post-transplant (N=156) %
Neutropenia: ANC/µL		
< 500	9	10
500 – < 750	6	6
750 – < 1000	7	5
Anemia: Hemoglobin g/dL		
< 6.5	0	1
6.5 – < 8.0	5	1
8.0 – < 9.5	17	15
Thrombocytopenia: Platelets/µL		
< 25000	0	0
25000 – < 50000	1	0
50000 – < 100000	7	3
Serum Creatinine: mg/dL		
> 2.5	17	14
> 1.5 – 2.5	50	48

*Laboratory abnormalities are those reported by investigators

Postmarketing Experience
In general, the adverse events reported during the postmarketing use of Valganciclovir were similar to those identified during the clinical trials and to those reported during the postmarketing use of ganciclovir.

OVERDOSAGE
Experience with Valgancidovir tablets
One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's estimated degree of renal impairment.

It is expected that an overdose of Valganciclovir tablets could also possibly result in increased renal toxicity.

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of Valganciclovir tablets. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered.

Experience with Intravenous Ganciclovir
Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during postmarketing experience. The majority of patients experienced one or more of the following adverse events:
- *Hematological toxicity:* pancytopenia, bone marrow depression, medullary aplasia, leukopenia, neutropenia, granulocytopenia
- *Hepatotoxicity:* hepatitis, liver function disorder
- *Renal toxicity:* worsening of hematuria in a patient with pre-existing renal impairment, acute renal failure, elevated creatinine
- *Gastrointestinal toxicity:* abdominal pain, diarrhea, vomiting
- *Neurotoxicity:* generalized tremor, convulsion

HANDLING INSTRUCTIONS
Caution should be exercised in the handling of CYMGAL® tablets. 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. Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumour agents (i.e. carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published. However, there is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate (see References)

Shelf life: Please refer to carton/strip.

Storage:
Store at 25°C, excursions permitted between 15°C to 30°C.
Keep out of reach of children.

PACKAGING INFORMATION
Available as strip pack of 10 tablets.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

Leaflet revised August 2019

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

References

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