National PBM Drug Monograph

Pegaptanib (Macugen®)

April 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA-approved Indication: Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist, approved for the treatment of neovascular (wet) age-related macular degeneration (AMD). It has been used as monotherapy or in combination with photodynamic therapy (PDT). Pegaptanib is unique in that it is approved for all lesion types of AMD.

Dosing: Pegaptanib is administered every six weeks by intravitreous injection. The dose used is 0.3 mg. Aseptic technique should be used during the injection process. This includes the use of sterile gloves, sterile drape and sterile eyelid speculum. Anesthesia and a broad spectrum antibiotic should be administered to the eye which will be treated.

Safety: Safety and tolerability data for pegaptanib is available from the two years of trial information published on the agent. This report involves 1186 patients involved in clinical trials of the agent. Pegaptanib does not appear to cause systemic adverse events, alterations in laboratory values, changes in mortality, hypersensitivity or development of antibodies to the agent. The occurrence of endophthalmitis appears directly related to aseptic technique, not the agent itself.

Efficacy: Pegaptanib demonstrated a statistically significant benefit as measured by the primary outcome measure of loss of fewer than 15 letters of visual acuity and the secondary measure of maintenance or gain of visual acuity. These results were evident as early as six weeks of therapy and continued throughout treatment. Results were not dependent upon type of lesion present, lesion size or baseline visual acuity.

Conclusion: Pegaptanib has been shown to provide a statistically significant benefit in all lesion types of AMD. These results were demonstrated as early as six weeks of therapy and continued over the 54 weeks of the trial. Treatment with pegaptanib reduced the percentage of patients with severe vision loss (loss of $\geq$30 letters of visual acuity), slowed progression to legal blindness and demonstrated a response (loss of < 15 letter of visual acuity) in a significant number of treated patients. The development of adverse events in treated patients was minimal and most often related to aseptic technique. The most commonly reported adverse events were ocular and mild in severity.

Recommendation: Pegaptanib provides a safe effective treatment for all lesion types of AMD. Further studies are needed to determine the importance of using concurrent laser therapy, duration of therapy and patients who may benefit the most from therapy.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pegaptanib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1]

Pegaptanib is an aptamer, an oligonucleotide (short strands of RNA) that assumes a specific three-dimensional shape to facilitate high- affinity binding to specific target molecules. Since pegaptanib spares nontarget proteins it is thought to cause no toxicity or immunogenicity. Pegaptanib binds to vascular endothelial growth factor (VEGF), thereby, inhibiting angiogenesis. Additionally, pegaptanib decreases permeability of the vascular bed and decreases inflammation.

The mean half-life of the agent after a 3.0 mg intravitreal dose (ten times the dose approved for use) is 10±4 days. Maximal plasma concentrations occur one to four days after injection. Pegaptanib is metabolized by endo- and exonucleases. The primary route of elimination for the parent drug and metabolites is the urine.

FDA Approved Indication(s) and Off-label Uses[1]

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist, approved for the treatment of neovascular (wet) age-related macular degeneration. It has been used as monotherapy or in combination with photodynamic therapy (PDT). Pegaptanib is also being investigated for the treatment of diabetic macular edema.

Current VA National Formulary Alternatives

The only comparative treatment is verteporfin combined with photodynamic therapy. Verteporfin is currently non formulary at the national level.

Dosage and Administration[1]

Pegaptanib is administered every six weeks by intravitreous injection. The dose used is 0.3 mg. Aseptic technique should be used during the injection process. This includes the use of sterile gloves, sterile drape and sterile eyelid speculum. Anesthesia and a broad spectrum antibiotic should be administered to the eye which will be treated. Following the injection patients should be monitored for elevation of intraocular pressure (IOP) and endophthalmitis.

Efficacy

The efficacy of pegaptanib has been evaluated in two concurrent, randomized, double-blind, multicenter trials[2]. The trail sites included the United States, Europe, Canada, South America, Australia and Israel. Patients were randomized to receive one of three does of pegaptanib (3mg, 1mg and 0.3 mg) or placebo (given as a sham injection). Treatment groups were similar in regards to age, race, gender, subtype of lesion, size of lesion, history of laser therapy and visual acuity. All lesion subtypes were allowed in the trial design (predominately classic, minimally classic and occult). During the second year of the trial patients were re-randomized to continue treatment or discontinue. Patients in the sham injection group were re-randomized to continue, discontinue or begin therapy with pegaptanib. Patients were allowed to receive verteporfin and photodynamic therapy if they qualified. The trial included a two year time frame. The primary efficacy outcome of the trials was the proportion of patients who had lost fewer than 15 letters (3 lines) of visual acuity at 54 weeks. There was evidence of a plateau effect with the dose of

pegaptanib employed, with the higher doses (3 and 1 mg) not conferring additional benefit. Therefore only the 0.3 mg dose will be included in further discussions.

Pegaptanib demonstrated a statistically significant benefit as measured by the primary outcome measure of loss of fewer than 15 letters of visual acuity and the secondary measure of maintenance or gain of visual acuity. These results were evident as early as six weeks of therapy and continued throughout treatment. Results were not dependent upon type of lesion present, lesion size or baseline visual acuity. The results of the trial are summarized in **Table 1**.

Table 1: Rate of Visual Acuity Loss

	Pegaptanib 0.3 mg		Sham injection		P value (vs. sham injection)
	24 weeks	54 weeks	24 weeks	54 weeks	
Loss of fewer than 15 lines of visual acuity	82%	70%	64%	55%	<0.001
Gain ≥ 5 letters		22%		12%	0.004
Visual acuity in study eye ≤20/200		38%		56%	<0.001

Adverse Events (Safety Data)[1,2]

Safety and tolerability data for pegaptanib is available from the two years of trial information published on the agent. This report involves 1186 patients involved in clinical trials of the agent. Pegaptanib does not appear to cause systemic adverse events, alterations in laboratory values, changes in mortality, hypersensitivity or development of antibodies to the agent.

Serious Adverse Events

Serious adverse events were related to the injection procedure employed. These occurred in <1% of the injections and include retinal detachment, iatrogenic traumatic cataract and endophthalmitis.

Common Adverse Events

The most common adverse events reported during clinical trials were transient and self limiting. Several of the adverse events reported were more common in the eyes treated with study drug than in those treated with sham injections, so that the relation of scleral penetration and injection procedure may account for the appearance of adverse events as well as pegaptanib. **Table 2** summarizes the adverse events reported. The rate of therapy discontinuation during trials of pegaptanib was not higher than that for the sham injection group. Pegaptanib appears to be well tolerated in patients with minimal development of adverse events.

Table 2: Adverse Events

Percent occurrence	Systemic Adverse Events	Ocular Adverse event
10-40%		Blurred vision, eye discharge, eye irritation, eye pain, hypertension, increased IOP, punctate keratitis, vitreous floaters and opacities, corneal edema
6-10%	Bronchitis, diarrhea, headache, dizziness, nausea	Blepharitis, conjunctivitis, photopsia
1-5%	Arthritis, chest pain, dyspepsia, hearing loss, vertigo, vomiting, contact dermatitis	Allergic conjunctivitis, corneal abrasion, eye swelling, eyelid irritation, mydriasis, periorbital hematoma, retinal edema, corneal deposits

Precautions/Contraindications[1]

Pegaptanib is administered by intravitreal injection. This type of injection may cause endophthalmitis and increased ocular pressure. Patients must be monitored for development of either of these events. The presence of ocular or periocular infection would be a contraindication for a patient to receive pegaptanib.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

Pegaptanib(generic name) Potential name confusion: Peganone®, paraplatin, imatinib (Gefitinib®), Protonix®.

Potential severity: Major with all agents since any of them given as an intravitreous injection could cause ocular damage.

Probability: Remote with Peganone®, imatinib, and the oral form of Protonix®, uncommon for the other agents due to vial size and strength (including Protonix® intravenous)

Macugen (trade name) Potential name confusion: Adagen, magnesium sulfate, glucagen®, mustargen, Salagen®.

Potential severity: Major with all agents since any of them given as an intravitreous injection could cause ocular damage

Probability: Remote with Salagen Major with all agents since any of them given as an intravitreous injection could cause ocular damage as it is an oral agent, uncommon for the other agents due to vial size and strength.

Drug Interactions[1]

There have been no reported drug interactions with pegaptanib. Since the agent does not utilize the hepatic enzyme system for metabolism it is unlikely that interactions will occur.

Data Compilation Tables

The NNT for the primary outcome of rate of visual acuity loss (measured as the loss of fewer than 15 letters) is shown in the following table:

(OUTCOME ON DRUG)	70%
(OUTCOME ON PBO)	55%
Treatment duration	54 weeks
Relative Risk Reduction	27%
Absolute Risk Reduction	15%
NNT	7

Acquisition Costs

Both verteporfin and pegaptanib have FSS prices on file. The acquisition costs of the two drugs cannot be directly compared as the use of verteporfin necessitates the use of photodynamic laser therapy and its associated costs as well as the infusion clinic services.. Additionally, pegaptanib is dosed every six weeks; verteporfin is dosed every 3 months if required.

Table

Drug	Dose	Cost per dose	Cost per year(drug only)
Pegaptanib	0.3 mg	$759.98	$6080
Verteporfin*	15 mg	$930.15	$3721

* requires use of photodynamic therapy with each injection, infusion clinic services

Pharmacoeconomic Analysis

There have been no formal pharmacoeconomic analyses with pegaptanib. The manufacturer has developed a Markov model which allows transitions between the various lesion types and is based on clinical trial efficacy. The model is constructed from a payer perspective. The results of the model are not available at the time of the monograph.

Conclusions

As the leading cause of irreversible blindness among the elderly population, AMD accounts for significant use of healthcare resources and contributes to a decreased quality of life for patients. Recent trials have demonstrated a potential benefit to the use high dose vitamin supplementation; however, the specific products and patient population remain to be defined. The only approved therapy for AMD is verteporfin and photodynamic therapy. This treatment modality is limited to patients with predominately classic lesions, thus leaving a proportion of the population with no available treatment. Pegaptanib has been shown to provide a statistically significant benefit in all lesion types of AMD. These results were demonstrated as early as six weeks of therapy and continued over the 54 weeks of the trial. Treatment with pegaptanib reduced the percentage of patients with severe vision loss (loss of $\geq$30 letters of visual acuity), slowed progression to legal blindness and demonstrated a response (loss of < 15 letter of visual acuity) in a significant number of treated patients. The development of adverse events in treated patients was minimal

and most often related to aseptic technique. The most commonly reported adverse events were ocular and mild in severity.

Recommendations

Pegaptanib provides a safe effective treatment for all lesion types of AMD. Administration of the agent is performed during a clinic visit and does not require additional photodynamic therapy. Further studies are needed to determine the importance of using concurrent laser therapy, duration of therapy and patients who may benefit the most from therapy.

References

1. Product Labeling. Macugen® (pegaptanib). Eyetech Pharmaceuticals. New York, NY. And Pfizer Inc. New York, NY. December 2004.
2. Gragoudas ES, Adamis AP, Cunningham ET, et al. Pegaptanib for Neovascular Age-Related Macular Degeneration. N Engl J Med 2004;351:2805-2016.
3. Ambati J, Ambati BK, Yoo SH, Lanchulev S, Adamis AP. Age- Related macular degeneration: etiology, pathogenesis and therapeutic strategies. Survey of Ophthalmology 2003;48(3):257-293.
4. Brown MM, Brown GC, Sharma SJ, Busbee B. Quality of life associated with visual loss: a time trade off utility analysis comparison with medical health status. Ophthalmology 2003;110:1076-1081.
5. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch ophthalmology 2004 Apr;122:598-614.

Prepared April 2005. Contact person: Kathryn Tortorice Pharm D. BCPS