ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Vitrasert.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

The Vitrasert implant is a polymer-based drug delivery system which contains ganciclovir compressed into tablets. The tablets contain a minimum of 4.5 mg of the active ingredient ganciclovir and 0.015 mg magnesium stearate. The delivery system consists of a semipermeable polyvinyl alcohol (PVA) layer, permitting diffusion of the drug, and a nonpermeable ethylene vinyl acetate (EVA) layer. The discontinuity in the EVA coating creates a diffusion port for the diffusion of ganciclovir from the implant into the eye.

3. **PHARMACEUTICAL FORM**

Vitrasert is an eye implant. The Vitrasert implant is a non-erodible polymer-based sustained release delivery system which contains ganciclovir compressed into a 2.5 mm diameter by 1 mm thick tablet. The tablet is coated on all sides with PVA and with a discontinuous film of EVA. The entire assembly is coated with PVA, and a suture tab made from PVA attached.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

The Vitrasert implant is indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) (See 4.4. Special warnings and special precautions for use).

4.2 **Posology and method of administration**

**Dosage and administration**

The Vitrasert implant is for intravitreal implantation only. Each Vitrasert implant provides sustained release of the antiviral drug for at least 3 months. In the clinical studies a median time to disease progression of 6-8 months was observed in patients treated with a Vitrasert implant. Following depletion of ganciclovir from the implant, as evidenced by progression of CMV retinitis, the Vitrasert implant can be replaced. In cases with disease progression within the first 3 months, the therapy with Vitrasert implant should be reconsidered.

**Surgical procedure**

The surgical procedure for intravitreal implantation of Vitrasert is performed under routine facial and retrobulbar or peribulbar block. A conjunctival incision is made in the inferotemporal quadrant at the limbus, and hemostasis is achieved using a bipolar diathermy. Vitrasert is prepared by passing a nylon suture 1.5 - 2.0 mm from the base of the device through the center of the strut. The excess strut is trimmed such that the distance from the suture to the end of the strut is only 0.5 mm. A 20-gauge microvitreo-retinal blade is used to enter the inferotemporal sclera 4 mm from the limbus to implant the Vitrasert in the pars plana. The incision is then enlarged to 4-5 mm circumferentially. Using an automated vitrectomy device, any prolapsed vitreous is excised.

The lips of the sclerotomy incision are held open to confirm that a full-thickness incision of the underlying pars plana has been made. The strut of the implant is then grasped with smooth-
bladed forceps and inserted into the eye with the drug pellet (top surface of the implant) facing the front of the eye. Care is exercised at this stage to not perforate or damage the membrane covering the drug pellet. The nylon suture is used to pass an anchoring suture through either side of the scleral incision and is then tied; the scleral incision is also closed with a running nylon suture. Balanced salt solution is injected through the incision to restore intraocular pressure. The implant is then inspected with the binocular indirect ophthalmoscope to verify intravitreal placement. The conjunctiva is closed with two plain collagen sutures or other suture material of the surgeon's choice. Post-surgical management using antibiotic and steroids are administered at the discretion of the surgeon.

Removal of the Vitrasert implant is performed under routine facial and retrobulbar or peribulbar block. The inferotemporal incision is opened by cutting the nylon suture, and incising the original incision site using a microvitreoretinal blade. The anchoring suture is used to remove the implant from the eye. Dissection may be required to free the existing implant, a vitrectomy of adherent vitreous using a mechanical suction cutting device may be necessary (See 4.4 Special warnings and special precautions for use).

A published report (Morley et al. (Ophthalmology 102(3), 388-392, 1995)) of nine eyes in eight patients receiving two or more Vitrasert Implants described removal and replacement of Vitrasert Implants from the original surgical site, or use of a contiguous site which involved approximately 2.0 mm of the original scleral wound as well as an additional 3.0 mm of new sclera inferior to the previous wound, or implantation through a completely separate site. However, randomized controlled trials comparing techniques of Vitrasert implant removal and reimplantation have not been conducted.

**Pediatric use**
There has been very limited clinical experience in treating CMV retinitis with the Vitrasert implant in patients under the age of 12 years.

**Use in the elderly**
No studies of the efficacy or safety of the Vitrasert implant in elderly patients have been conducted.

**4.3 Contra-indications**

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

**4.4 Special warnings and special precautions for use**

The Vitrasert implant provides local therapy limited to the implanted eye. There is an increased risk of involvement in the initially uninvolved contralateral eye and patients must be continuously monitored for signs of development. There is also an increased risk of extraocular CMV infections when compared to systemic treatment. In the event of clinical manifestations of extraocular CMV infection, systemic treatment should be initiated.

As with any surgical procedure, there is risk involved. Potential sight threatening complications accompanying intraocular surgery to place the Vitrasert implant into the vitreous cavity include vitreous hemorrhage, retinal detachment, endophthalmitis, uveitis, and cataract formation.

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-operation. This decrease in visual acuity is likely a result of the surgical procedure.

Data currently available are insufficient to assess the efficacy of the Vitrasert implant when used in combination with silicone oil or gas to treat retinal detachment.
A high level of surgical skill is required for implantation of the Vitrasert implant. A surgeon should have observed and assisted on surgical implantation of the Vitrasert implant prior to attempting the procedure.

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 resterilized by any method.

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 an ophthalmologist familiar with the retinal presentation of these conditions. The diagnosis of CMV retinitis may be supported by culture of CMV from urine, blood, throat, or other sites, but a negative CMV culture does not rule out CMV retinitis.

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 have ophthalmologic follow-up examinations at appropriate intervals following implantation of the Vitrasert implant. Some patients, such as those with sight-threatening disease (i.e., retinitis in the posterior pole), will require more frequent follow-up.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies were conducted.

4.6 Use during pregnancy and lactation

Ganciclovir has been shown to be embryotoxic and teratogenic in animal studies. Teratogenic effects included cleft palate, anophthalmia/microphthalmia, aplastic kidney and pancreas, hydrocephaly and brachygnathia.

Although each Vitrasert implant contains only 4.5 mg of ganciclovir, which is released locally in the vitreous over a period of 6-8 months, the safety of the implant in pregnant women has not been established. Therefore, the Vitrasert implant should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Adequate contraceptive regimens should be followed during use of the Vitrasert implant.

Impairment of fertility
Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice and hypoplasia of the testes and seminal vesicles in the male offspring 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 0.2 - 10 mg/kg.

Nursing mothers
It is not known whether ganciclovir from the Vitrasert implant is excreted in human milk. However, many drugs are excreted in human milk and, because carcinogenicity and teratogenicity effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. Mothers should be instructed to discontinue nursing if they have a Vitrasert implant.

4.7 Effects on ability to drive and use machines

After the surgical implantation of Vitrasert, patients may experience a temporary decrease in visual acuity. Patients should not drive or use machines until their vision has recovered.
4.8 Undesirable effects

The most frequent adverse events seen in patients treated with Vitrasert involved the eye, and included vitreous hemorrhage, retinal detachments, cataract formation, and macular changes. Since vitreous hemorrhage, hyphema, endophthalmitis and several of the cases of cataract formation occurred in the immediate post-operative period, a causal relationship with the surgical procedure is likely. Causality is unclear for the remaining ocular adverse events, since many of these manifestations are often associated with CMV retinitis. The risk of retinal detachment and endophthalmitis is increased following repeated implantation. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal lesions.

Adverse events with an incidence of $\geq 1.0\%$ seen in the 589 patients who received 956 Vitrasert Implants during clinical trials are the following:

<table>
<thead>
<tr>
<th>Ocular adverse events</th>
<th>No. of adverse events (after initial implantation)</th>
<th>No. of adverse events (after repeat implantation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=828</td>
<td>N=128</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>122</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>14.7</td>
<td>13.3</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>98</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>11.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Cataract/lens opacities</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Macular abnormality</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Intraocular pressure spike</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>(increase of $\geq 10$ mm Hg) *</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Optic disk/nerve changes</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Hyphema</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Vitritis</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Intraocular pressure measurements available for 738 of 956 implants.

Adverse events with an incidence of less than 1.0% were: retinopathy, anterior chamber cell and flare, synechia, hemorrhage (other than vitreous), cotton wool spots, keratopathy, astigmatism, uveitis, microangiopathy, iritis, choroiditis, papillitis, chemosis, phthisis bulbi, angle closure glaucoma with anterior chamber shallowing, vitreous detachment, vitreous traction, hypotony, severe postoperative inflammation, retinal tear, retinal hole, corneal dellen, subconjunctival hemorrhage, hypotony-related choroidal folds, pellet extrusion from scleral wound, and gliosis.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antivirals, ATC-code: J05A B06.
Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpesviruses 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 (ED50) of ganciclovir for human CMV isolates tested in vitro in several cell lines ranged from 0.2 to 3.0 µg/ml. The relationship between in vitro sensitivity of CMV to ganciclovir and clinical response has not been established. 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 of those cell types tested.

Available evidence indicates that upon entry into host cells, cytomegaloviruses induce one or more cellular kinases that phosphorylate ganciclovir to its triphosphate. It has been shown that there is approximately a 10-fold greater concentration of ganciclovir-triphosphate in CMV-infected cells than in uninfected cells, indicating a preferential phosphorylation of ganciclovir in virus-infected cells. In vitro, ganciclovir-triphosphate is catabolized slowly, with 60 to 70% of the original level remaining in the infected cells 18 hours after removal of ganciclovir from the extracellular medium. The antiviral activity of ganciclovir-triphosphate is believed to be the result in inhibition of viral DNA synthesis by two known modes: (1) competitive inhibition of viral DNA polymerases (2) direct incorporation into viral DNA, resulting in eventual termination of viral DNA elongation. The cellular DNA polymerase alpha is also inhibited, but at a higher concentration than required for viral DNA polymerase.

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.

5.2 Pharmacokinetic properties

Vitreous levels were measured in 17 eyes after implantation of the Vitrasert implant. Vitreous ganciclovir levels were below the limit of detection in 9 eyes. In the remaining 8 eyes, the mean vitreous level was 4.1 µg/ml (range 1.9 - 7.4 µg/ml).

The approximate in-vivo release rate, determined for 14 implants (3 exchanged, 11 autopsy) ranged from 0.5 µg/hour to 2.88 µg/hour (mean 1.4 µg/hour).

5.3 Preclinical safety data

Ganciclovir causes mutations and chromosome damage in mammalian cells in vitro and is clastogenic in vivo. In the mouse, ganciclovir is carcinogenic. The clinical relevance of the tumours is not clear. Ganciclovir should be considered a potential carcinogen in humans. The risk for human treatment from these toxic actions should be taken into account when considering the suitability of this product for the patient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The Vitrasert implant contains 0.015 mg magnesium stearate (USP) per tablet. The tablets are coated with ethylene vinyl acetate (EVA) and polyvinyl alcohol (PVA). The suture tab consists of PVA.

6.2 Incompatibilities
There are no known incompatibilities.

6.3 Shelf life

The shelf life of the implant is 24 months. Do not use the product beyond the expiry date listed on the pouch containing the implant. The implant must remain sterile, and the package should not be opened until use.

6.4 Special precautions for storage

Store at a temperature between 15 and 25 °C. Protect from freezing or excessive heat.

6.5 Nature and contents of container

The Vitrasert implant is supplied in individual unit boxes in a sterile Tyvek package.

6.6 Instructions for use, handling and disposal (if appropriate)

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. The Vitrasert implant should not be resterilized by any method.

Because the Vitrasert implant contains ganciclovir, which shares some of the properties of antineoplastic agents (i.e., carcinogenicity and mutagenicity), consideration should be given to handling and disposal of the Vitrasert implant according to guidance given for antineoplastic agents.

7. MARKETING AUTHORIZATION HOLDER

Chiron B.V.
Paasheuvelweg 30
1105 BJ Amsterdam
The Netherlands

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II
THE MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR IMPORT AND BATCH RELEASE AND CONDITIONS OR
RESTRICTIONS REGARDING SUPPLY AND USE
A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for import and batch release in the European Economic Area


B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to non-renewable restricted medical prescription.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
Package contains:
One Vitrasert implant containing 4.5 mg ganciclovir.
Inactive ingredients: polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA) and 0.015 mg magnesium stearate.

Sterile unless the package is damaged or opened.

For intravitreal implantation only.
Store at a temperature between 15 and 25°C.
Protect from freezing or excessive heat.

Usage: see package insert for dosing information.

Keep out of reach of children.

Prescription only product.

Marketing authorization holder:
Chiron B.V.
Paasheuvelweg 30
1105 BJ Amsterdam
The Netherlands

EU marketing authorization number: XXXXX
Lot # XXXXXXXX
Expiration date: month/year

Vitrascert should be disposed according to guidance given for antineoplastic agents.

Company logo
B. PACKAGE LEAFLET
INTRODUCTION

This leaflet provides important information about the Vitrasert implant. Please read it carefully. If you have any questions, or if you are not sure about anything ask your doctor or pharmacist. Do not feel uncomfortable about seeking information; the more you understand your therapy, the better.

Your doctor has decided to place a Vitrasert implant in one or both of your eyes. This leaflet explains what a Vitrasert implant is and what it does. It describes how it will be implanted and tells you some of the more common side effects you may experience.

WHAT IS VITRASERT IMPLANT?

Vitrasert implant is a small tablet, 2.5 mm in diameter and 1 mm thick, that has been put into a plastic case. Each tablet contains a minimum of 4.5 mg ganciclovir and 0.015 mg magnesium stearate. Ganciclovir is a so-called anti-viral, a medicine used to treat infections that are caused by viruses. The ganciclovir contained in the Vitrasert implant acts by inhibiting replication of cytomegalovirus, the virus that is causing your retinitis.

The material of the case, consisting of an impermeable layer of ethylene vinyl acetate (EVA) and a partial permeable layer of polyvinyl alcohol (PVA), allows the contents of the tablet to be released in a controlled manner after it has been implanted in your eye. The contents of the Vitrasert implant are released into the eye over an extended period. Under these conditions, the duration of clinical effect is 6-8 months.

WHO MAKES AND SELLS VITRASERT IMPLANT?

The marketing authorisation holder for Vitrasert is Chiron B.V., Amsterdam, The Netherlands.

WHAT IS VITRASERT IMPLANT FOR?

The Vitrasert implant is used to treat inflammation of the retina, the innermost layer of the eye. This inflammation is caused by a virus called cytomegalovirus (CMV) and often occurs in patients with the acquired immunodeficiency syndrome (AIDS). Doctors call your disease CMV retinitis.

WHEN CAN YOU NOT BE TREATED WITH THE VITRASERT IMPLANT?

A number of tests will be performed in the hospital. Based on the outcome of these tests your doctor will decide whether implantation of the Vitrasert implant is a suitable treatment for you. Sometimes it will not be possible to have a Vitrasert implant. This is the case when:
- you are allergic to ganciclovir or acyclovir
- you have other medical conditions making eye surgery not possible, such as a low platelet count or an external ocular infection.

CAN VITRASERT IMPLANT BE USED IN COMBINATION WITH OTHER MEDICINES?

No specific interaction studies with other drugs have been performed with the Vitrasert implant. You should always inform your doctor about all medication you are using before the Vitrasert implant is placed in your eye.
ARE THERE ANY SPECIAL WARNINGS?

As with any surgical procedure, there are some risks involved. Possible sight threatening complications of the eye surgery to place the Vitraser t implant in the inside of the eye include the following: bleeding inside the eye, formation of cloudy spots in the eye, detachment of the innermost layer of the eye (called the retina) and inflammation of small blood vessels in the eye or the eye socket.

Right after the Vitraser implant has been placed in your eye, you will almost certainly be able to see less clearly with that eye. This is probably caused by the surgery you have undergone, and will return to normal in most cases.

The Vitraser implant is not a cure for CMV retinitis. Sometimes the infection in your eye can get worse. Also, it only treats the eye in which it has been implanted. For these reasons, you will be checked for development of CMV retinitis in both eyes after you have had the Vitraser implant. Your doctor will decide how often you should return to have your eyes and vision checked.

Because CMV is a disease that can also affect other parts of the body you will also be checked for any CMV infections in other parts of your body.

Will the Vitraser implant affect your ability to drive or use machines?

After the surgical implantation of the Vitraser implant, you will almost certainly be able to see less clearly with that eye. You should not drive or use machines until your vision has recovered.

Is Vitraser implant safe to use during pregnancy and breast feeding?

The effects of Vitraser implant in pregnant women have not been studied. You should avoid becoming pregnant while you have the Vitraser implant in your eye. If you think you are pregnant, you should tell your doctor, and discuss with him whether the expected benefit from the treatment with a Vitraser implant will outweigh the possible risk to your baby. Adequate contraceptive measurements should be followed during the use of a Vitraser implant.

If you are breast-feeding a baby, you should change to artificial milk while you have a Vitraser implant in your eye.

Can the Vitraser implant be used in children?

There are not enough data to decide whether it is safe to use the Vitraser implant in children.

Can the Vitraser implant be used in the elderly?

No studies of the safety or efficacy of Vitraser implant in elderly patients have been performed.

HOW IS THE VITRASERT IMPLANT INSERTED?

The Vitraser implant is for implantation in the gelatinous material inside the eyeball. An eye surgeon will implant the Vitraser implant in your eye under local anaesthesia. The surgeon will make a small slit of about 4-5 mm in your eye through which he places the Vitraser implant inside your eye. The implant has a small lip. A nylon thread is passed through this lip. This thread is also used to close the incision, thereby anchoring the Vitraser implant at the same time. The implant contains at least 4.5 mg ganciclovir which is slowly released into your eye. The implant will remain inside the eye for a period of 6-8 months. Your doctor will check your eyes and vision regularly. Based on his findings, he may decide to replace the old implant by a new one.

Following surgery, your doctor may give you drugs to prevent possible infections.

Can overdosage with Vitraser implant be treated?
The implant releases only minute quantities of drug and it is unlikely that an overdosage will occur.

**SIDE-EFFECTS**

In patients who have received a Vitrasert implant various side effects have been seen. The most frequent side effects were seen in the eye. They included bleeding inside the eye, detachment of the innermost layer of the eye (called the retina), formation of cloudy spots in the eye, and colour changes in parts of the retina.

Other side effects were increased eye pressure, changes in the optic disk and optic nerve, bleeding in the front part of the eye, and inflammation inside the eye.

It is important that you have your eyes and vision checked frequently by your doctor so that he can check the state of your CMV retinitis and look for possible side effects that may have occurred.

If you notice any effect that might be a side effect, which has not been mentioned in this package leaflet, even if it is not worrying you, contact your doctor immediately.

**STORAGE CONDITIONS AND STORAGE TIME**

The Vitrasert implant should be stored at a temperature between 15 and 25°C and should not be implanted after the expiration date mentioned on the label. Protect the Vitrasert implant from freezing or excessive heat.

Do not open the packaging because the contents must remain sterile.

**Date of last revision of this package leaflet:**