

Macugen

Generic Name: pegaptanib sodium

Dosage Form: injection, solution

Macugen®

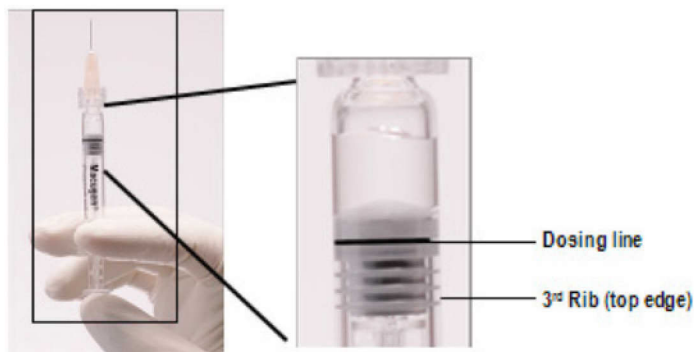
(pegaptanib sodium injection)

DESCRIPTION

Macugen® (pegaptanib sodium injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreal injection. Macugen is supplied in a single-dose, pre-filled syringe and is formulated as a 3.47 mg/mL solution, measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 µL. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection.

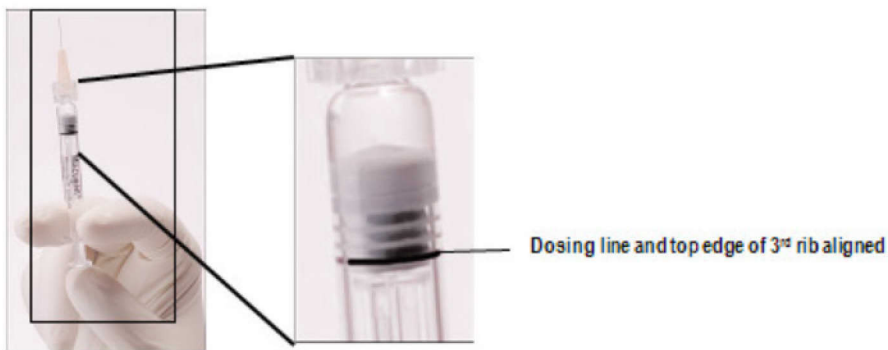
Pegaptanib sodium is a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue.

Pegaptanib sodium is represented by the following structural formula:



(Actual air bubble formation may vary)

Where R is



and n is approximately 450.

The chemical name for pegaptanib sodium is as follows: RNA, ((2' - deoxy - 2' - fluoro)C - Gm - Gm - A - A - (2' - deoxy - 2' - fluoro)U - (2' - deoxy - 2' - fluoro)C - Am - Gm - (2' - deoxy - 2' - fluoro)U - Gm - Am - Am - (2' - deoxy - 2' - fluoro)U - Gm - (2' - deoxy - 2' - fluoro)C - (2' - deoxy - 2' - fluoro)U - (2' - deoxy - 2' - fluoro)U - Am - (2' - deoxy - 2' - fluoro)U - Am - (2' - deoxy - 2' - fluoro)C - Am - (2' - deoxy - 2' - fluoro)U - (2' - deoxy - 2' - fluoro)C - (2' - deoxy - 2' - fluoro)C - Gm - (3'→3') - dT), 5'-ester with α, α' - [4,12 - dioxo - 6 - [[5 - (phosphonoxy)pentyl]amino]carbonyl] - 3,13 - dioxo - 5,11 - diaza - 1,15 - pentadecanediyl]bis[ω - methoxypoly(oxy - 1,2 - ethanediyl)], sodium salt.

The molecular formula for pegaptanib sodium is $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.

Macugen is formulated to have an osmolality of 280-360 mOsm/Kg, and a pH of 6-7.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist. VEGF is a secreted protein that selectively binds and activates its receptors located primarily on the surface of vascular endothelial cells. VEGF induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration (AMD), a leading cause of blindness. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.

Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. Under in vitro testing conditions, pegaptanib binds to the major pathological VEGF isoform, extracellular VEGF₁₆₅, thereby inhibiting VEGF₁₆₅ binding to its VEGF receptors. The inhibition of VEGF₁₆₄, the rodent counterpart of human VEGF₁₆₅, was effective at suppressing pathological neovascularization.

Pharmacokinetics

Absorption

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreal administration. The rate of absorption from the eye is the rate limiting step in the disposition of pegaptanib in animals and is likely to be the rate limiting step in humans.

In humans, a mean maximum plasma concentration of about 80 ng/mL occurs within 1 to 4 days after a 3 mg monocular dose (10 times the recommended dose). The mean area under the plasma concentration-time curve (AUC) is about 25 $\mu\text{g}\cdot\text{hr}/\text{mL}$ at this dose.

Distribution/Metabolism/Excretion

Twenty-four hours after intravitreal administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina, and aqueous fluid. After intravitreal and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreal dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled pegaptanib intravenous and intravitreal doses. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Based on preclinical data, pegaptanib is metabolized by endo- and exonucleases.

In humans, after a 3 mg monocular dose (10 times the recommended dose), the average (\pm standard deviation) apparent plasma half-life of pegaptanib is 10 (\pm 4) days.

Special Populations

Plasma concentrations do not appear to be affected by age or gender, but have not been studied in patients under the age of 50.

Renal Insufficiency

Dose adjustment for patients with renal impairment is not needed when administering the 0.3 mg dose.

Following a single 3 mg dose (10 times the recommended dose), in patients with severe (N=7), moderate (N=18), and mild (N=10) renal impairment, the mean (CV%) pegaptanib AUC values were 37.8 (17%), 26.7 (31%), and 23.6 (21%) $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively. The corresponding C_{max} values were 96.8 (23%), 81.6 (29.2%), and 66.5 (47%) ng/mL , respectively.

In patients with renal impairment, following administration of 3 mg pegaptanib doses every 6 weeks, the last detectable pegaptanib concentrations in plasma after the fourth dose were highly variable (ranging from 8 ng/mL to 66 ng/mL) and the variability was more pronounced in patients with severe renal impairment.

Hemodialysis

Macugen has not been studied in patients requiring hemodialysis.

Hepatic Impairment

Macugen has not been studied in patients with hepatic impairment.

Clinical Studies

Macugen was studied in two controlled, double-masked, and identically designed randomized studies in patients with neovascular AMD. Patients were randomized to receive control (sham treatment) or 0.3 mg, 1 mg or 3 mg Macugen administered as intravitreal injections every 6 weeks for 48 weeks. A total of approximately 1200 patients were enrolled with 892 patients receiving Macugen and 298 receiving a sham injection. The median age of the patients was 77 years. Patients received a mean 8.5 treatments out of a possible 9 total treatments across all treatment arms. Patients were re-randomized between treatment and no treatment during the second year. Patients who continued treatment in year 2 received a mean of 16 treatments out of a possible total 17 overall.

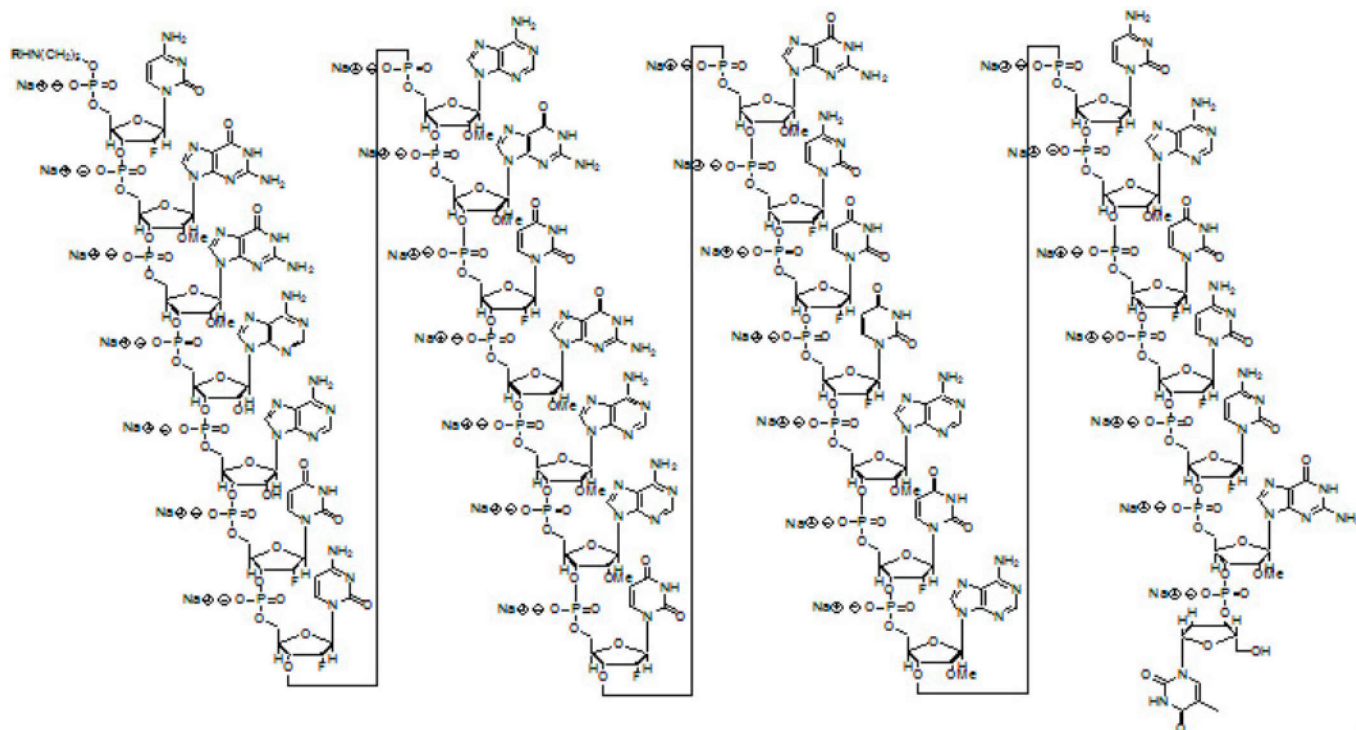
The two trials enrolled patients with neovascular AMD characteristics including classic, occult, and mixed lesions of up to 12 disc areas and baseline visual acuity in the study eye between 20/40 and 20/320. The primary efficacy endpoint was the proportion of patients losing less than 15 letters of visual acuity, from

baseline up to 54 week assessment. Verteporfin photodynamic therapy (PDT) usage was permitted at the discretion of the investigators in patients with predominantly classic lesions.

The groups treated with Macugen 0.3 mg exhibited a statistically significant result in both trials for the primary efficacy endpoint at 1 year: Study EOP1003, Macugen 73% vs. Sham 60%; Study EOP1004, Macugen 67% vs. Sham 53%. Concomitant use of PDT overall was low. More sham treated patients (75/296) received PDT than Macugen 0.3 mg treated patients (58/294).

On average, Macugen 0.3 mg treated patients and sham treated patients continued to experience vision loss. However, the rate of vision decline in the Macugen treated group was slower than the rate in the patients who received sham treatment. See Figure 1.

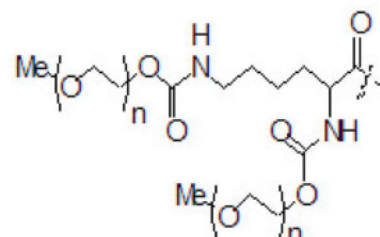
Figure 1



At the end of the first year (week 54), approximately 1050 of the original 1200 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. See Figure 2.

Macugen was less effective during the second year than during the first year. The percentage of patients losing less than 15 letters from baseline to week 102 was: Study EOP1003, Macugen 38/67 (57%); Sham 30/54 (56%); Study EOP1004, Macugen 40/66 (61%); Sham 18/53 (34%).

Figure 2



Dose levels above 0.3 mg did not demonstrate any additional benefit.

The safety or efficacy of Macugen beyond 2 years has not been demonstrated.

INDICATIONS AND USAGE

Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration.

CONTRAINDICATIONS

Macugen is contraindicated in patients with ocular or periocular infections.

Macugen is contraindicated in patients with known hypersensitivity to pegaptanib sodium or any other excipient in this product.

WARNINGS

Intravitreal injections including those with Macugen have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering Macugen. In addition, patients should be monitored during the week following the injection to permit early treatment, should an infection occur (see DOSAGE AND ADMINISTRATION).

Increases in intraocular pressure have been seen within 30 minutes of injection with Macugen. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately.

PRECAUTIONS

General

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the post-marketing experience following the Macugen intravitreal administration procedure (see ADVERSE EVENTS and DOSAGE AND ADMINISTRATION).

Information for Patients

In the days following Macugen administration, patients are at risk for the development of endophthalmitis. If the eye becomes red, sensitive to light, painful or develops a change in vision, the patient should seek the immediate care with their ophthalmologist.

Drug Interactions

Drug interaction studies have not been conducted with Macugen. Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system.

Two early clinical studies conducted in patients who received Macugen alone and in combination with PDT revealed no apparent difference in the plasma pharmacokinetics of pegaptanib.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with pegaptanib have not been conducted.

Pegaptanib and its monomer component nucleotides (2'-MA, 2'-MG, 2'-FU, 2'-FC) were evaluated for genotoxicity in a battery of in vitro and in vivo assay systems. Pegaptanib, 2'-O-methyladenosine (2'-MA), and 2'-O-methylguanosine (2'-MG) were negative in all assay systems evaluated. 2'-fluorouridine (2'-FU) and 2'-

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.