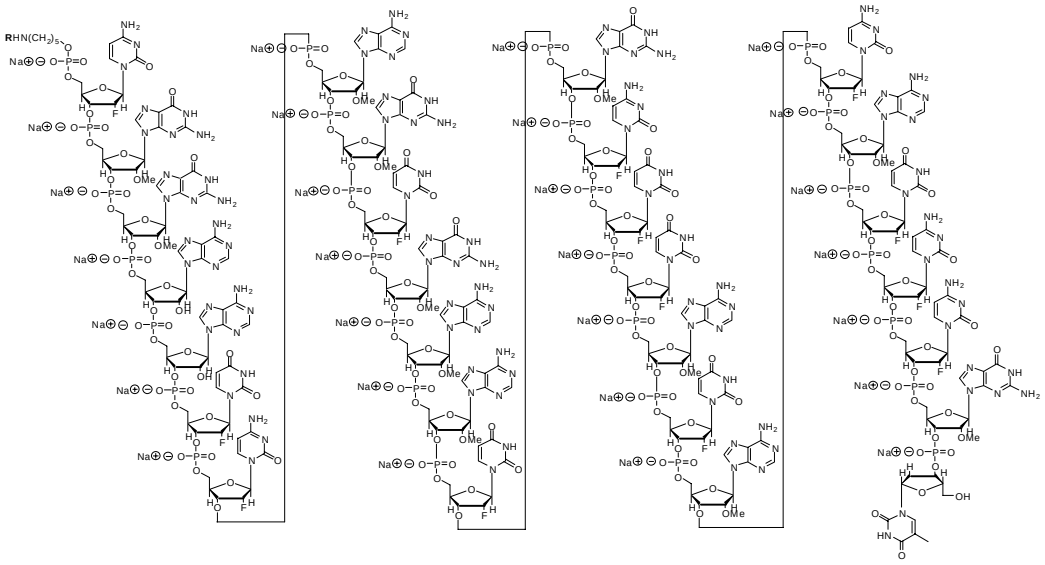
MACUGEN®
(pegaptanib sodium injection)

DESCRIPTION

MACUGEN® (pegaptanib sodium injection) is a sterile, aqueous solution containing pegaptanib sodium for intravitreous 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.

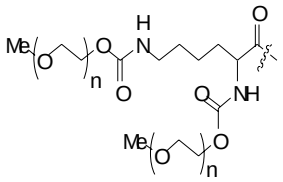
Pegaptanib sodium is a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue.

Pegaptanib sodium is represented by the following structural formula:



Samsung v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Exhibit 2025

Where R is



and n is approximately 450.

The chemical name for pegaptanib sodium is as follows: RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2′-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT), 5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-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 $VEGF_{165}$, thereby inhibiting $VEGF_{165}$ binding to its VEGF receptors. The inhibition of $VEGF_{164}$, the rodent counterpart of human $VEGF_{165}$, was effective at suppressing pathological neovascularization.

Pharmacokinetics

Absorption

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreous 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 μg·hr/mL at this dose.

Distribution/Metabolism/Excretion
Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina, and aqueous fluid. After intravitreous and intravenous administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous 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 intravitreous 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 (± standard deviation) apparent plasma half-life of pegaptanib is 10 (±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%) µg.hr/mL, respectively. The corresponding Cmax 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 intravitreous 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.

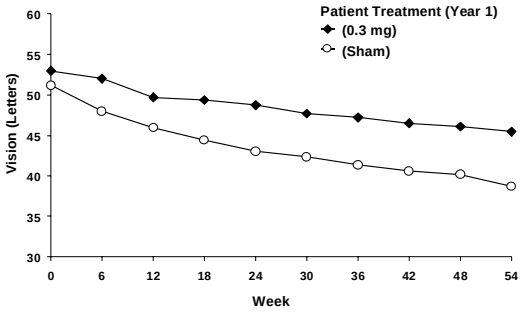
The groups treated with Macugen 0.3 mg exhibited a statistically significant result in both trials for the primary efficacy endpoint at 1 year: Study EOP1003, Macugen 73% vs. Sham 60%; Study EOP1004, Macugen 67% vs. Sham 53%. Concomitant use of PDT overall was low. More sham treated patients (75/296)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

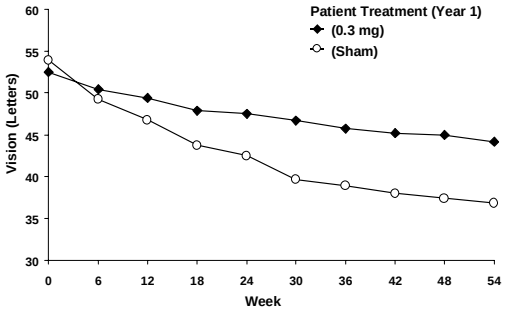
Figure 1

Mean Visual Acuity: Year 1

EOP1003



EOP1004

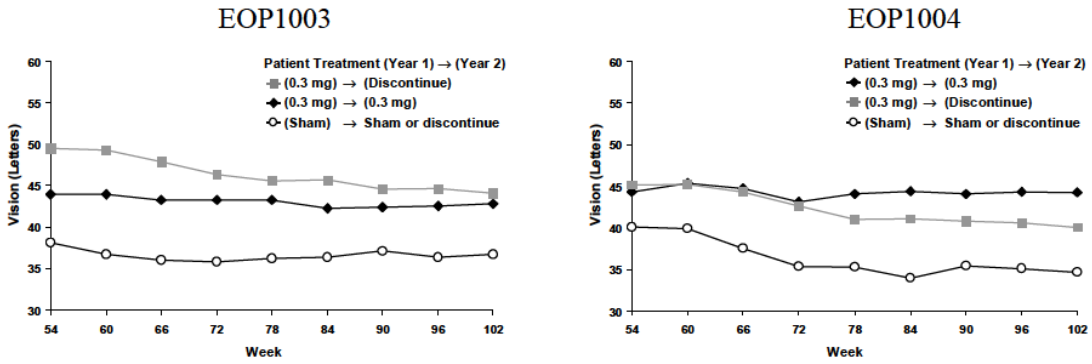


At the end of the first year (week 54), approximately 1050 of the original 1200 patients were re-randomized to either continue the same treatment or to discontinue treatment through week 102. See Figure 2.

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

Mean Visual Acuity: Year 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.

WARNINGS

Intravitreous 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.

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'-fluorocytidine (2'-FC) were nonclastogenic and were negative in all *S. typhimurium* tester strains, but produced a non-dose related increase in revertant frequency in a single *E. coli* tester strain. Pegaptanib, 2'-FU, and 2'-FC tested negative in cell transformation assays.

No data are available to evaluate male or female mating or fertility indices.

Pregnancy
Teratogenic Effects: Pregnancy Category B.
Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or fetal mortality in mice at intravenous doses of up to 40 mg/kg/day (about 7,000 times the recommended human monocular ophthalmic dose of 0.3 mg/eye). Pegaptanib crosses the placenta in mice.

There are no studies in pregnant women. The potential risk to humans is unknown. Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether pegaptanib is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Macugen is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of Macugen in pediatric patients have not been studied.

Geriatric Use
Approximately 94% (834/892) of the patients treated with Macugen were ≥ 65 years of age and approximately 62% (553/892) were ≥ 75 years of age. No difference in treatment effect or systemic exposure was seen with increasing age.

ADVERSE EVENTS

Serious adverse events related to the injection procedure occurring in < 1% of intravitreous injections included endophthalmitis (see **WARNINGS**), retinal detachment, and iatrogenic traumatic cataract.

The most frequently reported adverse events in patients treated with Macugen 0.3 mg for up to two years were anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. These events occurred in approximately 10-40% of patients.

The following events were reported in 6-10% of patients receiving Macugen 0.3 mg therapy:

Ocular: blepharitis, conjunctivitis, photopsia, vitreous disorder.

Non-Ocular: bronchitis, diarrhea, dizziness, headache, nausea, urinary tract infection.

The following events were reported in 1-5% of patients receiving Macugen 0.3 mg therapy:

Ocular: allergic conjunctivitis, conjunctival edema, corneal abrasion, corneal deposits, corneal epithelium disorder, endophthalmitis, eye inflammation, eye swelling, eyelid irritation, meibomianitis, mydriasis, periorbital hematoma, retinal edema, vitreous hemorrhage.

Non-Ocular: arthritis, bone spur, carotid artery occlusion, cerebrovascular accident, chest pain, contact dermatitis, contusion, diabetes mellitus, dyspepsia, hearing loss, pleural effusion, transient ischemic attack, urinary retention, vertigo, vomiting.

OVERDOSAGE

Doses of Macugen up to 10 times the recommended dosage of 0.3 mg have been studied. No additional adverse events have been noted but there is decreased efficacy with doses above 1 mg.

DOSAGE AND ADMINISTRATION

Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

Macugen should be inspected visually for particulate matter and discoloration prior to administration. Administration of the syringe contents involves attaching the threaded plastic plunger rod to the rubber stopper inside the barrel of the syringe. Do not pull back on the plunger. The syringe needle cap is then removed to allow administration of the product.

The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

No special dosage modification is required for any of the populations that have been studied (i.e. gender, elderly).

The safety and efficacy of Macugen therapy administered to both eyes concurrently have not been studied.

HOW SUPPLIED

Macugen (pegaptanib sodium injection) is supplied in a single use 1 mL glass syringe with a gray rubber plunger containing 0.3 mg in a 90 uL deliverable volume. Each syringe is fitted with a fixed 27 gauge needle covered with a gray rubber needle shield and a rigid plastic outside sheath. All are contained in a foil pouch. The accompanying polystyrene plunger rod and white flange are in a separate foil pouch. The two foil pouches are packaged in a carton.

Storage
Store in the refrigerator at 2° to 8°C (36° to 46°F). Do not freeze or shake vigorously.
Rx only.

NDC 68782-001-01

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