NAME OF THE MEDICINAL PRODUCT

MACUGEN

QUALITATIVE AND QUANTITATIVE COMPOSITION

A single dose pre-filled syringe containing a 3.47 mg/ml solution to deliver a dose of 0.3 mg pegaptanib sodium (as the free acid from of the oligonucleotide) in a nominal volume of 90 microlitres.

PHARMACEUTICAL FORM

Solution for injection.

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

FOR INTRAVITEROUS INJECTION ONLY

Treatment with pegaptanib sodium is for intravitreous injection only and should be given by ophthalmologist experienced in intravitreous injections.

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

The product should be inspected visually for particulate matter and discoloration prior to administration.

The injection procedure should be carried out under aseptic conditions, which includes the use of sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing intravitreal procedure (see section **Special warnings and special precautions for use**). Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

Prior to administration the threaded polystyrene plunger rod is attached to the rubber stopper inside the barrel of the syringe. To avoid compromising sterility of the product, the plunger rod should not be pulled back until the administration. A snap on flange is provided to facilitate syringe handling during the administration. The syringe needle cap is then removed to allow administration of the product.

Following the injection, patients should be monitored for elevation in intraocular pressure, perfusion of the optic nerve head and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophtalmitis without delay.

Pegaptanib sodium therapy administered to both eyes concurrently has not been studied.

The safety and efficacy of pegaptanib sodium has not been evaluated beyond 2 years.

Specific patient groups:

Hepatic impairment:
Pegaptanib sodium has not been studied in patients with hepatic impairment.
However, no special considerations are needed in this population (see section **Pharmacokinetic Properties – Special Populations:** Hepatic Impairment)

Renal insufficiency:
Pegaptanib sodium has not been adequately studied in patients with severe renal insufficiency (creatinine clearance < 30 ml/min). No special consideration are needed in patients with creatinine clearance above 30 ml/min. (See section **Pharmacokinetic Properties – Special Populations:** Renal Insufficiency).

Gender:
No special considerations are needed. (See section **Pharmacokinetic Properties – Special Populations:** Gender)

Contraindications

Active or suspected ocular or periocular infection.

Known hypersensitivity to pegaptanib sodium or any excipients in this product.

Special warnings and special precautions for use

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

There is a small risk of endophtalmitis associated with the intraviterous injection procedure (0.1 % per injection in clinical studies). (See section **Posology and Method of Administration**).
Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the post-marketing experience following the pegabtanib intravitreal administrations 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 section **Posology and Method of Administration**)

Interaction with other medicinal products and other forms of Interactions

Drug interaction studies have not been conducted with pegaptanib sodium.

Pegaptanib is metabolized by nucleases and therefore cytochrome P450 mediated drug interactions are unlikely.

Two early clinical studies conducted in patients who received pegaptanib sodium alone and/or in combination with photodynamic therapy (PDT) revealed no apparent difference in the plasma pharmacokinetics of pegaptanib.

Pregnancy and lactation

Pregnancy;
Pegaptanib sodium has not been studied in pregnant women. The potential risk to humans is unknown. The systemic exposure to pegaptanib is expected to be very low after ocular administration. Nevertheless, pegaptanib sodium should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or foetal 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.

Lactation: It is not known whether pegptanib sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pegaptanib sodium is administered to a nursing woman.

Effects on ability to drive and use machines

Patients may experience temporary visual blurring after receiving pegaptanib sodium by intravitreous injection. Patients should therefore not drive or use machines until this has resolved.

Undesirable effects

Pegaptanib sodium was administered to 892 patients in controlled studies for one year total number of injection = 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/patients = 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; 0.7% of the patients experienced a serious adverse event potentially related to study drug, and 0.3% experienced an serious adverse event potentially related to the study drug that led to study treatment discontinuation.

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 in the first year.

Psychiatric disorders: Depression and nightmare

Nervous system disorders: Headache

Eye disorders: These ocular adverse reactions were considered potentially related to treatment with pegaptanib sodium (either injection procedure or due to pegaptanib sodium), and for the most part were considered related to the injection procedure. Abnormal sensation in eye, anterior chamber inflammation, anterior uveitis, asthenopia, blepharitis, cataract, chalazion, conjunctival haemorrhage, conjunctival hyperaemia, conjunctival edema, conjunctivitis, conjunctivitis allergic, corneal abrasion, corneal deposits, corneal disorder, corneal dystrophy, corneal edema, corneal epithelium defect, corneal epithelium disorder, corneal erosion, decreased intraocular pressure, deposit eye, dry eye, ectropion, endophthalmitis, eye discharge, eye hemorrhage, eye

inflammation, eye irritation, eye movement disorder, eye pain, eye pruritus, eye redness, eye swelling, eyelid edema, eyelid irritation, eyelid pruritus, eyelid ptosis, hyphema, increased intraocular pressure, injection site reaction, injection site vesicles, iris disorder, iritis, intraocular pressure, injection site reaction, injection site vesicles, iris disorder, iritis, keratitis, lacrimation increased, macular degeneration, mydriasis, ocular discomfort, ocular hypertension, ocular icterus, optic nerve cupping , periorbital hematoma, photophobia, photopsia, punctuate keratitis, pupillary deformity, pupillary disorder, pupillary reflex impaired, retinal artery occlusion, retinal detachment, retinal exudates, retinal hemorrhage, retinal scar, retinal tear, retinal vein occlusion, vision blurred, visual acuity reduced, visual disturbance, vitreous detachment, vitreous disorder, vitreous floaters, vitreous hemorrhage, vitreous opacities, and vitreous prolapse.

Ear and Labyrinth Disorders: Deafness, Meniere's disease aggravated, and vertigo

Cardiac Disorders: Palpitations.

Vascular Disorders: Aortic aneurism and hypertension.

Respiratory, Thoracic and Mediastinal Disorders: Nasopharyngitis and rhinorrhea.

Gastrointestinal Disorders: Dyspepsia and vomiting.

Skin and Subcutaneous Tissue Disorder: Contact dermatitis, eczema, hair color changes, night sweats, pruritus, and rash.

Musculoskeletal and Connective Tissu Disordes: Back pain.

General Disorders and Administration Site Conditions: Chest pain, fatique, influenza like illness, rigors, and tenderness.

Investigations: Increased gamma-glutamyltransferase

Injury, Poisoning and Procedural Complications: Abrasion

Three hundred seventy four (374) patients received continuous treatment with pegaptanib sodium 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 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-Martketing Experience: Rare cases of anaphylaxis/anaphylactoid reactions, including angioderma, have been reported in patients following administration of pegaptanib along with various medications administered as part of the injection preparation procedure (see section **Posology and Method of administration and Special warnings and precautions for use**).

Overdose

Doses of pegaptanib sodium up to 10 times the recommended dosage of 0.3 mg have been studied. No additional adverse events have been noted.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pegaptanib sodium is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular Vascular Endothelial Growth Factor (VEGF)165 inhibiting its activity. VEGF is a secreted protein that induces angiogenesis, vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of (AMD). (VEGF)165 is the VEGF isoform preferentially involved in pathological ocular neovascularization. The selective inhibition in animals with pegaptanib sodium proved as effective at suppressing pathological neovascularization 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.

Pegaptanib sodium was studied in two controlled, double-masked, and identically designed randomized studies (EOP1003; EOP1004) in patients with neovascular AMD. A total of 1208 patients were enrolled and 1190 were treated (892 pegaptanib sodium, 298 sham) with a median age of 77 years. Patients received a mean of between 8.4-8.6 treatments out of a possible 9 total across all treatment arms in the first year.

Patients were randomized to receive control (sham treatment) or 0.3 mg, 1 mg, or 3 mg pegaptanib sodium administered as intravitreous injections every 6 weeks for 48 weeks. 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 20/40and 20/320. Verteporfin photodynamic therapy (PDT) was permitted at the discretion of the investigators in patients with predominantly classic lesions.

The primary efficacy endpoint was the proportion of patients losing less than 15 letters of visual acuity from baseline up to 54 week assessment. At one year, pegaptanib sodium 0.3 mg exhibited a statistically significant treatment benefit in both trials for the primary efficacy endpoint (prespecified pooled analysis, pegaptanib sodium 0.3 mg 70% versus sham 55%).

When combining both studies, patients treated with pegaptanib treated with 0.3 mg had less severe vision loss (30 or more letters of vision from baseline to week 54) compared with the sham patients (pegaptanib sodium 0.3 mg, 10 % vs. sham 22 %, p-value =<.0001).

When combining both studies, the proportion of patients treated with 0.3 mg pegaptanib sodium reaching a vision of 20/200 or worse at week 54 was lower than in sham patients (pegaptanib sodium 0.3 mg, 38 % vs. sham 56 %, p-value = <.0001).

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.

Pegaptanib sodium 0.3 mg showed treatment benefit regardless of baseline lesion subtype, lesion size and visual acuity as well as age, gender, iris pigmentation and prior and/or baseline PDT usage.

During the second year of treatment, the percentage of patients losing less than 15 letters from baseline to week 102 was: pegaptanib sodium 0.3 mg 59% versus sham 45%.

On average, pegaptanib sodium 0.3 mg treated patients and sham treated patients continued to

experience vision loss. However, the rate of vision decline in the pegaptanib sodium treated group was slower than the rate in the patients who received sham treatment.

Pharmacokinetic properties

Absorption:
In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreal administration. The rateof 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-lafe of pegaptanib after a 3 mg (10-times the recommended dose) monocular dose is 10 + 4 days.

A mean maximum plasma concentration of about 80 ng/ml occurs within 1 to 4 days after a 3 mg 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 intravitreously every 6 weeks. At doses below 0.5 mg/eye, pegaptanib plasma concentration do not likely exceed 10 ng/ml.

The absolute bioavailability of pegaptanib after intravitreous administration has not been assessed in humans, but is approximately 70-100% in rabbits, dogs and monkeys.

In animals that received doses of Macugen up to 0.5 mg/eye to both eyes, plasma concentration were 0.03% to 0.15% of those in the vitreous humor.

Distribution/Metabolism/Excretion:
In mice, rats, rabbits, dogs and monkeys, pegaptanib distributes primarily into plasma volume and is not extensively distributed to peripheral tissues after intravenous administration. Twenty-four hours after intravitreous administration of a radiolabeled dose of pegaptanib sodium to both eyes of rabbits, radioactivity was mainly distributed in vitreous humor, retina and aqueous humor. After intravitreous 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. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled pegaptanib sodium intravenous and intravitreous doses. Pegaptanib is metabolized by endo- and exonucleases. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Special Populations:

Gender:
Pegaptanib pharmacokinetics are similar in female and male patients and within the age range 50 to 90 years. (See section **Posology and Method of Administration – Spesific Patients Groups:** Gender)

Renal Insufficiency:
A decrease in creatinine clearance from 70 ml/min to 30 ml/min was associated with a 2.3 fold increase in pegaptanib AUC. However, a dosage adjustment for patients treated with the recommended 0.3 mg pegaptanib sodium 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. (See section **Posology and Method of Administration** – Renal Insufficiency)

Hepatic Impairment:
Pegaptanib pharmacokinetics have not been studied in patients with hepatic impairment. However, the systemic exposure is expected to be within a well tolerated range in patients with hepatic impairment, as a 10 fold higher dose (3 mg/eye) was well tolerated. There is therefore no need for dose adjustment or special precautions in this population.

Preclinical safety data
Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenis studies with pegaptanib have not been conducted.

Pegaptanib sodium produced no maternal toxicity and no evidence of teratogenicity or foetal mortality in mice at intravenous doses of 1 to 40 mg/kg/day. Reduced body weight (5%) and minimal delayed ossification in forepaw phalanges were observed; these findings were within baseline values for this species and were considered not clinically relevant. In the 40 mg/kg/day group, the maximum pegaptanib sodium plasma concentrations in dams were 20000 fold greater than those observed in humans (3mg dose group, 10 times greater than recommended dose). In the 40 mg/kg/day group, pegaptanib sodium concentrations in the amniotic fluid were 0.05% of the maternal plasma levels.

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

PHARMACEUTICAL PARTICULARS
List of excipients
Sodium chloride
Monobasic sodium phosphate monohydrate
Dibasic sodium phosphate heptahydrate
Sodium hydroxide
Hydrochloric acid
Water for injection

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Special precautions for storage

Store in a refrigator (2˚C - 8˚C). Do not freeze.

Nature and contents of Container

Pegaptanib sodium is supplied in a single dose pack. Each pack contains 2 pouches in a carton. One pouch contains the 1 ml pre-filled syringe. Type I glass, with a pre-attached 27 gauge needle. The second pouch contains a polystyrene plunger rod and snap-on flange.

Instruction for use and handling (and disposal)

Pegaptanib sodium is for single use only. Do not use if the solution appears cloudy, particles are observed or if there is evidence of damage to the syringe.

Pegaptanib sodim (in pouch) should be used within eight hours once removed from the refrigator. Allow the pre-filled syringe to reach room temperature before injecting.

Pegaptanib sodium (in a pouch) may be re-refrigerated as long as the re-refrigerated syringe is not left out at room temperature for a cumulative time period exceeding eight hours. Removal and re-refrigeration of pegaptanib sodium should be done only if necessary and the number of times this is done kept a minimum.

Pegaptanib sodium (in pouch) should be discarded if kept at room temperature for more than eight hours.

To prevent contamination, the pegaptanib sodium syringe should not be removed from the pouch until the patients has been prepared for injection, and the dose is ready to be administered.

If an unpouched syringe is not used, it should be discarded. Pegaptanib sodium cannot be re-refrigeration once removed from the pouch.

Any unused product or waste material should be disposed of in accordance with local requirements.

SUPPLY

Box, contains off 1 pouch 1 ml pre-filled syringe + 1 pouch plastic plunger & snap-on flange;

Manufactured by:
Gilead Sciences, Inc., San Dimas, USA

Release site :
Pfizer Health AB, Stockholm, Sweden

Packed by:
Cardinal Health Packaging Services, Philadelphia, USA

Imported by:
PT. Pfizer Indonesia
PO.BOX 2706 Jakarta
Indonesia