

Fomivirsen

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1. DESCRIPTION

Fomivirsen sodium (Vitravene, IONIS Pharmaceuticals, Carlsbad, CA, and Novartis Pharmaceuticals, Switzerland), is a 21-base phosphorothioate DNA antisense oligonucleotide developed for intravitreal injection as a treatment for CMV retinitis. The oligonucleotide is designed to be complementary to a cytomegalovirus (CMV) messenger RNA (mRNA) that encodes for the major immediate early (IE2) region proteins of this virus. It was the first to be developed in its class of a group of highly specific and novel therapeutics, antisense oligonucleotides and consequently does not have a typical drug structure. The sequence of the fomivirsen oligonucleotide is 5'-GCG TTT GCT CTT CTT CTT GCG-3'.

Fomivirsen sodium intravitreal injectable (fomivirsen) is a white to off-white, hygroscopic, amorphous powder, with the molecular formula $C_{204}H_{243}N_{63}O_{114}P_{20}S_{20}Na_{20}$ and a molecular weight of 7122. Fomivirsen is available as a sterile, aqueous, preservative-free and bicarbonate-buffered solution. Each milliliter of fomivirsen contains 6.6 mg of the active ingredient.

The inactive ingredients in each milliliter of fomivirsen are sodium bicarbonate, sodium chloride, sodium carbonate, and water (for injection). Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Fomivirsen is formulated to have an osmolality of 290 mOsm/kg and a pH of 8.7.

Fomivirsen is formulated for intravitreal injection only and is approved solely for the local treatment of CMV retinitis in patients with advanced HIV infection (i.e. AIDS) who are intolerant of or have a contraindication to other treatment(s) to CMV retinitis or are insufficiently responsive to other treatments for CMV retinitis (Grillone and Lanz, 2001). It has also been used off label to treat CMV retinitis in patients not infected with HIV, such as those with an underlying immunodeficiency (solid organ, stem cell, or bone marrow transplant; cancer chemotherapy; CD4 deficiency; or other conditions).

Fomivirsen is a member of the first generation of antisense oligonucleotides known as phosphorothioates. In this class of compounds, one of the oxygen atoms in the phosphate backbone is replaced by a sulfur atom. This modification results

in a negatively charged molecule that is chiral at each phosphorothioate and serves to stabilize the molecule against DNase and RNase degradation, a significant improvement over the parent phosphodiester (Cook, 2001).

Improvements in antisense chemistry in the past have conveyed increased stability to the molecules, increasing *in vivo* half-lives and allowing for less frequent dosing (Crooke, 2001; Crooke, 2008). Modifying the paired C-G motifs by cytosine methylation reduces the proinflammatory effects that are typically seen with phosphorothioates (Vollmer *et al.*, 2002).

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

The antiviral activity of fomivirsen was investigated against multiple clinical strains of human CMV, using plaque reduction assay (Henry *et al.*, 2001). Fomivirsen showed potent antiviral activity that was quantitatively similar to ganciclovir, foscarnet, and cidofovir. It is important that fomivirsen maintained antiviral activity against all isolates, even those exhibiting resistance to the DNA polymerase inhibitors (ganciclovir, foscarnet, and cidofovir). Fomivirsen has no activity toward other viruses.

The 50% effective concentration (EC_{50}) of fomivirsen for CMV replication was between 0.1 and 1.0 μ M (mean 0.6 μ M) against all strains of human CMV, regardless of whether they were susceptible or resistant to other antiviral drugs (specifically, ganciclovir, foscarnet, and cidofovir) (Henry *et al.*, 2001).

2b. Emerging resistance and cross-resistance

Development of resistance to fomivirsen is less likely than with standard DNA polymerase inhibitors because of its mechanism of action. However, according to the package insert originally prepared in 1998 for US Food and Drug Administration (FDA) review and approval of fomivirsen in the USA (no more recent FDA product information is available), it was possible,