Vaglonax®
Valganciclovir

FORMS AND PRESENTATION

Vaglonax®: 450mg; Film coated tablets; Box of 60.

COMPOSITION

Vaglonax®: Each film coated tablet contains valganciclovir hydrochloride equivalent to valganciclovir 450 mg.

Excipients: Microcrystalline cellulose, crospovidone, povidone, stearic acid, hydroxyl propylmethyl cellulose, titanium dioxide, polyethylene glycol, red iron oxide, polysorbate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05A B14.

Mechanism of action

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolized to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and 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, HHV8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV).

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. Triphosphate metabolism has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 and between 6 and 24 hours respectively, after the removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells.

Pharmacokinetic properties

Absorption

Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolized in the intestinal wall and liver to ganciclovir. Systemic exposure to valganciclovir is transient and low. The bioavailability of ganciclovir from oral dosing of valganciclovir is approximately 60 % across all the patient populations studied and the resultant exposure to ganciclovir is similar to that after its intravenous administration. For comparison, the bioavailability of ganciclovir after administration of 1000 mg oral ganciclovir (as capsules) is 6 - 8 %.

Food effect

When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30 %) and mean ganciclovir Cmax values (approximately 14 %) than in the fasting state. Also, the inter-individual variation in exposure of ganciclovir decreases when taking valganciclovir with food. valganciclovir has only been administered with food in clinical studies.

Therefore, it is recommended that valganciclovir be administered with food.

Distribution

Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. The steady state volume of distribution (Vd) of ganciclovir after intravenous administration was 0.680 ± 0.161 l/kg (n=114).

Biotransformation

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

Elimination

Following dosing with oral valganciclovir, the drug is rapidly hydrolyzed to ganciclovir. Ganciclovir is eliminated from the systemic circulation by glomerular filtration and active tubular secretion. In patients with normal renal function greater than 90% of IV administered ganciclovir was recovered un-metabolized in the urine within 24 hours. In patients with normal renal function the post-peak plasma concentrations of ganciclovir after administration of valganciclovir decline with a half-life ranging from 0.4 h to 2.0 h.

INDICATIONS

Vaglonax® is indicated for the:

• Induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS).

• Prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

CONTRAINDICATIONS

Vaglonax® is contra-indicated:

• In patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients listed.

• During breast-feeding.

PRECAUTIONS

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

Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. Valganciclovir should be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers.

Women of child bearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Men must be advised to practice barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy. Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term.

Myelosuppression

Severe leukopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anaemia 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 level is less than 8 g/dl. When extending prophylaxis beyond 100 days the possible risk of developing leukopenia and neutropenia should be taken into account.

Valganciclovir should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts should be monitored regularly during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and paediatrics, at a minimum each time the patient attends the transplant clinic. In patients developing severe leukopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered.

Difference in bioavailability with oral ganciclovir

The bioavailability of ganciclovir after a single dose of 900 mg valganciclovir is approximately 60 %, compared with approximately 6 % after administration of 1000 mg oral ganciclovir (as capsules). Excessive exposure to ganciclovir may be associated with life-threatening adverse reactions. Therefore, careful adherence to the dose recommendations is advised when instituting therapy, when switching from induction to maintenance therapy and in patients who may switch from oral ganciclovir to valganciclovir 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.

Renal impairment

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required.

Valganciclovir film-coated tablets should not be used in patients on haemodialysis.

Use with other medicines

Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. Valganciclovir film-coated tablets should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks.

Patients treated with Valganciclovir film-coated tablets and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity.

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. If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

PREGNANCY AND LACTATION

Contraception in males and females

As a result of the potential for reproductive toxicity and teratogenicity, women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Male patients must be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir unless it is certain that the female partner is not at risk of pregnancy.

Pregnancy

The safety of Valganciclovir for use in pregnant women has not been established. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir there is a theoretical risk of teratogenicity in humans.

Valganciclovir should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the foetus.

Lactation

Breast-feeding must be discontinued during treatment with valganciclovir.

DRUG INTERACTIONS

Drug interactions with valganciclovir

In-vivo drug interaction studies with Valganciclovir have not been performed. Since valganciclovir is extensively and rapidly metabolized to ganciclovir; drug interactions associated with ganciclovir will be expected for valganciclovir.

Drug interactions with ganciclovir

Probenecid: Patients taking probenecid and valganciclovir should be closely monitored for ganciclovir toxicity.

Didanosine: Patients should be closely monitored for didanosine toxicity e.g pancreatitis.

Other antiretrovirals: Cytochrome P450 isoenzymes play no role in ganciclovir pharmacokinetics. As a consequence, pharmacokinetic interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors are not anticipated.

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.

Zidovudine: Both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia. A pharmacodynamic interaction may occur during concomitant administration of these drugs. Some patients may not tolerate concomitant therapy at full dosage.

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 (e.g. zidovudine, didanosine, stavudine) and nucleotide analogues (e.g. tenofovir, adefovir), immunosuppressants (e.g. ciclosporin, tacrolimus, mycophenolate mofetil), antineoplastic agents (e.g. doxorubicin, vinblastine, vincristine, hydroxyurea) and anti-infective 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.

ADVERSE EFFECTS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

- Infections and infestations: candida infections including oral candidiasis, upper respiratory tract infection (very common); sepsis, influenza, cellulitis, urinary tract infection (Common).
- Blood and lymphatic system disorders: neutropenia, anemia (very common); thrombocytopenia, leucopenia, pancytopenia (common); bone marrow failure (uncommon); aplastic anemia, agranulocytosis, granulocytopenia (rare).
- Immune system disorders: hypersensitivity (common), anaphylactic reaction (rare).
- Metabolic and nutrition disorders: decreased appetite (very common), weight decreased (common).
- Psychiatric disorders: depression, anxiety, confusional state (common); Agitation, psychotic disorder, thinking abnormal, hallucination (uncommon).
- Nervous system disorders: headache (very common); insomnia, dysgeusia, (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness, Seizure (common); tremor (uncommon).
- Eye disorders: macular oedema, retinal detachment, vitreous floaters, eye pain, visual impairment, conjunctivitis (common).
- Ear and labyrinth disorders: ear pain (common); deafness (uncommon).
- Cardiac disorders: arrhythmia (uncommon).
- Vascular disorders: hypotension (common).
- Respiratory, thoracic and mediastinal disorders: dyspnoea, Cough (very common).
- Gastrointestinal disorders: diarrhea, nausea, abdominal pain, vomiting (very common); upper abdominal pain, dyspepsia, constipation, flatulence, dysphagia, mouth ulceration, abdominal distension, pancreatitis (common).
- Hepatobiliary disorders: hepatic function abnormal, blood alkaline phosphatase increased, aspartate aminotransferase increased (common); alanine aminotransferase increased (common).
- Skin and subcutaneous disorders: dermatitis (very common); night sweats, pruritus, rash, alopecia (common); urticaria, dry skin (uncommon).
- Musculoskeletal, Connective Tissue and Bone Disorders: back pain, myalgia, arthralgia, muscle spasms (common).
- Renal and urinary disorder: creatinine clearance renal decreased, renal impairment, blood creatinine increased (common); haematuria, renal failure (uncommon).

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- Reproductive system and breast disorders: male infertility (uncommon).
- General disorders and administration site conditions: fatigue, pyrexia (very common); chills, pain, malaise, asthenia (common); chest pain (uncommon).

Severe thrombocytopenia may be associated with potentially life-threatening bleeding.

Pediatric population

The most frequently reported adverse reactions on treatment in pediatric were diarrhea, nausea, neutropenia, leucopenia and anemia.

In solid organ transplant patients, the overall safety profile was similar in pediatric patients as compared to adults. However, the rates of certain adverse events, such as upper respiratory tract infection, pyrexia, abdominal pain and dysuria, which may be characteristic of the pediatric population, were reported in higher incidence in pediatrics than in adults. Neutropenia was also reported with slightly higher incidence in the two studies conducted in pediatric solid organ transplant patients as compared to adults, but there was no correlation between neutropenia and infectious adverse events in the pediatric population.

In kidney transplant pediatric patients, prolongation of valganciclovir exposure up to 200 days was not associated with an overall increase in the incidence of adverse events. The incidence of severe neutropenia (ANC < 500/µL) was higher in pediatric kidney patients treated until Day 200 as compared to pediatric patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200.

Only limited data are available in neonates or infants with symptomatic congenital CMV infection treated with valganciclovir, however the safety appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

DOSAGE AND ADMINISTRATION

Posology

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

Valganciclovir is rapidly and extensively metabolized to ganciclovir after oral dosing. Oral valganciclovir 900 mg b.i.d. is therapeutically equivalent to intravenous ganciclovir 5 mg/kg b.i.d.

Treatment of cytomegalovirus (CMV) retinitis

Adult patients

Induction treatment of CMV retinitis

For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir (two Vaglonax® 450 mg tablets) twice a day for 21 days and, whenever possible, taken with food. Prolonged induction treatment may increase the risk of bone marrow toxicity.

Maintenance treatment of CMV retinitis:

Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900mg valganciclovir (two Vaglonax® 450 mg tablets) once daily and, whenever possible, taken with food. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

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

Paediatric population

The safety and efficacy of Valganciclovir in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.

Prevention of CMV disease in solid organ transplantation

Adult patients

For kidney transplant patients, the recommended dose is 900 mg (two Vaglonax® 450 mg tablets) once daily, starting within 10 days post-transplantation and continuing until 100 days post-transplantation. Prophylaxis may be continued until 200 days post-transplantation.

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg (two Vaglonax® 450 mg tablets) once daily, starting within 10 days post-transplantation and continuing until 100 days post-transplantation.

Whenever possible, the tablets should be taken with food.

Paediatric population

In paediatric solid organ transplant patients, aged from birth, who are at risk of developing CMV disease, the recommended once daily dose of Vaglonax® is based on body surface area (BSA) and creatinine clearance (Clcr) derived from Schwartz formula (ClcrS), and is calculated using the following equation: Paediatric Dose (mg) = 7 x BSA x ClcrS.

For paediatric kidney transplant patients, the recommended once daily mg dose (7 x BSA x ClcrS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.

For paediatric patients who have received a solid organ transplant other than kidney, the recommended once daily mg dose (7x BSA x ClcrS) should start within 10 days post-transplantation and continue until 100 days post-transplantation.

All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, Vaglonax® film-coated tablets may be used if the calculated doses are within 10% of available tablet doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.

It is recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during the prophylaxis period.

Special dosage instructions

Paediatric population:

Dosing of paediatric SOT patients is individualized based on a patient's renal function, together with body surface area.

Elderly patients:

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, Vaglonax® should be administered to elderly patients with special consideration of their renal status (see table below).

Patients with renal impairment:

Serum creatinine levels or estimated creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance, as shown in the table below. An estimated creatinine clearance (ml/min) can be related to serum creatinine by the following formulae:

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

For females = 0.85 × male value.

Creatinine Clearance (ml/min)	Induction dose of Valganciclovir	Maintenance / Prevention dose of Valganciclovir
≥60	900 mg (2 tablets) twice daily	900 mg (2 tablets) once daily
40 - 59	450 mg (1 tablet) twice daily	450 mg (1 tablet) once daily
25 - 39	450 mg (1 tablet) once daily	450 mg (1 tablet) every 2 days
10 - 24	450 mg (1 tablet) every 2 days	450 mg (1 tablet) twice weekly
< 10	not recommended	not recommended

Patients undergoing haemodialysis:

For patients on haemodialysis (Clcr < 10 ml/min) a dose recommendation cannot be given. Thus Vaglonax® film-coated tablets should not be used in these patients.

Patients with hepatic impairment:

Safety and efficacy of valganciclovir tablets have not been established in patients with hepatic impairment.

Patients with severe leukopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia:

If there is a significant deterioration of blood cell counts during therapy with valganciclovir, treatment with haematopoietic growth factors and/or dose interruption should be considered.

Method of administration

Vaglonax® is administered orally, and whenever possible, should be taken with food.

For paediatric patients who are unable to swallow valganciclovir film-coated tablets, valganciclovir powder for oral solution can be administered.

Precautions to be taken before handling or administering the medicinal product

The tablets should not be broken or crushed. Since Vaglonax® 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, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

OVERDOSAGE

Overdose experience with valganciclovir and intravenous ganciclovir

It is expected that an overdose of valganciclovir could possibly result in increased renal toxicity.

Reports of overdoses with intravenous ganciclovir, some with fatal outcomes, have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. The majority of patients experienced one or more of the following adverse events:

- Haematological toxicity: myelosuppression including pancytopenia, bone marrow failure, leukopenia, neutropenia, granulocytopenia.
- Hepatotoxicity: hepatitis, liver function disorder.
- Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine.
- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting.
- Neurotoxicity: generalized tremor, seizure.

Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of Revision: April 2019.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh- Lebanon