

DATA SHEET

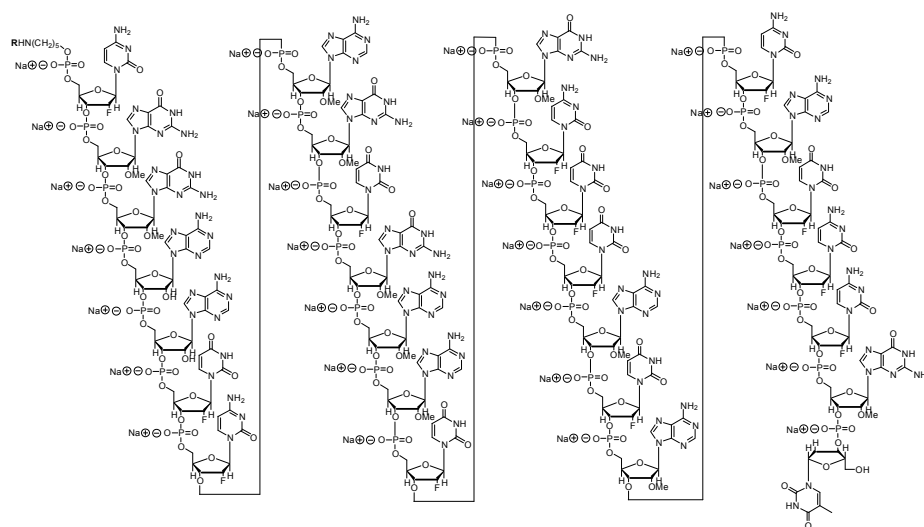
MACUGEN* (pegaptanib sodium) solution for injection

NAME OF THE MEDICINE

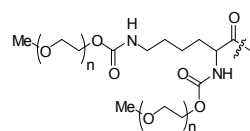
Non-proprietary name pegaptanib sodium

The molecular formula of 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 total molecular weight is approximately 50 kilodaltons.

Pegaptanib sodium is represented by the following structural formula:



Where R is



and n is approximately 450.

CAS Number: 222716-86-1

DESCRIPTION

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.

MACUGEN (pegaptanib sodium) is supplied as 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 3.47mg/ml solution to deliver a dose of 0.3mg pegaptanib sodium (based on oligonucleotide weight) in a nominal volume of 90 µL. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid and sodium hydroxide in water for injection.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Ocular Vascular Disorder Agent, ATC code: S01LA03.

Pegaptanib sodium 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, 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 neovascularisation.

Pegaptanib sodium is an aptamer, a modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF with high affinity and selectivity. Pegaptanib sodium binds to the major pathological VEGF isoform, extracellular VEGF₁₆₅, with high affinity (K_d = 200 pM) and specificity, thereby inhibiting VEGF₁₆₅ binding to its VEGF receptors. Pegaptanib sodium does not bind significantly to VEGF₁₂₁.

In animal models, VEGF₁₆₄ (the rodent counterpart of human VEGF₁₆₅) was specifically upregulated in disease. The selective inhibition of VEGF₁₆₄ with pegaptanib sodium proved as effective at suppressing pathological neovascularisation as pan-VEGF inhibition, however pegaptanib sodium spared the normal vasculature whereas pan-VEGF inhibition did not. Reductions in the growth of mean total lesion size, choroidal neovascularisation (CNV) size, and fluorescein leak size, resulting from the anti-angiogenic and anti-permeability effects in the retina have all been shown in patients with AMD treated with pegaptanib sodium.

Pharmacokinetics

Absorption

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

A mean maximum plasma concentration of about 80ng/mL occurs within 1 to 4 days after a 3mg monocular dose in humans. The mean area under the plasma concentration-time curve (AUC) is about 25 µg.hr/mL at this dose. Pegaptanib does not accumulate in the plasma

when administered intravitreally every 6 weeks. At doses below 0.5mg/eye, pegaptanib plasma concentrations do not likely exceed 10ng/ml.

The absolute bioavailability of pegaptanib (parent drug) after intravitreal administration has not been assessed in humans, but is approximately 70-100% in rabbits, dogs, and monkeys. In animals that received doses of pegaptanib sodium of 0.5 mg/eye to both eyes, plasma concentrations were 0.03% to 0.15% of those in the vitreous humor.

Distribution

In mice, rats, rabbits, dogs and monkeys, pegaptanib distributes primarily into the plasma and is not extensively distributed to peripheral tissues after intravenous administration. Twenty-four hours after intravitreal administration of a radiolabeled dose of pegaptanib sodium to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina and aqueous fluid. After intravitreal and intravenous administrations of radiolabeled pegaptanib sodium to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreal dose) were obtained in the kidney.

Metabolism

Pegaptanib is metabolised by endo- and exonucleases. In rabbits, the component nucleotide, 2'-fluorouridine (2'-FU) was found in plasma and urine after single radiolabeled pegaptanib sodium intravenous and intravitreal doses.

Elimination

In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Special Populations

Gender Plasma concentrations of pegaptanib in male and female patients are similar.

Elderly Subjects Plasma concentrations of pegaptanib were similar among patients 50 to 90 years of age.

Renal Insufficiency Based on a clinical study (EOP1006) with pegaptanib sodium injection 3 mg, a decrease in creatinine clearance from 70ml/min to 30 ml/min was associated with a 2.3 fold increase in AUC. However, a dosage adjustment for patients treated with the recommended 0.3 mg MACUGEN dose and whose creatinine clearance is >30 ml/min is not warranted. The pharmacokinetic data indicates that 0.3 mg dose would not exceed exposure seen with 3 mg which was a well tolerated dose. Patients with severe renal insufficiency (creatinine clearance < 30 ml/min) have not been adequately studied. Pegaptanib sodium has not been studied in patients requiring haemodialysis.(See PRECAUTIONS)

Hepatic Impairment Pegaptanib sodium has not been studied in patients with hepatic impairment. (See PRECAUTIONS)

CLINICAL TRIALS

MACUGEN was studied in two adequate and well-controlled, double-masked, and identically designed randomised studies (EOP1003; EOP1004) in patients with neovascular AMD.

In the first year, a total of 1208 patients were enrolled and 1190 were treated (892 MACUGEN, 298 sham) with a median age of 77 years. Patients were randomised to receive control (sham treatment) or 0.3mg, 1mg, or 3mg MACUGEN administered as intravitreal injections every 6 weeks for 48 weeks, and received a mean of between 8.4-8.6 treatments out of a possible 9 total across all treatment arms.

The two trials enrolled patients with a broad range of neovascular AMD characteristics, including all lesion subtypes, lesion sizes 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.

At one year, MACUGEN 0.3mg exhibited a statistically significant treatment benefit in both trials for the primary efficacy endpoint. (MACUGEN 0.3mg 70% versus Sham 55%; $p < 0.0001$ in the combined analysis). See Table 1 below.

MACUGEN 0.3mg showed treatment benefit regardless of baseline lesion sub-type, lesion size and visual acuity as well as age, gender, iris pigmentation and prior and/or baseline PDT usage. Concomitant use of PDT overall was low. More sham treated patients (75/296) received PDT than MACUGEN 0.3mg treated patients (58/294).

Table 1 Change in Visual Acuity From Baseline Up to 54 Weeks

Change in visual acuity (ETDRS letters)	Number (%) of patients		
	MACUGEN 0.3 mg n=294	Sham n=296	p values
≥15 letters gain	18 (6%)	6 (2%)	0.0401
≥0 letters gain	98 (33%)	67 (23%)	0.0032
< 15 letters loss	206 (70%)	164(55%)	0.0001
< 30 letters loss	266 (90%)	231(78%)	<0.0001

ETDRS= Early Treatment Diabetic Retinopathy Study

Dose levels of 1mg and 3mg were effective but did not exhibit additional clinical benefit over and above those seen at the 0.3mg dose level.

Patients receiving MACUGEN 0.3mg experienced a treatment benefit in mean change of visual acuity as early as 6 weeks (MACUGEN 0.3mg -1.53 letters vs. Sham -4.03 letters; $p=0.0069$). This treatment benefit was sustained through 54 weeks (MACUGEN 0.3mg -7.99 letters vs. Sham -15.03 letters; $p<0.0001$).

Patients receiving sham treatment were more than twice as likely to experience severe vision loss (≥ 30 letters of visual acuity from baseline) compared with patients receiving MACUGEN 0.3mg (22% vs. 10%, $p<0.0001$).

Patients receiving MACUGEN 0.3mg were less likely to have 20/200 or worse vision at week 54 than those receiving sham treatment (38% vs. 56%, p<0.0001).

At the end of the first year (week 54), approximately 1050 of the original 1208 patients were re-randomised to either continue the same treatment or to discontinue treatment through week 102.

At the end of the second year of treatment, the percentage of patients losing less than 15 letters of visual acuity from baseline to week 102 was: MACUGEN 0.3 mg 59 % versus Sham 45% (p=0.0385 in the combined analysis). See Table 2 below.

Table 2 Change in Visual Acuity From Baseline Up to 102 Weeks

Change in visual acuity (ETDRS letters)	Number (%) of patients		
	MACUGEN 0.3 mg n=133	Sham n=107	p values
< 15 letters loss	78 (59%)*	48 (45%)	0.0385

On average, the rate of vision decline in the MACUGEN treated group was slower than the rate in the patients who received sham treatment.

INDICATIONS

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

CONTRAINDICATIONS

MACUGEN is contraindicated in patients with active or suspected ocular or periocular infection or a known hypersensitivity to any component of this preparation.

PRECAUTIONS

MACUGEN is for intravitreal injection only.

MACUGEN has not been studied in patients with hepatic impairment and has not been adequately studied in patients with severe renal insufficiency (i.e. creatinine clearances below 30 mL/min). Therefore, clinicians should exercise appropriate clinical judgement before deciding to administer MACUGEN in these patient populations. (See PHARMACOLOGY, Pharmacokinetics).

As expected with intravitreal injections, transient increases in intraocular pressure may be seen. Therefore, perfusion of the optic nerve head should be verified and post injection elevations of intraocular pressure should be managed appropriately.

There is a small risk of endophthalmitis associated with any intravitreal injection procedure (for MACUGEN in the clinical setting, the incidence was 0.14% per injection). Proper aseptic injection technique should always be utilised when administering MACUGEN (See DOSAGE AND ADMINISTRATION, Instructions for use and handling). Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the post-marketing experience following the pegaptanib intravitreal administration procedure. A direct relationship to pegaptanib or any of the various medications administered as part of the injection preparation procedure or other factors has not been established in these cases. (See DOSAGE AND ADMINISTRATION).

Use During Pregnancy (Category B3)

Developmental toxicology studies of MACUGEN have been performed in mice at intravenous doses of 1 mg/kg/day to 40 mg/kg/day. MACUGEN produced no maternal toxicity and no evidence of teratogenicity or fetal mortality. A nominal (5%) decrease in fetal body weight and minimal delayed phalangeal ossification were observed in the absence of other ossification delays or clear evidence of maternal toxicity. In the 40 mg/kg/day group, the maximum MACUGEN plasma concentrations in dams were 20,000 fold greater than those observed in humans (3 mg dose group, 10 times greater than recommended dose). MACUGEN crosses the placenta in mice. In the 40 mg/kg/day group, MACUGEN concentrations in the amniotic fluid were 0.05% of the maternal plasma levels. The 40 mg/kg/day regimen represents about 7,000 times the recommended human monocular ophthalmic dose of 0.3 mg/eye every six weeks.

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

Use During Lactation

It is not known whether MACUGEN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MACUGEN is used in a breastfeeding woman.

Use in the Elderly

Approximately 93% (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.

Use in Children

MACUGEN has not been studied for use in paediatric patients.

Carcinogenesis, Mutagenesis and Impairment of Fertility

MACUGEN 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. MACUGEN, 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 bacterial mutagenicity tester strains (*S. typhimurium*), but produced a small increase in revertant frequency with no relationship to dose in a single bacterial mutagenicity tester strain (*E. coli*). MACUGEN, 2'-FU and 2'-FC tested negative in cell transformation assays. Based on this information there is no risk of genotoxicity.

Lifetime rodent carcinogenicity studies with MACUGEN have not been conducted.

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

Drug Interactions

Drug interaction studies have not been conducted with MACUGEN. MACUGEN is metabolised by nucleases and therefore cytochrome P450 mediated drug interactions are unlikely.

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 MACUGEN.

Exploratory analysis based on the clinical trial data indicated that there is no significant adverse interaction between concomitantly administered MACUGEN and photodynamic therapy with verteporfin.

Immunogenicity

No anti-MACUGEN IgG antibodies were detected in patients treated with MACUGEN.

Effects on the ability to drive or operate machinery

Patients may experience temporary visual blurring after receiving MACUGEN by intravitreal injection. Patients who develop these symptoms should not drive or use machines until this has resolved.

ADVERSE REACTIONS

MACUGEN was administered to 892 patients in controlled studies for one year (total number of injections = 7545, mean number of injections/patient = 8.5) at doses of 0.3, 1.0 and 3.0 mg. All three doses shared a similar safety profile. In the 295 patients who were treated with the recommended dose of 0.3 mg for one year (total number of injections = 2478, mean number of injections/patient = 8.4), 84% of the patients experienced an adverse event attributed by the investigators as being related to the injection procedure, 3% of the patients experienced a Serious Adverse Event potentially related to the injection procedure, and 1% experienced an adverse event potentially related to the injection procedure that led to study treatment discontinuation. Twenty seven percent (27%) of the patients experienced an adverse event attributed by the investigators as being related to the study drug. Two patients (0.7%)

experienced Serious Adverse Events potentially related to study drug. One of these patients had an aortic aneurysm; the other had a retinal detachment and retinal haemorrhage, which led to discontinuation of treatment.

Serious ocular Adverse Events reported in MACUGEN treated patients included endophthalmitis (12 cases, 1%), retinal haemorrhage (3 cases, <1%), vitreous haemorrhage (2 cases, <1%) and retinal detachment (4 cases, < 1%).

The safety data described below summarise all procedure and drug potentially related adverse events in the 295 patients in the 0.3 mg treatment group. The adverse reactions are listed by system organ class and frequency (very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), and uncommon ($\geq 1/1000$ and $< 1/100$)).

Psychiatric disorders

Uncommon nightmare, depression

Nervous system disorders

Common headache

Eye disorders

These ocular adverse reactions were considered potentially related to treatment with MACUGEN (either injection procedure or due to MACUGEN), and for the most part were considered related to the injection procedure.

Very common	anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis, vitreous floaters and vitreous opacities
Common	abnormal sensation in eye, cataract, conjunctival haemorrhage, conjunctival hyperaemia, conjunctival oedema, conjunctivitis, corneal dystrophy, corneal epithelium defect, corneal epithelium disorder, corneal oedema, dry eye, endophthalmitis, eye discharge, eye inflammation, eye irritation, eye pruritus, eye redness, eye swelling, eyelid oedema, lacrimation increased, macular degeneration, mydriasis, ocular discomfort, ocular hypertension, periorbital haematoma, photophobia, photopsia, retinal haemorrhage, vision blurred, visual acuity reduced, visual disturbance, vitreous detachment, and vitreous disorder
Uncommon	asthenopia, blepharitis, conjunctivitis allergic, corneal deposits, eye haemorrhage, eyelids pruritus, keratitis, vitreous haemorrhage, pupillary reflex impaired, corneal abrasion, retinal exudates, eyelid ptosis, retinal scar, chalazion, corneal erosion, decreased intraocular pressure, injection site reaction, injection site vesicles, retinal detachment, corneal disorder, retinal artery occlusion, retinal tear, ectropion, eye movement disorder, eyelid irritation, hyphaema, pupillary disorder, iris disorder, ocular icterus, anterior uveitis, deposit eye, iritis, optic nerve cupping, pupillary deformity, retinal vein occlusion, and vitreous prolapse

Ear and labyrinth disorders

Uncommon deafness, Meniere's disease aggravated, vertigo

Cardiac disorders

Uncommon palpitations

Vascular disorders

Uncommon hypertension, aortic aneurysm

Respiratory, thoracic and mediastinal disorders

Common rhinorrhea

Uncommon nasopharyngitis

Gastrointestinal disorders

Uncommon vomiting, dyspepsia

Skin and subcutaneous tissue disorders

Uncommon contact dermatitis, eczema, hair colour changes, rash, pruritus, night sweats

Musculoskeletal and connective tissue disorders

Uncommon back pain

General disorders and administration site conditions

Uncommon fatigue, rigors, tenderness, chest pain, influenza like illness

Investigations

Uncommon increased gamma-glutamyltransferase activity

Injury, poisoning and procedural complications

Uncommon abrasion

Three hundred and seventy four (374) patients received continuous treatment with MACUGEN for up to 2 years (128 at 0.3 mg, 126 at 1 mg, and 120 at 3 mg). The overall safety data were consistent with the Year 1 safety data, and no new safety signals emerged. In the 128 patients who were treated with the recommended dose of 0.3 mg for up to 2 years (total number of injections in the second year = 913, mean number of injections in the second year = 6.9), there were no evident consistent increases in frequency of adverse events compared to those seen during the first year.

Post-marketing experience: rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in patients following administration of pegaptanib along with various medications administered as part of the injection preparation procedure. (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

FOR INTRAVITREOUS INJECTION ONLY.

Treatment with MACUGEN is for intravitreal injection only and should be given by ophthalmologists experienced in intravitreal injections.

MACUGEN 0.3mg should be administered once every six weeks (9 injections per year) by intravitreal injection into the eligible eye.

Use in one patient on one occasion only. MACUGEN contains no antimicrobial preservative. Discard any residue. Do not use if the solution appears cloudy, particles are observed or if there is evidence of damage to the syringe. MACUGEN should be inspected visually for particulate matter and discoloration prior to administration.

The safety and efficacy of MACUGEN therapy administered to both eyes concurrently has not been studied.

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

The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure. (See PRECAUTIONS).

Instructions for use and handling

To optimise safety the injection procedure should be carried out under aseptic conditions, which include the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Adequate anaesthesia, antibiotic drops and a povidone-iodine flush (or a suitable alternative) should be administered prior to the injection. For patients allergic to, or intolerant of, povidone-iodine, topical broad-spectrum antibiotic drops may be used for 3 days prior to the procedure. Performing a paracentesis prior to the injection is not recommended. Broad-spectrum antibiotic drops should be continued for 2 days following the injection and patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

To assemble the syringe for administration, attach the threaded plastic plunger rod to the rubber stopper. To avoid compromising sterility of the product, do not pull back on the plunger rod. Do not push on the plunger rod or remove the syringe tip cap until ready to administer the product. A snap-on flange is provided to facilitate syringe handling during administration. Discard any unused product.

OVERDOSAGE

Overdosage with MACUGEN has not been reported in clinical trials. Doses of MACUGEN up to 10 times the recommended dosage of 0.3mg have been studied. No additional adverse events have been noted.

PRESENTATION

MACUGEN is supplied in a single-dose, pre-filled syringe containing 0.3mg pegaptanib sodium in a 90 µL deliverable volume. Each pack contains 2 pouches in a carton. One pouch contains the 1 ml pre-filled Type 1 glass syringe with a pre-attached 27-gauge needle. The second pouch contains a plastic plunger and snap-on flange.

Pharmaceutical precautions

Special Precautions

Store at 2°C to 8°C (Refrigerate. Do not freeze)

Shelf life

18 Months

Medicine classification

Prescription medicine

NAME AND ADDRESS

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DATE OF PREPARATION

16 April 2007

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