

drug information perspectives

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Pegaptanib
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PEGAPTANIB

SYNONYMS: NX1838, EYE001

TRADE NAME: Macugen

CLASSIFICATION: Vascular endothelial growth factor antagonist; aptamer; antiangiogenic agent

ACTION

VEGF antagonist. Binds to extracellular vascular endothelial growth factor (VEGF)-165 (the major soluble form of VEGF), reducing its ability to bind to its receptors on vascular endothelial cells and to exert its physiological effects of inducing angiogenesis and increasing vascular permeability and inflammation. Reduces abnormal neovascularization while sparing normal vasculature. It is a 28-base ribonucleic acid aptamer linked to 2 polyethylene glycol moieties (pegylated) to increase its half-life.

PHARMACOKINETICS

- **Half-life:** 10 days in plasma following IV injection in humans, 84 hours following intravitreal injection in animals. Vitreous half-life 4 days in primates.
- **Absorption:** Bioavailability in animals 70-100%.
- **Distribution:** Reaches the systemic circulation in humans. Mainly distributes into vitreous fluid, retina and aqueous fluid as well as the kidney in animals.
- **Metabolism:** Metabolized by endonucleases and exonucleases.
- **Elimination:** In animals, eliminated as parent drug and metabolites mainly in urine.
- **Special populations:** *Hepatic impairment:* No data. *Renal impairment:* No data at usual dose. At higher doses, AUC increases. No data in severe renal impairment.

USES AND EFFICACY

Uses: Treatment of subfoveal choroidal neovascularization (CNV) of the eye due to **exudative (wet) age-related macular degeneration.**

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Major clinical trials

VISION (VEGF Inhibition Study In Ocular Neovascularization, 2004): 1186 patients with exudative age-related macular degeneration were randomized to receive intravitreal pegaptanib at doses of 0.3, 1.0 or 3.0 mg every 6 weeks. Patients had all subtypes of lesions (24-27% mainly classic, 34-38% minimally classic, 38-40% occult) and lesion sizes up to 12 optic disk areas, visual acuity 50-53 at baseline. Verteporfin was used as well in about 20-25% of each study group. After 54 weeks, statistically significantly more patients treated with pegaptanib 0.3 mg responded (defined as increase, no change or less than 3 lines of vision loss; pegaptanib 70% vs. sham injection 55%; absolute difference 15%; NNT 6.7). No change or a vision increase occurred in 33% of patients given pegaptanib (vs. sham 23%, $p=0.003$). A gain in visual acuity was seen in 22% with pegaptanib vs. sham 12%. Severe vision loss occurred less commonly with pegaptanib (10% vs. sham injection 22%, $p<0.001$). At the end of one year, 67% of patients given pegaptanib lost some vision compared with 77% given sham injection. Higher doses were not more beneficial. Patient response was not related to lesion type, lesion size, baseline visual acuity or use of verteporfin. No systemic side effects were detected; serious side effects occurred in 2.6% of patients given pegaptanib for one year (NNH=38; 5 traumatic injuries to the lens, 6 retinal detachments, and 12 cases of endophthalmitis). A rerandomized continuation of the study into a second year found similar results, except that the disease progressed. Study limitations: The sham injection group had larger lesions at baseline, which may have biased the results in favour of pegaptanib, since outcome is generally associated with lesion size. Results were not reported for the different lesion subtypes. Some patients also received verteporfin.

Clinical course: Benefit in visual acuity is significantly greater than no treatment at 6 weeks and continues to increase for 48 weeks. Choroidal neovascularization is reduced initially but regrows.

Place in therapy

Exudative age-related macular degeneration: Lowers the rate of loss of visual acuity. Considering all lesion subtypes, overall results are similar to those obtained with verteporfin photodynamic therapy, with response (defined as improved, no change or mild vision decrease) at one year in 44-55% of patients given placebo, 49-77% with verteporfin, and 70% with pegaptanib). The absolute difference in favour of treatment is similar (15%) vs. placebo for verteporfin and pegaptanib, but larger (28%) for verteporfin in patients with predominantly classic lesions, and 50% for verteporfin in classic lesions with no occult features. Pegaptanib is not as effective as newer therapies, e.g. ranibizumab (not available in Canada) and off-label intravitreal bevacizumab (Avastin), which bind to all of the active forms of VEGF. Some clinicians recommend that pegaptanib should no longer be used in ocular pathology.

Advantages

- Approved for all lesion subtypes of subfoveal exudative age-related macular degeneration (classic or occult).
- Not an antibody therefore it will not elicit immune responses or antibody formation.
- May be slightly more likely to initially improve vision (22% of patients) compared with verteporfin (12-16%) and placebo (7-12%).

Disadvantages

- Requires repeated intravitreal injection into the eye, which may have low patient acceptance and can lead to ocular complications.
- May increase intraocular pressure.
- Few patients will have improved visual acuity.
- Inhibits only one form of VEGF.
- Limited data.
- Lesion size continues to increase over time despite treatment.
- Optimal treatment duration is unknown.
- Long-term safety is unclear. VEGF is required for normal wound healing, bone growth, cyclic endometrial development, placental vascularization, and the formation of collateral vessels in ischemic limbs and myocardium, and is involved in neuronal function in the brain.

Investigational/Unapproved Uses:

- **Combination with verteporfin:** In a phase II pegaptanib study, 11 patients also received verteporfin. At three months, 60% of these patients had mildly improved vision. Larger studies are needed to confirm these encouraging results.

- **Diabetic retinopathy:** Intraocular levels of VEGF correlate with the severity of vascularization in diabetic retinopathy. In a phase II study in diabetic macular edema, visual acuity was more likely to improve, and fewer patients needed photocoagulation therapy.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity** (anaphylaxis and anaphylactoid reactions have occurred).
- Suspected or apparent **ocular infection** (risk of infection).
- For ophthalmic use only.

Precautions

- **Increased intraocular pressure:** monitor IOP and optic nerve perfusion (increased IOP occurs). Conduct a follow-up appointment in the first week after injection.
- **Administration:** Use proper aseptic technique for injection and monitor for infection in the week after injection (endophthalmitis can occur). Broad spectrum ocular antibiotics are administered prior to injection and for two days afterwards. Avoid touching or puncturing the lens (traumatic cataracts have occurred).
- **Children** (no data).
- **Concurrent injection into both eyes:** no data.
- **Report** any unexpected or serious reactions to Health Canada's adverse reaction monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789).

PREGNANCY AND LACTATION

Not teratogenic in animals. VEGF is essential for embryonic vessel formation. In young monkeys, impaired reproductive function and physeal dysplasia have occurred when exposed to antibodies to VEGF. No human data. Consider risk versus benefit.

SIDE EFFECTS

Frequency of occurrence is given in brackets.

Gastrointestinal: Vomiting (3% per year vs. placebo 0).

Hypersensitivity: Anaphylaxis, anaphylactoid reactions, angioedema (rare, onset within a few hours).

Ocular: Increased intraocular pressure (14% per year vs. placebo 3%, usually 30 minutes after injection, increases to mean 24 mm Hg, range up to 36 mm Hg, transient, resolves within 5-7 days); glaucoma (1 case). Endophthalmitis (intraocular infection, 1.3% of patients per year vs. placebo 0, usually in the first week after injection, commonly coagulase-negative Staphylococcus epidermiditis; associated with poor aseptic technique such as failure to use an eyelid speculum; may result in severe vision loss). Traumatic cataracts (0.6% per year, if the intravitreal needle touches or punctures the lens). Anterior chamber inflammation (16% per year vs. placebo 6%); blurred vision (9% per year vs. placebo 5%); cataracts (20% per year vs. placebo 18%); conjunctival hemorrhage (8% per year vs. placebo 6%); conjunctivitis (5% per year vs. placebo 3%); corneal abrasion (1% per year vs. placebo 0); corneal edema (9% per year vs. placebo 7%); eye discharge (11% per year vs. placebo 8%); eye hemorrhage (2% per year vs. placebo 0); eye pain (34% per year vs placebo 29%); ocular discomfort (6% per year vs. placebo 4%); photopsia (7% per year vs. placebo 3%); punctuate keratitis (32% per year vs placebo 27%); retinal degeneration (1% per year vs. placebo 0); retinal detachment (cases); vitreous floaters (33% per year vs. placebo 8%); vitreous hemorrhage (2% per year vs. placebo 0); vitreous opacities (19% per year vs. placebo 10%).

INTERACTIONS

No data.

PARENTERAL ADMINISTRATION

Injection: For intravitreal injection only. The injection is kept refrigerated prior to use, but may be kept at room temperature for up to 8 hours. It is not necessary to bring it to room temperature prior to injection. Do not shake it vigorously. Do not pull back on the syringe plunger. Use aseptic technique, including sterile gloves, sterile drape, and sterile eyelid speculum. Administer local anesthesia and broad-spectrum antibiotics.

DOSAGE

Adult:

Intravitreal: 0.3 mg once every 6 weeks by intravitreal injection into the eye.

Renal impairment: No dosage adjustment required.

Hepatic impairment: No data.

NURSING IMPLICATIONS

Use proper aseptic technique, including sterile gloves and sterile drape for the injection, to reduce the risk of eye infection. Do not use the solution if it is discoloured, cloudy or particles are seen.

Monitor the patient for any increase in intraocular pressure, usually within 30 minutes after injection, or hypersensitivity reactions such as anaphylaxis within several hours.

Store the medication under refrigeration. Do not freeze. Do not remove the syringe from the pouch until the patient is ready for injection.

PATIENT INSTRUCTIONS

Pegaptanib (peg-AP-ta-nib) is used to stabilize vision in patients with age-related macular degeneration of the wet (exudative) type.

Before having this treatment, be sure to tell your eye doctor if you have ever had a reaction to this medication, and if you have any symptoms of eye infection such as eye irritation, redness, sensitivity to light, swelling or pain in the eye area. Also inform your doctor if you have a history of increased intraocular eye pressure or glaucoma.

Following treatment, there is a possibility of eye infection as well as other eye problems. If you notice redness of your eye, sensitivity to light, eye pain or change in vision, consult your eye doctor as soon as possible. If your doctor has asked you to use any antibiotics or other drugs to reduce the risk of infection, be sure to follow the instructions exactly as directed.

If you have experienced any unexpected or serious reactions to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number. Also ensure that your physicians are informed and record all reactions for the future.

PRESENTATION

Injection: 0.3 mg per single-use prefilled syringe.

References are available on request.