

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Vitravene 6.6 mg/ml solution for injection

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains 1.65 mg of fomivirsen sodium (6.6 mg/ml)  
For excipients, see 6.1.

## **3. PHARMACEUTICAL FORM**

Solution for injection.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

For the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).

Until further experience is gained, fomivirsen should be used only when other therapy has been ineffective or is considered unsuitable.

### **4.2 Posology and method of administration**

Treatment with Vitravene should be given by ophthalmologists experienced in intravitreal injections.

Vitravene is for intravitreal injection only. Standard local anaesthetic and antimicrobial preparation of the affected eye are required prior to treatment. Treatment with fomivirsen involves an induction and a maintenance phase. The dose for each phase is based upon the prior treatment status of CMV retinitis (CMVR). For newly diagnosed disease, the recommended dosage is 165 µg/eye (0.025 ml). For previously treated disease, the recommended dose is 330 µg/eye (0.05 ml).

If severe intraocular inflammation occurs, it is recommended that Vitravene therapy is suspended until the inflammation improves.

#### **Newly diagnosed disease**

Three consecutive weekly intravitreal injections of 165 µg/eye (0.025 ml) should be administered as the induction portion of the dosing regimen. Thereafter, one 165 µg intravitreal injection every 2 weeks should be administered as the maintenance regimen.

#### **Previously treated disease**

One intravitreal injection of 330 µg/eye (0.05 ml) every other week for two doses should be administered as the induction portion of the dosing regimen. For maintenance, an intravitreal injection of one 330 µg dose should be administered once every 4 weeks.

#### **Paediatric use**

The safety and efficacy of fomivirsen has not been established for the treatment of CMV disease in patients under 18 years of age.

#### **Use in the elderly**

The safety and efficacy of fomivirsen has not been established for the treatment of CMV disease in patients over 60 years of age.

#### **Injection procedure**

- a. The globe of the affected eye should be stabilised with a cotton tip applicator.
- b. Slowly deliver either 0.025 ml (165 µg) or 0.05 ml (330 µg) of Vitravene 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian.

- c. The needle should be fully inserted, aiming to the centre of the globe, before the medicinal product is injected.
- d. As the needle is withdrawn, the cotton tip applicator should apply pressure to the site in order to reduce fluid loss.

Suggested post-injection procedures

Light perception and optic nerve head perfusion should be monitored by ophthalmoscopy. If perfusion is not complete and the IOP elevated, anterior chamber paracentesis should be considered. Regular follow-up of the patient for disease monitoring and treatment response should be maintained at intervals appropriate to the patient's condition.

Local inflammation post-injection can be controlled with local anti-inflammatory agents.

#### **4.3 Contraindications**

Vitravene is contraindicated in patients with hypersensitivity to fomivirsen or to any of the excipients. It is also contraindicated in situations where intravitreal injections should be avoided, such as external ocular infections.

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

**Fomivirsen provides local therapy limited to the injected eye. AIDS patients with CMV retinitis in one eye have an increased risk of disease in the contralateral eye and this must be carefully monitored. Also, the existence of extraocular CMV must be assessed and systemic therapy initiated as appropriate.**

As with any intraocular treatment, there are risks involved with the injection procedure. These can include vitreal haemorrhage, retinal detachment, endophthalmitis, uveitis and cataract formation.

Intraocular pressure should be monitored at each visit and elevations of intraocular pressure, if sustained, should be managed with anti-glaucoma medications.

The diagnosis of CMV retinitis is ophthalmologic and should be made by indirect ophthalmoscopy. Other conditions that should be considered in the differential diagnosis of CMV retinitis include ocular infections caused by syphilis, candidiasis, toxoplasmosis, histoplasmosis, herpes simplex virus and varicella-zoster virus as well as retinal scars, and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason, it is essential that a physician familiar with the retinal presentation of these conditions establishes the diagnosis of CMV.

Fomivirsen is not a cure for CMV retinitis and patients must be followed to ensure that disease control is maintained. Patients with sight-threatening disease should be frequently monitored.

Due to the risk of enhanced potential for inflammatory events, fomivirsen is not recommended in patients who have recently (2-4 weeks) been treated with either intravenous or intravitreal cidofovir.

There is no experience with fomivirsen as primary therapy in patients with advanced (zone 1) CMVR.

Patients should be monitored regularly for visual field changes.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The interaction in humans between fomivirsen and other substances has not been studied. Results from *in vitro* tests demonstrated that the antiviral activity of fomivirsen against human CMV was additive with that of ganciclovir and foscarnet. There was no inhibition of anti-CMV activity of fomivirsen against human CMV by zidovudine or zalcitabine, two medicinal products that are often administered to patients with AIDS.

#### **4.6 Pregnancy and lactation**

Animal reproductive studies have not been conducted with fomivirsen. It is also not known whether fomivirsen can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. It is not known whether fomivirsen is excreted in human milk and hence the potential for causing adverse effects in nursing infants is unknown. Health experts recommend that HIV-infected women should not breast feed their infants under any circumstances in order to avoid transmission of HIV. There are no studies in pregnant or lactating women. Fomivirsen should be used during pregnancy and lactation only if the potential benefit justifies the potential risk.

#### 4.7 Effects on ability to drive and use machines

Patients may experience temporary visual blurring after receiving fomivirsen by intravitreal injection. They should not drive or use machines until this has resolved.

#### 4.8 Undesirable effects

Due to the local intravitreal administration of fomivirsen, and the absence of systemic exposure, adverse events are confined to the treated eye(s).

Ocular events and the incidence of occurrence are as follows:

##### Frequent ( $\geq 5\%$ )

*165  $\mu\text{g}$  dose:* abnormal vision, anterior chamber inflammation, blurred vision, cataract, eye pain, intraocular pressure increase, retinal disorder, vitreous disorder.

*330  $\mu\text{g}$  dose:* abnormal vision, anterior chamber inflammation, blurred vision, cataract, conjunctival haemorrhage, eye pain, floaters, intraocular pressure increase, retinal detachment, retinal oedema, retinal haemorrhage, uveitis, vitritis.

##### Frequent ( $\geq 1 - < 5\%$ )

*165  $\mu\text{g}$  dose:* conjunctival haemorrhage, conjunctivitis, corneal oedema, cystoid macular oedema, eye irritation, floaters, HIV ocular microangiopathy, peripheral vision decrease, photophobia, retinal detachment, retinal oedema, retinal haemorrhage, retinal pigment epithelium stippling, retinal vascular disorder, uveitis, vitreous haemorrhage, vitritis.

*330  $\mu\text{g}$  dose:* conjunctivitis, conjunctival hyperaemia, corneal opacity, dry eye, eye irritation, eye pallor, keratitis, lens pigment deposits, optic nerve disorder, orbital cellulitis, photopsia, retinal disorder, visual acuity decrease.

##### Uncommon ( $< 1\%$ )

*165  $\mu\text{g}$  dose:* blepharitis, chromatopsia, colour blindness, conjunctival hyperaemia, corneal lesion, night blindness, desaturation of colour vision, endophthalmitis, eye disorder, hyphema, hypotony, injection site reaction, tearing, keratitis, photopsia, pupil disorder, retinal tear, visual acuity decrease.

*Intraocular inflammation:* Intraocular inflammation (including anterior chamber inflammation, uveitis, and vitritis) is the most commonly reported adverse event. Inflammation is not dose related, e.g., anterior chamber inflammation was noted in 10% of the eyes treated with the 165  $\mu\text{g}$  and in 7% of the eyes with the 330  $\mu\text{g}$  dose regimen. Inflammatory reactions are more common during induction dosing.

*Intraocular pressure changes:* Transient elevations in intraocular pressure occur with the same incidence in eyes treated with the 330  $\mu\text{g}$  dose regimen and the 165  $\mu\text{g}$  dose regimen. Most often these are single transient events. In most cases, the pressure elevations return to the normal range without any treatment or with temporary use of topical medications.

*Retinal detachments:* Retinal detachments are relatively common in CMV retinitis and occur after fomivirsen intravitreal injections. The incidence of retinal detachments was 3.6% in the 165  $\mu\text{g}$  dose group and 10% in the 330  $\mu\text{g}$  dose regimen. The higher rate for eyes treated with 330  $\mu\text{g}$  was not unexpected, as these eyes had previously treated, refractory CMV retinitis and histories of other ocular complications of AIDS.

*Retinal oedema:* Retinal oedema has been reported with both the 165  $\mu\text{g}$  (4% of eyes) and 330  $\mu\text{g}$  (7% of eyes) doses of fomivirsen. Cystoid macular oedema has also been reported.

*Visual abnormalities:* Decreased visual acuity, and desaturation of colour vision have been reported independently or concurrently with signs of intraocular inflammation. Blurred vision, photophobia, photopsia, floaters, and ocular pain are commonly reported prior to treatment as well as during treatment with fomivirsen.

There have been 5 instances (7%) in which patients treated with the 165  $\mu\text{g}$  dose have been withdrawn from treatment because of ocular adverse events. 10% of the patients treated with 330  $\mu\text{g}$  of fomivirsen have been withdrawn from treatment because of ocular adverse events.

## 4.9 Overdose

In clinical trials with fomivirsen, one patient with advanced CMV retinitis unresponsive to other antiviral treatments was accidentally dosed once bilaterally with 990 µg per eye. Anterior chamber paracentesis was performed bilaterally and vision was restored. The next scheduled dose (one week later) was skipped, and the patient's CMV retinitis responded well to therapy. No additional measures were taken, and the patient continued to receive the 330 µg dose as treatment.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for intravitreal use, ATC code: S01 AD.

#### Mechanism of action

Fomivirsen is a phosphorothioate oligonucleotide constructed to inhibit human cytomegalovirus replication through an antisense mechanism. The nucleotide sequence of fomivirsen is complementary to a sequence in mRNA transcripts of the major immediate early region 2 (IE2) of human CMV. This region of mRNA encodes several proteins responsible for regulation of viral gene expression that are essential for replication of infectious CMV. Inhibition of virus replication and IE2 protein synthesis *in vitro* are believed to result from binding of fomivirsen to the target mRNA. *In vitro* studies have shown that non-antisense mechanisms may contribute to the total antiviral activity.

### ***In vitro* antiviral activity**

Fomivirsen has been shown to inhibit human CMV in assays measuring viral antigen production, plaque formation, and infectious virus yield. Fomivirsen inhibits virus replication for both wild type laboratory strains and clinical isolates of human CMV. In human fibroblast cell lines, the median effective inhibitory concentration (EC<sub>50</sub>) of fomivirsen for virus antigen production was approximately 0.34±0.25 µM. On the basis of molar concentrations, the potency of fomivirsen was at least 40-fold greater than ganciclovir. Fomivirsen also inhibited virus-induced plaque formation and infectious virus yield at these concentrations. In retinal pigment epithelium cells, fomivirsen was an even more potent inhibitor of human CMV replication with an EC<sub>50</sub> value of 0.03±0.02 µM. The potency of fomivirsen was consistent in 21 independent clinical viral isolates, including several resistant to one or more of the available DNA polymerase inhibitors approved for treatment of cytomegalovirus retinitis (ganciclovir, foscarnet, or cidofovir). The absence of cross-resistance with the DNA polymerase inhibitors is consistent with an alternative mechanism of action. The antiviral activity of fomivirsen was not due to the inhibition of cellular processes as there was no effect on cell growth, metabolism or viability until concentrations were 2-orders of magnitude above the antiviral EC<sub>50</sub> (≥50 µg/ml).

### ***In vivo* antiviral activity**

*In vivo* activity against human CMV was confirmed with controlled clinical trials of fomivirsen for the treatment of CMV retinitis in patients with AIDS.

A randomised, controlled clinical trial was conducted evaluating immediate treatment versus delayed treatment of a 165 µg dose of fomivirsen in patients with newly diagnosed CMV retinitis. Patients in the immediate treatment group received three weekly 165 µg doses (induction) followed by 165 µg doses on alternate weeks (maintenance). Patients in the delayed treatment group were monitored weekly for disease progression; when progression occurred, these patients could receive fomivirsen on the identical schedule and dose as the immediate treatment group. Based on the primary efficacy parameters (masked assessment of fundus photographs), results revealed a median time to progression of 71 days in the immediate treatment group versus 13 days in the delayed treatment group, in the intent to treat analysis.

An additional randomised, controlled trial was conducted with the 330 µg dose of fomivirsen to compare two dosage schedules in patients with advanced CMV retinitis. Patients were assigned in a randomised fashion to receive either three weekly 330µg doses (induction) followed by 330 µg (maintenance) on alternate weeks or two 330 µg doses, one on day 1, one on day 15 (induction), followed by 330 µg every fourth week (maintenance).

An intent to treat analysis showed no significant difference in median time to progression between the two dosing regimens, with an interpolated median time to CMVR progression of 90+ days as determined by fundus photography. In addition, it was noted that there was no difference in time to progression for patients on concomitant oral ganciclovir at baseline compared to those not on ganciclovir.

### **Resistance**

Through persistent selection pressure *in vitro* it was possible to isolate a clone of human CMV that was 10-fold less sensitive to inhibition of replication than the parent strain. The molecular basis for the resistance has not been elucidated but is not due to mutation at the mRNA target site. Because it was possible to select a resistant strain of virus, it is possible that resistant strains may occur in clinical use.

### **Cross-resistance**

Fomivirsen showed potent activity in human CMV clinical isolates resistant to ganciclovir, foscarnet, and cidofovir. The antisense mechanism and molecular target of action of fomivirsen is distinctly different from that of other inhibitors of CMV replication which function by inhibiting the viral DNA polymerase. Fomivirsen was active in all the 21 analysed isolates. The EC<sub>50</sub> values for fomivirsen in the clinical isolates resistant to DNA polymerase inhibitors were indistinguishable from the EC<sub>50</sub> values of isolates shown to be sensitive to these agents.

Antiviral activity of fomivirsen against clinical isolates resistant to DNA polymerase inhibitors:

Clinical Isolates	No. of Isolates	Fomivirsen EC <sub>50</sub> (µM)
All isolates examined	21 <sup>a</sup>	0.57 ± 0.41
Ganciclovir-resistant	12/17 <sup>b</sup>	0.53 ± 0.19
Foscarnet-resistant	7/17 <sup>b</sup>	0.61 ± 0.19

<sup>a</sup> Total number of clinical CMV isolates examined in four separate laboratories.

<sup>b</sup> Ratio of the number of clinical isolates with demonstrated viral resistance to the total number of isolates evaluated for resistance to each DNA polymerase inhibitors.

## 5.2 Pharmacokinetic properties

Fomivirsen is administered by intravitreal injection, and no fomivirsen or its oligonucleotide metabolites have been detected in the plasma of patients administered the substance (n=16). Considering the difficulty in obtaining routine samples of ocular fluids (i.e., vitreous humor) the assessment of ocular pharmacokinetic parameters in patients has been limited. However, the ocular pharmacokinetics, including distribution, metabolism, and excretion of fomivirsen have been characterised in non-clinical model systems.

### Preclinical

Intravitreal injections in rabbits and monkeys produced peak concentrations of fomivirsen in vitreous immediately after injection with concentrations proportional to dose. Fomivirsen was cleared from the vitreous over the course of 7 to 10 days, by a combination of tissue distribution, metabolism, and vitreal egress. The half-lives of vitreal clearance were 63 hours in rabbits and 22 hours in monkeys.

Fomivirsen was detectable in retina within hours after injection, and concentrations increased for 3 to 5 days. Fomivirsen concentrations were greatest in the retina and iris, with very low exposure to the optic nerve. Following administration of clinically relevant doses to the rabbit, retinal concentrations remained above 1 µM for 10 days after administration of a single dose. The tissue concentration is above the *in vitro* antivirally active IC<sub>50</sub> concentration range for HCMV laboratory strains and clinical HCMV isolates (≤ 1 µM). In monkeys, the estimated half-life of fomivirsen in retina was dose-dependent and ranged between 45 and 78 hours. Following repeated intravitreal injection, there was slight accumulation in the retina with every-other-week administration of a dose equivalent to the 330 µg human dose or weekly administration of a dose similar to the 165 µg dose level. The long residence times in retina, and to a lesser extent vitreous, provide a pharmacokinetic basis for the treatment intervals in humans.

Metabolites of fomivirsen were detected in the retina and vitreous. Fomivirsen is metabolised by exo- and endonucleases in a process starting with a sequential removal of nucleotide residues from the terminal ends of the oligonucleotide yielding shortened forms, finally leading to mononucleotide metabolites. The metabolic derivatives are shorter the longer the interval since administration. Faecal excretion is only a minor route of elimination. Low molecular weight metabolites follow the pathways of endogenous nucleotides.

Little or no fomivirsen, or its oligonucleotide metabolites could be detected outside the eyes of monkeys treated with intravitreal injections of fomivirsen at clinically relevant doses. Quantitation limits for fomivirsen in tissues and plasma are orders of magnitude lower than concentrations of oligonucleotide required to produce toxicity.

## Clinical

In a limited clinical ocular pharmacokinetics study with doses of 165 µg and 330 µg, the maximum observed vitreal concentrations of fomivirsen occurred at the 1 hour time point following intravitreal injection. The fomivirsen  $C_{max}$  in vitreous ranged from 0.01-11.8 µM with the 165 µg dose (n=5) and from 6.2-32.7 µM with the 330 µg dose (n=2). By Day 8, the fomivirsen concentration in vitreous was approximately 1% of the concentration seen at the 1 hour time point. Little to no metabolism was seen at the 1 hour time point but by Day 8, fomivirsen comprised approximately 40% of the total measurable oligonucleotide. Vitreal concentrations of fomivirsen remained above the *in vitro*  $EC_{50}$  until 12 days after the 165 µg dose, but were below the limit of detection (< 10 nM) by Day 17. The complete lack of detectable fomivirsen or its oligonucleotide metabolites in plasma at any time evaluated, suggests that intravitreal injections of small doses of fomivirsen result in primarily local exposure with little or no systemic exposure.

The clinical pharmacokinetics data correlate well with the information from animal studies. Exposure of the vitreous to fomivirsen appears to be dose dependent. Although the half-life in patients could not be calculated, the rate of elimination appeared similar to that determined in monkeys, with measurable concentrations present for 1 week and the substance almost completely eliminated within 2 weeks. There was also evidence of exonuclease mediated metabolism in vitreous, similar to that observed in animal models.

## 5.3 Preclinical safety data

### Ocular tolerability studies

Intravitreal injections of fomivirsen to rabbits and monkeys resulted in proinflammatory ocular reactions at clinically relevant exposure. The observed ocular reactions were related to the inflammations. The overall incidence of inflammatory changes was similar between monkeys and patients, but the inflammatory changes in monkeys were more severe than those observed clinically. Additional inflammatory changes in monkeys included synechia, retinal vasculitis, retinitis, neovascularization of the iris, and retinal detachment. Ocular exposures in excess of the maximal human intravitreal exposure could not be investigated in the animals because of the inflammations.

The systemic exposure was negligible following intravitreal administration of fomivirsen, and no systemic toxicity occurred. Fomivirsen showed no genotoxic potential.

Based on the absence of exposure of reproductive organs to fomivirsen after intravitreal injection, no fertility or teratology studies have been performed.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium bicarbonate, sodium carbonate, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

2 years.



#### **6.4 Special precautions for storage**

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton.

#### **6.5 Nature and contents of container**

Vitravene is packaged in a clear Type 1 glass borosilicate vial closed with Teflon-faced butyl rubber stopper and aluminium flip-off seal. There is a 0.25 ml declared volume in each 2 ml single dose vial.

#### **6.6 Instructions for use and handling, and disposal**

Method of Preparation and Handling

Fomivirsen sodium is administered by intravitreal injection (0.025 ml or 0.05 ml/eye) following application of standard topical anesthetics and antimicrobials using a 30 gauge needle on a low-volume (e.g. tuberculin) syringe. The following steps should be used:

- a. Remove plastic cap from Vitravene vial.
- b. Disinfect rubber stopper using 70% ethyl alcohol.
- c. Attach a 5 µm filter needle to the low-volume injection syringe (e.g. tuberculin syringe) for solution withdrawal (to further guard against the introduction of stopper particulate).
- d. Withdraw approximately 0.15 ml through the filter needle.
- e. Remove filter needle and attach a 30 gauge needle to syringe.
- f. Eject excess volume and air from syringe.

Partially used vials should be discarded.

### **7. MARKETING AUTHORISATION HOLDER**

CIBA Vision Europe, Ltd  
Flanders Road, Hedge End  
Southampton, SO30 2LG  
United Kingdom

### **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**

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**
- C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

## **A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer responsible for batch release

Laboratoires CIBA Vision FAURE, Rue de la Lombardière, 07104 Annonay Cedex, France

Manufacturing Authorisation issued on 28 July 1995 by Agence du Médicament, Boulevard Anatole France, 93285 Saint-Denis Cedex, France.

## **B. CONDITIONS OF THE MARKETING AUTHORISATION**

### **• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

## **C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER**

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects:

The applicant agreed to provide additional long-term safety data for the above medicinal product. A surveillance program in the EU and North America is to be initiated immediately after the Commission Decision. The program, which contents were presented to the CPMP at its plenary session on 20 April 1999, will continue until the safety database, in addition to the MAA, contains data from at least 300 patients treated ( $\geq 1$  injection) *and* of which at least 100 patients have been treated during six months or more. The database will be analysed continuously, and presented to the CPMP on an annual basis.

The applicant committed to encourage treating physicians to submit safety information using a purpose-made CRF. A draft CRF is attached to the Letter of Undertaking. Prior to implementation it will be discussed with clinicians and approved by the Rapporteur. Thereafter,

- blank CRFs will be provided to all known prescribers of anti-CMVR therapy
- the applicant sales representatives will ask for the CRFs when calling on prescribers
- physicians will be reminded (by telephone) to submit CRFs for follow-up visits.

The applicant has the ambition to monitor all patients, and will use all efforts to capture CRF data for at least 50% of all patients treated in the EU and North America until the target numbers above have been met.

The applicant further committed to submit variation applications that would be necessary in the light of the experience gained in the post-marketing surveillance program.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Vitravene 6.6 mg/ml solution for injection.  
fomivirsen sodium

1.65 mg of fomivirsen sodium per vial (6.6 mg/ml).

Sodium bicarbonate, sodium carbonate, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

Solution for injection, 2 ml single dose vial containing 0.25 ml.

Intraocular use.

Keep out of the reach and sight of children.

See Package Leaflet for instruction for use.

EXP {month/year}

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton. Discard any unused solution.

CIBA Vision Europe, Ltd  
Flanders Road, Hedge End  
Southampton, SO30 2LG  
UK

EU/0/00/000/000

LOT {number}

Medicinal product subject to medical prescription.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

Vitravene 6.6 mg/ml solution for injection

Intraocular use.

EXP {month/year}

LOT {number}

1.65 mg of fomivirsen sodium per single dose vial.

**B. PACKAGE LEAFLET**



Read all of this leaflet carefully before you start using this medicine. Keep this leaflet. You may need it again. If you have further questions, please ask your doctor.

Vitravene 6.6 mg/ml solution for injection  
fomivirsen sodium

***What is the active substance?***

The active substance is fomivirsen sodium at a concentration of 6.6 mg/ml. Each vial contains 1.65 mg of fomivirsen sodium.

***What else does Vitravene contain?***

The other ingredients are:

sodium bicarbonate and sodium carbonate as buffers, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

***Who is responsible for marketing Vitravene?***

CIBA Vision Europe, Ltd  
Flanders Road, Hedge End  
Southampton SO30 2LG  
United Kingdom

***Who is responsible for the manufacturing of Vitravene?***

Laboratoires CIBA Vision FAURE  
Rue de la Lombardière  
07104 Annonay Cedex  
France

## **1. WHAT VITRAVENE IS AND WHAT IT IS USED FOR**

***What is Vitravene?***

Vitravene is a solution for injection in a clear glass vial for injection (0.25 ml).

***How does Vitravene work?***

Vitravene is an antiviral medication which blocks the replication of cytomegalovirus (CMV). It only affects the genetic material of the virus in the eye and does not affect human cells.

***Why use Vitravene?***

Vitravene is indicated for the local treatment of CMV retinitis in patients with Acquired ImmunoDeficiency Syndrome (AIDS).

***What is CMV retinitis?***

CMV retinitis is an eye infection of the light sensitive layer at the back of the eye (retina) caused by the virus cytomegalovirus (CMV). CMV is a herpes type virus. In adults able to fight infection in a normal way, CMV may cause only a mild infection. In this case, no treatment is required. Patients with Acquired ImmunoDeficiency Syndrome (AIDS) are at high risk of developing CMV retinitis or other forms of CMV disease. CMV attacks the retina of the eye and may affect vision, and may cause blindness. Treatment for CMV retinitis is necessary to reduce the risk of blindness.

## **2. BEFORE YOU USE VITRAVENE**

***When should Vitravene not be used?***

Do not use Vitravene if you are allergic to fomivirsen or any of the other ingredients of Vitravene or if you have an external eye infection.

***What needs to be taken into consideration for children and the elderly?***

The safety of Vitravene in patients under 18 years or over 60 years of age has not been established.

***What else needs to be observed?***

Vitravene is not a cure for CMV retinitis but, with repeated dosing, it can slow down the infection and the damage it causes. Occasionally, the infection can get worse and may need a change of therapy. Also, Vitravene only controls the virus in the eye being treated. It is possible to get a CMV infection in the other eye or other parts of the body. For these reasons, it is important that you return to the doctor(s) as often as instructed so that any viral activity in the treated eye and the rest of the body can be checked.

***What needs to be considered during pregnancy or while breast-feeding?***

### ***Pregnancy***

If you are pregnant or planning to become pregnant, Vitravene must be used only in agreement with your doctor.

### ***Breast-feeding***

If you are breast-feeding, Vitravene must be used only in agreement with your doctor. Health experts recommend that HIV-infected women should not breast feed their infants under any circumstances in order to avoid transmission of HIV.

### ***What has to be observed if driving or using machines?***

There is no specific information to suggest that Vitravene affects your ability to drive and use machinery. However, blurred vision has been reported during treatment with Vitravene. If this occurs, you should avoid driving or operating machinery.

## **3. HOW TO USE VITRAVENE**

### ***How is Vitravene used?***

Vitravene needs to be injected into the gelatinous material inside the eyeball close to the site of infection (intravitreal injection).

The amount of Vitravene to be used in your case depends on how your CMV retinitis has been treated previously. If it is the first time that you are affected by this disease (newly diagnosed), the recommended dose is 165 microgram/eye (0.025 ml/eye). If you were previously treated for this disease, the recommended dose is 330 microgram/eye (0.05 ml/eye).

Treatment with Vitravene requires an induction and a maintenance phase.

#### Newly diagnosed disease:

Induction Phase: 1 injection every week for 3 weeks. (3 injections)

Maintenance Phase: 1 injection every 2 weeks.

#### Previously treated disease:

Induction Phase: 1 injection followed by another 2 weeks later. (2 injections)

Maintenance Phase: 1 injection every 4 weeks.

### ***How will Vitravene be prepared and administered?***

Vitravene should be administered only by a trained physician.

Prior to the injection, the doctor will use a local anaesthetic (usually eye drops) to reduce the sensation in your eye. The injection into the eye is a simple and quick procedure. To make the procedure safer for the eye, antimicrobial eye drops will also be applied.

### ***Administration (intravitreal injection):***

*The following instructions for use are intended for the administrator only.*

The following steps should be taken:

#### Method of preparation and handling

The eye which will receive treatment should be anaesthetised and antimicrobial pre-treatment should be given. The following steps are then recommended:

- a. Remove plastic cap from Vitravene vial.
- b. Disinfect rubber stopper using 70% ethyl alcohol.
- c. Attach a 5 micron filter needle to the low-volume injection syringe (e.g. tuberculine syringe) for solution withdrawal (to further guard against the introduction of stopper particulate).
- d. Withdraw approximately 0.15 ml through the filter needle.
- e. Remove filter needle and attach a 30 gauge needle to syringe.
- f. Eject excess volume and air from syringe.

#### Injection procedure

- a. The globe of the affected eye should be stabilised with a cotton tip applicator
- b. Slowly deliver either 0.025 ml (165 microgram) or 0.050 ml (330 microgram) of Vitravene 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian.
- c. The needle should be fully inserted, aiming to the center of the globe, before the medicine is injected.
- d. As the needle is withdrawn, the cotton tip applicator should apply pressure to the site in order to reduce fluid loss.

#### Suggested post-injection procedures

Light perception and optic nerve head perfusion should be monitored by ophthalmoscopy. If perfusion is not complete and the IOP is elevated, anterior chamber paracentesis should be considered. Regular follow-up of the patient for disease monitoring and treatment response should be maintained at intervals appropriate to the patient's condition. Local inflammation post-injection can be controlled with local anti-inflammatory agents.

Vitravene is supplied in single dose vials. Partially used vials must be discarded.

#### ***What to do if you miss a dose?***

You will need to have the treated and untreated eyes checked for progress even after the treatment is started. If you miss a dose, you need to contact the doctor to arrange another appointment as soon as possible.

## **4. POSSIBLE SIDE EFFECTS**

#### ***What undesirable effects may Vitravene cause?***

Like all medicines, Vitravene can have side effects. In patients who have received Vitravene various side effects have been reported. All of them involve the eye and the most common ones are: inflammation inside the eye, increased eye pressure, detachment, swelling or bleeding of the light-sensitive layer of the eye (called the retina), bleeding in the transparent skin of the eye, cataract, pain and abnormal vision.

It is important that your eyes and vision are checked frequently by the doctor who checks the response to the treatment and looks for possible side effects that may have occurred.

If you notice anything unusual, which has not been mentioned in this package leaflet, even if it is not worrying you, contact your doctor or pharmacist immediately.

## **5. STORING VITRAVENE**

#### ***How should Vitravene vials be stored?***

Keep out of the reach and sight of children. Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton. Do not use after the expiry date stated on the label

**This leaflet was approved on {date}.**

## Further information

*For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.*

### **België/Belgique/Belgien**

CIBA Vision S.A. Benelux N.V.  
Omega Business Park  
Industrieterrein Noord - Sector D  
Pand 22, Wayenborgstraat 22  
B-2800 Mechelen  
Tél: +32-15-28 64 64

### **Danmark**

CIBA Vision Denmark A/S  
Ny Ostergade 7,1.tv.  
DK-4000 Roskilde  
Tlf: +45-46-38 0020

### **Deutschland**

CIBA Vision Vertriebs GmbH Ophtha  
Bauhofstr. 16  
D-63762 Grossostheim  
Tel: +49-6026-941-0

### **Ελλάδα**

Σάββας Θ Θεοδωρίδης  
Πατρώου 8-10  
10557 Αθήνα  
Τηλ: +301-3238811-13

### **España**

CIBA Vision, S.A.  
Marina, 206  
E-08013 Barcelona  
Tel: +34-93-265 2321

### **France**

CIBA Vision Ophthalmics  
8, rue Colomies/BP 1129  
F-31036 Toulouse Cedex  
Tél: +33-561 76 6900

### **Ireland**

CIBA Vision Ophthalmics UK Ltd  
Park West, Royal London Park  
Flanders Road, Hedge End  
UK-Southampton, Hamps. S030 2LG  
Tel: +44-1489-775 514

### **Italia**

CIBA Vision Ophthalmics  
Via Emanuele Filiberto 130  
I-00185 Roma  
Tel. +39-06-772 697-1

### **Luxembourg/Luxemburg**

CIBA Vision S.A. Benelux N.V.  
Omega Business Park  
Industrieterrein Noord - Sector D  
Pand 22, Wayenborgstraat 22  
B-2800 Mechelen  
Tél: +32-15-28 64 65

### **Nederland**

CIBA Vision Ophtha Nederland  
Postbus 3126  
NL-4800 DC Breda  
Tel: +31-76-531 6785

### **Österreich**

CIBA Vision GmbH  
Modecenterstr. 14  
A-1030 Wien  
Tel: +43-17 989 294

### **Portugal**

NOVARTIS FARMA- Produtos Farmacêuticos S.A.  
Divisão CIBA Vision  
Rua Alto do Montijo, Lotes 1 e 2  
Edifício Monsante, 4º - B  
P-2795 Carnaxide  
Tel: +351-1-424 12 12

### **Suomi/Finland**

CIBA Vision Finland Oy  
Pasilanraiti 5  
FIN-00240 Helsinki  
Puh/Tfn: +358-9-476-91 300

### **Sverige**

CIBA Vision AB  
Datavägen 24  
S-436 32 Askim  
Tfn: +46-31-68 63 33

### **United Kingdom**

CIBA Vision Ophthalmics UK Ltd  
Park West, Royal London Park  
Flanders Road, Hedge End  
UK-Southampton, Hamps. S030 2LG  
Tel: +44-1489-775 514