

# VITRASERT

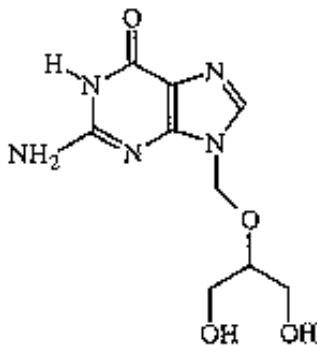
## GANCICLOVIR INTRAVITREAL IMPLANT FOR INTRAVITREAL IMPLANTATION ONLY

### DESCRIPTION

The Vitrasert implant contains a minimum of 4.5 mg of the antiviral drug ganciclovir. The implant is designed to release ganciclovir at a rate of approximately 1µg/hr over a 6-8 months period.

Each Vitrasert Implant contains the inactive ingredient, magnesium stearate, 0.25%, and is coated with ethylene/VA copolymer and polyvinyl alcohol.

The chemical name of ganciclovir is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, and has the following structure:



CAS-82410-32-0

Ganciclovir is a white to off-white crystalline powder with a molecular formula of  $C_9H_{13}N_5O_4$  and molecular weight of 255.23. Ganciclovir has a solubility of 4.3 mg/mL in water at 25°C.

### PHARMACOLOGY

#### **Virology**

Ganciclovir is a synthetic nucleoside analogue of 2-deoxyguanosine that inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include cytomegalovirus (CMV), herpes simplex virus - 1 and - 2 (HSV-1, HSV -2), Epstein-Barr virus (EBV) and varicella zoster

virus (VZV). Clinical studies have been limited to assessment of efficacy in patients with CMV infection.

Median effective inhibitory doses (ED<sub>50</sub>) of ganciclovir for human CMV isolates tested in vitro in several cell lines ranged from 0.2 to 3.0 µg/mL. The current definition of in-vitro CMV resistance to ganciclovir is IC<sub>50</sub> >3µg/mL. Ganciclovir inhibits mammalian cell proliferation in vitro at higher concentrations (10 to 60 µg/mL) with bone marrow colony forming cells being the most sensitive (ID<sub>50</sub>= 10 µg/mL) of those cell types tested.

Emergence of viral resistance has been reported based on in vitro sensitivity testing of CMV isolates from patients receiving intravenous ganciclovir treatment. The prevalence of resistant isolates is unknown, and there is a possibility that some patients may be infected with strains of CMV resistant to ganciclovir. Therefore, the possibility of viral resistance should be considered in patients who show poor clinical response.

### **Pharmacokinetics**

In a clinical trial of Vitrasert Implants, 26 patients (30 eyes) received a total of 39 primary implants and 12 exchange implants (performed 32 weeks after the implant was inserted or earlier if progression of CMV retinitis occurred). Because most of the exchanged implants were empty, the time the implant actually ran out of drug was unknown, and a precise in-vivo release rate could not be calculated. However, approximate in-vivo release rates could be determined for the exchanged implants, which ranged from 1.00 µg/h to more than 1.62 µg/h.

In 14 implants (3 exchanged, 11 autopsy) in which the in-vivo release rate could accurately be calculated, the mean release rate was 1.40 µg/h, with a range from 0.5 to 2.88 µg/h. The mean vitreous drug levels in eight eyes (4 collected at the time of retinal detachment surgery; 2 collected from autopsy eyes within 6 hours of death and prior to fixation; 2 collected from implant exchanges) was 4.1 µg/mL.

### **Clinical Trials**

In a randomised, controlled parallel group trial (GCVI-601-CMV) conducted between May 1993 and December 1994, treatment with the 1 µg/hr and 2 µg/hr Vitrasert Implant was compared to treatment with intravenous ganciclovir in 188 patients with AIDS and newly diagnosed CMV retinitis. Patients randomised to the intravenous ganciclovir treatment group received intravenous ganciclovir solution at induction doses (5 mg/kg twice daily) for 14 days, followed by maintenance dosing (5 mg/kg once daily). Based on masked assessment of fundus photographs and intent to treat analysis (ITTA), the median time to progression was approximately 221 days for the 1µg/hr Vitrasert Implant treatment group compared to 72 days for the intravenous ganciclovir treatment group.

Development of CMV retinitis in previously uninvolved fellow eyes of patients presenting with unilateral disease was assessed in patients in GCVI-601-CMV study. Although intergroup comparisons for the 1µg/hr Vitrasert Implant group and the intravenous ganciclovir group did not reach statistical significance, the relative risk of CMV progression in the unaffected eye, for all intent to treat implant patients was approximately twice as great as those administered IV-ganciclovir ( relative risk, 0.515; p=0.1913)

Extraocular CMV infections were diagnosed in 11.7% of the patients who were given an implant, in contrast to 0% of those receiving intravenous ganciclovir. The median time from implantation to the development of extraocular disease was four months. The most common site of infection was the lungs (5/111, 4.5%) followed by the colon/rectum (3/111, 2.7%) and central nervous system (2/111, 1.8%).

For all randomised patients in study GCVI-601-CMV, the time to 25% for all cause mortality was 140 days in the implant group and 158 days in the intravenous ganciclovir group (p=0.32), with a relative risk of dying being somewhat lower (although not significantly) for the intravenous ganciclovir treated patients (RR 0.68, p= 0.12). In a subgroup of 112 patients from this study who were followed and given options for further treatment, the median time for death was 226 days in the patient group who initially received the implant and 223 days in the group who initially received intravenous ganciclovir.

Interpretation of these data is somewhat confounded by the earlier time to progression of retinal disease in patients receiving intravenous ganciclovir which resulted in their being removed from the study much sooner than those treated with an implant.

## **INDICATIONS**

Vitrasert is indicated for the treatment of confirmed CMV retinitis in patients with AIDS.

The diagnosis of CMV retinitis is ophthalmologic and should be made by indirect ophthalmoscopy. Other conditions in the differential diagnosis of CMV retinitis include candidiasis, toxoplasmosis, histoplasmosis, retinal scars, and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason, it is essential that the diagnosis of CMV be established by a physician familiar with the retinal presentation of these conditions.

The Vitrasert Implant is for intravitreal implantation only.

## **CONTRAINDICATIONS.**

The Vitrasert Implant is contraindicated in patients with hypersensitivity to ganciclovir or acyclovir, and in patients with any contraindications for intraocular surgery, such as external infection or severe thrombocytopenia.

### **WARNINGS.**

CMV retinitis may be associated with CMV disease elsewhere in the body. The Vitrasert Implant provides localised therapy limited to the implanted eye. The Vitrasert Implant does not provide treatment for systemic CMV disease. Patients should be monitored for extraocular CMV disease.

As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place the Vitrasert Implant into the vitreous cavity may include, but are not limited to, the following: vitreous loss, vitreous haemorrhage, cataract formation, retinal detachment, uveitis, endophthalmitis, and decrease in visual acuity.

Following implantation of the Vitrasert Implant, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately two to four weeks post-operatively. This decrease in visual acuity is likely a result of the surgical implant procedure.

The Vitrasert Implant is sterilised by ethylene oxide.

### **PRECAUTIONS**

#### **General**

As with all intraocular surgery, sterility of the surgical field and the Vitrasert Implant should be rigorously maintained. The Vitrasert Implant should be handled only by the suture tab in order to avoid damaging the polymer coatings since this could affect release rate of ganciclovir inside the eye. The Vitrasert Implant should not be resterilised by any method.

A high level of surgical skill is required for implantation of the Vitrasert Implant. A surgeon should have observed or assisted in surgical implantation of the Vitrasert Implant prior to attempting the procedure.

### **Information for Patients**

The Vitrasert Implant is not a cure for CMV retinitis, and some immunocompromised patients may continue to experience progression of retinitis with the Vitrasert Implant. Patients should be

advised to have ophthalmologic follow-up examinations of both eyes of appropriate intervals following implantation of the Vitrasert Implant.

As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place the Vitrasert Implant into the vitreous cavity may include, but are not limited to, the following: intraocular infection or inflammation, detachment of the retina and formation of cataract in the natural crystalline lens.

Following implantation of the Vitrasert Implant, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately two to four weeks post-operatively. This decrease in visual acuity is likely a result of the surgical procedure.

The Vitrasert Implant only treats eyes in which it has been implanted. Additionally, because CMV is a systemic disease, patients should be monitored for extraocular CMV infections (e.g., pneumonitis, colitis) in the body.

### **Drug Interactions**

No drug interactions have been observed with the Vitrasert Implant. There is limited experience with use of retinal tamponades in conjunction with the Vitrasert Implant.

### **Carcinogenesis**

Ganciclovir was carcinogenic in the mouse after oral doses of 20 and 1000 mg/kg/day. Except for histiocytic carcinoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Based on such studies, ganciclovir should be considered a potential carcinogen in humans.

### **Mutagenesis**

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes in vitro at concentrations between 50-500 and 250-2000 µg/mL respectively. Based

on this mutagenic potential, male and female patients should be advised to practice a form of contraception during ganciclovir treatment.

### **Impairment of Fertility**

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryoletality in female mice following intravenous doses of 90 mg/kg/day.

Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or intravenous administration of doses ranging from 2 - 10 mg/kg. Based on these findings, ganciclovir has the potential to cause temporary or permanent suppression of fertility in women and temporary or permanent inhibition of spermatogenesis in men.

### **Use in Pregnancy: Category D**

There have been no studies of Vitrasert in pregnant women and therefore, it should not be given to this group of population.

The active ingredient, ganciclovir in Vitrasert has been shown to be embryotoxic in rabbits and mice following intravenous administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day, respectively. Effects observed in rabbits included: foetal growth retardation, embryoletality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephalic, and brachygnathia. In mice, effects observed were maternal/foetal toxicity and embryoletality.

### **Use in Lactation.**

It is not known if ganciclovir from the Vitrasert implant is excreted in human milk. Since many drugs are excreted in human milk and, because of evidence of carcinogenicity and teratogenicity effects caused in animals treated with ganciclovir, mothers should be instructed to discontinue nursing if they have a Vitrasert implant.

### **Paediatric Use**

Safety and effectiveness in paediatric patients below 12 years of age have not been established.

### **ADVERSE REACTIONS.**

During clinical trials, the most frequent adverse events seen in patients treated with the Vitrasert Implant involved the eye.

During the first two months following implantation, visual acuity loss of 3 lines or more, vitreous haemorrhage, and retinal detachments occurred in approximately 10 - 20% of patients. Cataract formation/lens opacities, macular abnormalities, intraocular pressure spikes, optic disk/nerve changes, hyphemas and uveitis occurred in approximately 1 - 5%.

Adverse events with an incidence of less than 1% were: retinopathy, anterior chamber cell and flare, synechia, haemorrhage (other than vitreous), cotton wool spots, keratopathy, astigmatism, endophthalmitis, microangiopathy, sclerosis, choroiditis, chemosis, phthisis bulbi, angle closure glaucoma with anterior chamber shallowing, vitreous detachment, vitreous traction, hypotony, severe post-operative inflammation, retinal tear, retinal hole, corneal dellen, choroidal folds, pellet extrusion from scleral wound and gliosis.

## **DOSAGE AND ADMINISTRATION.**

### **Dosage and Administration**

Each Vitrasert Implant contains a minimum of 4.5 mg of ganciclovir, and is designed to release the drug over a 6 to 8 month period of time. The Vitrasert implant is designed to release ganciclovir at a rate of approximately 1µg/hr. Following depletion of ganciclovir from the Vitrasert Implant, as evidenced by progression of retinitis, the Vitrasert Implant may be removed and replaced.

### **Handling and Disposal**

Caution should be exercised in handling of the Vitrasert Implant in order to avoid damage to the polymer coating on the implant, which may result in an increased rate of drug release from the

implant. Thus, the Vitrasert Implant should be handled only by the suture tab. Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure.

Because the Vitrasert Implant contains ganciclovir, which shares some of the properties of anti-tumour agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal of the Vitrasert Implant according to guidelines issued for antineoplastic drugs.

## **OVERDOSAGE**

Oral overdosage with the Vitrasert implant has neither been reported nor experienced. However occurrence of adverse events should not be excluded and patients should be observed carefully.

## **PRESENTATION.**

The Vitrasert Implant is supplied in the individual unit boxes in a sterile tyvek package. Store below 30°C . Protect from freezing, excessive heat and light.

**MANUFACTURER.**

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©Copyright 1997 Chiron Vision Corporation. All rights reserved.  
U.S. Patent # 5,378,475. Foreign Patents pending.  
U.S. Patent # 4,355,032, # 4,507,305 (ganciclovir compound)

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