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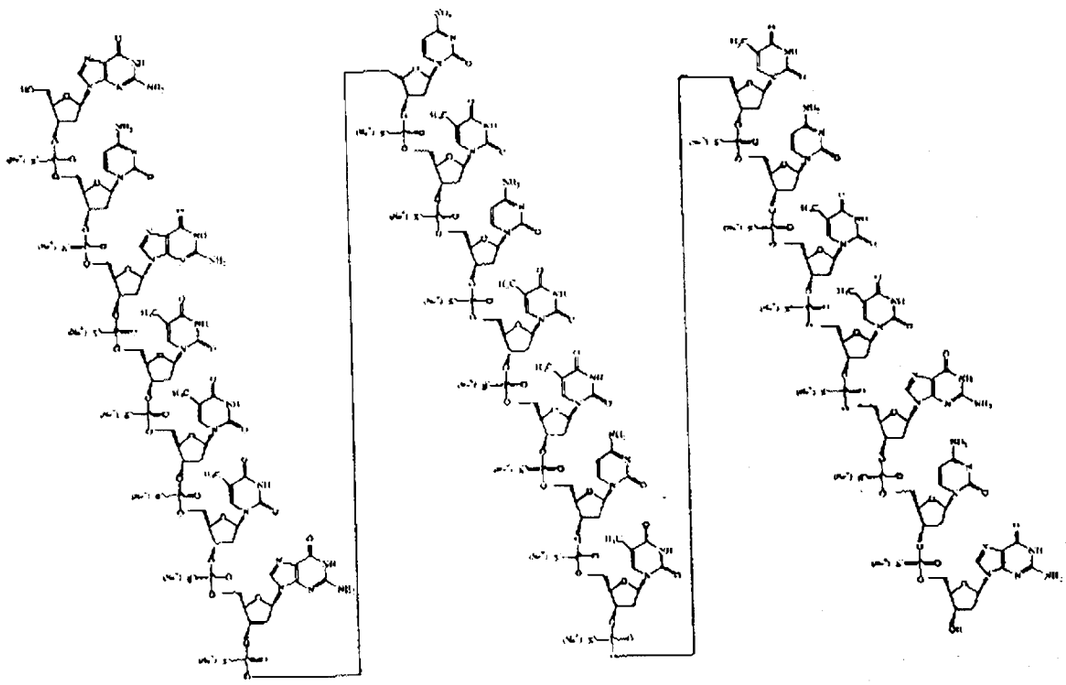
VITRAVENE™ Injection

Fomivirsen sodium intravitreal injectable

DESCRIPTION

Vitravene™ (fomivirsen sodium intravitreal injectable) is a sterile, aqueous, preservative-free, bicarbonate-buffered solution for intravitreal injection.

Fomivirsen sodium is represented by the following structural formula:



Fomivirsen sodium is a phosphorothioate oligonucleotide, twenty-one nucleotides in length, with the following sequence:

5'-GCG TTT GCT CTT CTT CTT GCG-3'

The chemical name for fomivirsen sodium is as follows:

2′-Deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*- phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*- phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′*O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosine, 20-sodium salt.

Fomivirsen sodium is a white to off-white, hygroscopic, amorphous powder with a molecular formula of $C_{204}H_{243}N_{63}O_{114}P_{20}S_{20}Na_{20}$ and a molecular weight of 7,122.

Each mL of Vitravene™ contains:

ACTIVE: Fomivirsen sodium 6.6mg

INACTIVES: Sodium bicarbonate, sodium chloride, sodium carbonate, and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Vitravene™ Injection is formulated to have an osmolality of 290mOsm/kg, and a pH of 8.7.

CLINICAL PHARMACOLOGY

VIROLOGY

Mechanism of Action

Fomivirsen is a phosphorothioate oligonucleotide that inhibits human cytomegalovirus (HCMV) 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 HCMV. This region of mRNA encodes several proteins responsible for regulation of viral gene expression that are essential for production of infectious CMV. Binding of fomivirsen to the target mRNA results in inhibition of IE2 protein synthesis, subsequently inhibiting virus replication.

Resistance

Through persistent selection pressure *in vitro* it was possible to isolate a clone of HCMV that was 10-fold less sensitive to inhibition of replication than the parent strain. The

molecular basis for the resistance has not been elucidated. It is possible that resistant strains may occur in clinical use.

Cross-resistance

The antisense mechanism of action and molecular target of fomivirsen are different from that of other inhibitors of HCMV replication, which function by inhibiting the viral DNA polymerase. Fomivirsen was equally potent against 21 independent clinical HCMV isolates, including several that were resistant to ganciclovir, foscarnet and/or cidofovir. Isolates which are resistant to fomivirsen may be sensitive to ganciclovir, focarnet and/or cidofovir.

Pharmacokinetics

The assessment of ocular pharmacokinetic parameters in patients has been limited and is still ongoing.

ANIMAL STUDIES

Ocular Kinetics: Fomivirsen is cleared from the vitreous in rabbits over the course of 7 to 10 days, by a combination of tissue distribution and metabolism. In the eye, fomivirsen concentrations were greatest in the retina and iris. Fomivirsen was detectable in retina within hours after injection, and concentrations increased over 3 to 5 days.

Metabolism and Elimination: Metabolism is the primary route of elimination from the eye. Metabolites of fomivirsen are detected in the retina and vitreous in animals. Fomivirsen sodium is metabolized by exonucleases in a process that sequentially removes residues from the terminal ends of the oligonucleotide yielding shortened oligonucleotides and mononucleotide metabolites. Data with related compounds indicate that mononucleotide metabolites are further catabolized similar to endogenous nucleotides and are excreted as low molecular weight metabolites. In rabbits, a small amount of fomivirsen-derived radioactivity was eliminated in urine (16%) or feces (3%) as low molecular weight metabolites. Expired air has been shown to be a major route of excretion for CO_2 generated by catabolism of nucleotides after administration of phosphorothioate oligonucleotides.

Systemic Exposure: Systemic exposure to fomivirsen following single or repeated intravitreal injections in monkeys was below limits of quantitation (70 ng/mL in plasma and 350 ng/g in tissue). In monkeys treated every other week for up to 3 months with fomivirsen there were isolated instances when fomivirsen's metabolites were observed in liver, kidney, and plasma at a concentration near the level of detection (14ng/mL in plasma and 70ng/g in tissue).

Protein Binding: Analysis of vitreous samples from treated rabbits and monkeys indicate that approximately 40% of fomivirsen is bound to proteins.

CLINICAL STUDIES

Clinical ocular pharmacokinetic studies have not yet been completed.

Limited, open label, controlled clinical studies evaluating the safety and efficacy of Vitravene™ have been conducted in patients with newly diagnosed CMV retinitis and in patients who have failed previous therapies. Based on the assessment of fundus photographs, the median time to CMV retinitis progression was approximately 80 days in patients receiving a dose of 330 µg. Many of these patients were also receiving protease inhibitor treatment. In the subgroup of newly diagnosed patients who received delayed treatment, most had CMV retinitis progression within two weeks. Head to head comparisons with other medications available to treat CMV retinitis has not been completed.

INDICATION AND USAGE

Vitravene™ is indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) who are intolerant of or have a contraindication to other treatment(s) for CMV retinitis or who were insufficiently responsive to previous treatment(s) for CMV retinitis.

The diagnosis and evaluation of CMV retinitis is ophthalmologic and should be made by comprehensive retinal examination including 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 establish the diagnosis of CMV retinitis.

CONTRAINDICATIONS:

Vitravene™ is contraindicated in those persons who have a known hypersensitivity to any component of this preparation.

WARNINGS

Vitravene™ is for intravitreal injection use only.

CMV retinitis may be associated with CMV disease elsewhere in the body. Vitravene™ intravitreal injection provides localized therapy limited to the treated eye. The use of Vitravene™ does not provide treatment for systemic CMV disease. Patients should be monitored for extraocular CMV disease or disease in the contralateral eye.

Vitravene™ is not recommended for use in patients who have recently (2-4 weeks) been treated with either intravenous or intravitreal cidofovir because of the risk of exaggerated ocular inflammation.

PRECAUTIONS

General

FOR OPHTHALMIC USE ONLY.

Ocular inflammation (uveitis) including iritis and vitritis has been reported to occur in approximately 1 in 4 patients. Inflammatory reactions are more common during induction dosing. Topical corticosteroids have been useful in the medical management of inflammatory changes, and with both medical management and time, patients may be able to continue to receive intraviteal injections of fomivirsen sodium after the inflammation has resolved.

Increased intraocular pressure has been commonly reported. The increase is usually a transient event and in most cases the pressure returns to the normal range without any treatment or with temporary use of topical medications. Intraocular pressure should be monitored at each visit and elevations of intraocular pressure, if sustained, should be managed with medications to lower intraocular pressure.

Information for patients

Vitravene™ intravitreal injection is not a cure for CMV retinitis, and some immunocompromised patients may continue to experience progression of retinitis during and following treatment. Patients receiving Vitravene™ should be advised to have regular ophthalmologic follow-up examinations. Patients may also experience other manifestations of CMV disease despite Vitravene™ therapy.

Vitravene™ treats only the eye(s) in which it has been injected. CMV may exist as a systemic disease, in addition to CMV retinitis. Therefore, patients should be monitored for extraocular CMV infections (e.g., pneumonitis, colitis) and retinitis in the opposite eye, if only one infected eye is being treated.

HIV-infected patients should continue taking antiretroviral therapy as otherwise indicated.

Drug Interactions

The interaction in humans between fomivirsen sodium and other drugs has not been studied.

Results from *in vitro* tests demonstrated no inhibition of anti-HCMV activity of fomivirsen by AZT or ddC.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic potential of fomivirsen sodium.

Vitravene was not mutagenic in Salmonella/Microsome (Ames) and mouse lymphoma tests or clastogenic in the *in vivo* mouse micronucleous assay. However, equivocal results were observed in the chromosome aberration test with Chinese hamster ovary cells.

No studies have been conducted to evaluate the potential of fomivirsen sodium to affect fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproductive studies have not been conducted with fomivirsen sodium. It is also not known whether fomivirsen sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

There are no adequate and well-controlled studies in pregnant women. Vitravene™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether fomivirsen sodium is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Vitravene™, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Vitravene™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

The most frequently observed adverse experiences have been cases of ocular inflammation (uveitis) including iritis and vitritis. Ocular inflammation has been reported to occur in approximately 1 in 4 patients. Inflammatory reactions are more common during induction dosing. Delaying additional treatment with Vitravene and the use of topical corticosteroids have been useful in the medical management of inflammatory changes (See Precautions, General).

Adverse experiences reported in approximately 5 to 20% of patients have included:

Ocular: abnormal vision, anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, decreased visual acuity, desaturation of color vision, eye pain, floaters, increased intraocular pressure, photophobia, retinal detachment, retinal edema, retinal hemorrhage, retinal pigment changes, uveitis, vitritis.

Systemic: abdominal pain, anemia, asthenia, diarrhea, fever, headache, infection, nausea, pnuemonia, rash, sepsis, sinusitis, systemic CMV, vomiting.

Adverse experiences reported in approximately 2 to 5% of patients have included

Ocular: application site reaction, conjunctival hyperemia, conjunctivitis, corneal edema, decreased peripheral vision, eye irritation, hypotony, keratic precipitates, optic neuritis, photopsia, retinal vascular disease, visual field defect, vitreous hemorrhage, vitreous opacity.

Systemic: abnormal liver function, abnormal thinking, allergic reactions, anorexia, back pain, bronchitis, cachexia, catheter infection, chest pain, decreased weight, dehydration, depression, dizziness, dyspnea, flu syndrome, increased cough, increased GGTP, kidney failure, lymphoma like reaction, neuropathy, neutropenia, oral monilia, pain, pancreatitis, sweating, thrombocytopenia.

OVERDOSAGE

In clinical trials with fomivirsen, one patient with advanced CMVR unresponsive to other antiviral treatments was accidentally dosed once bilaterally with 990µg per eye. Anterior chamber paracentesis was performed bilaterally and vision was retained.

DOSAGE AND ADMINISTRATION

Treatment with Vitravene™ involves an induction and a maintenance phase. The recommended dose of Vitravene is 330µg (0.05 mL). The induction dose of Vitravene should be one injection every other week for two doses. Subsequent maintenance doses should be administered once every four weeks after induction.

For unacceptable inflammation in the face of controlled CMVR, it is worthwhile interrupting therapy until the level of inflammation decreases and therapy can resume.

For patients whose disease progresses on fomivirsen during maintenance, an attempt at reinduction at the same dose may result in resumed disease control.

Instructions for Intravitreal Injection

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

- Remove plastic cap from vial containing fomivirsen sodium.
- Disinfect rubber stopper with 70% ethyl alcohol.
- Attach a 5 micron filter needle to the injection syringe for solution withdrawal (to further guard against the introduction of stopper particulate).
- Withdraw approximately 0.15mL through the filter needle.
- Remove filter needle and attach a 30 gauge needle to syringe containing fomivirsen sodium.
- Eject excess volume and air from syringe.
- Stabilize globe with cotton tip applicator and insert needle fully through an area 3.5 to 4mm posterior to the limbus (avoiding the horizontal meridian) aiming toward the center of the globe, keeping fingers off the plunger until the needle has been completely inserted. Deliver the injection volume (0.05 mL) by injecting slowly. Roll cotton tip applicator over injection site as needle is withdrawn to reduce loss of eye fluid.

Instructions for Post-Injection Monitoring

Monitor light perception and optic nerve head perfusion: if not completely perfused by 7-10 minutes, perform anterior chamber paracentesis with a 30 gauge needle on a plungerless tuberculin syringe at the slit lamp.

HOW SUPPLIED:

Vitravene™ Injection is supplied in preservative-free, single-use vials containing 0.25mL, 6.6mg/mL. The product is intended for intravitreal injection only.

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Store between 2–25°C (35–77°F). Protect from excessive heat and light.

℞ only

Manufactured for:

Isis Pharmaceuticals, Inc.

U.S. Patent No. Xxxxxx