

**pegaptanib 0.3mg, solution for intravitreal injection (Macugen<sup>®</sup>)**

**No. (290/06)**

**Pfizer Ltd**

7 July 2006

The Scottish Medicines Consortium has completed its assessment of the above product and advises Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Pegaptanib for intravitreal injection (Macugen<sup>®</sup>)** is accepted for restricted use within NHS Scotland for the treatment of neovascular (wet) age-related macular degeneration (AMD).

It has been shown to reduce the rate of loss of visual acuity in patients with subfoveal neovascular AMD. Pegaptanib should be restricted to patients with visual acuity between 6/12 to 6/60 (inclusive) and should be stopped if visual acuity falls below 6/60 during treatment or where severe visual loss is experienced.

The cost effectiveness of pegaptanib in patients who are also receiving photodynamic therapy has, however, not been demonstrated.

Overleaf is the detailed advice on this product.

**Vice Chairman  
Scottish Medicines Consortium**

**pegaptanib 0.3mg intravitreal  
injection  
(Macugen<sup>®</sup>)**

**Indication**

Neovascular (wet) age-related macular degeneration (AMD)

**Dosing information**

0.3 mg by intravitreal injection into the affected eye once every six weeks (9 injections per year). It should be administered by an ophthalmologist experienced in intravitreal injection.

**UK launch date**

22 May 2006

**Cost of relevant comparators**

The cost of nine vials of pegaptanib, required for one year's therapy, is given below and is based on the cost per vial given in the company's submission.

Verteporfin was used concomitantly in trials. Costs are given for information below, assuming one 15 mg vial per dose. In the event of recurrent choroidal neovascularisation (CNV) leakage, verteporfin therapy may be given up to 4 times per year.

Preparation	Dose	Cost per annum
<b>Pegaptanib (Macugen)</b>	<b>0.3 mg by intravitreal injection every 6 weeks (9 times a year)</b>	<b>£4626</b>
Verteporfin (Visudyne)	6mg/m <sup>2</sup> by intravenous infusion repeated up to four times a year	£850-£3400 plus cost of photodynamic therapy (PDT)

**Summary of evidence on comparative efficacy**

Age-related degeneration of the macula, the central portion of the retina, is a common cause of visual impairment, primarily affecting central vision, in patients over 50 years of age. Neovascular ('wet') AMD is an advanced form of the disease which accounts for a small proportion of cases but for the majority of AMD-related blindness. It involves proliferation of blood vessels (angiogenesis) behind the retina associated with penetration of the retina, bleeding and exudation. The resulting damage causes irreversible loss of visual acuity and may progress to blindness. Vascular endothelial growth factor, which is inhibited by pegaptanib, is one of the factors which induces angiogenesis and promotes vascular permeability and inflammation.

Two virtually identical randomised, controlled, masked trials recruited 1186 patients with subfoveal CNV secondary to AMD. Patients were aged >50 years with defined visual impairment, which could include legal blindness. They included all angiographic subtypes of lesions and lesions ≤ 12 optic disk areas.

Patients were initially assigned to one of three doses of pegaptanib by intravitreal injection every six weeks: 0.3 mg, 1 mg or 3mg. In a control group patients were given a sham injection whereby a needle-less syringe was pressed to the eye. Precautions were taken to mask treatment assignment from investigators and participants. At the investigator's discretion, patients with predominantly classic lesions could receive photodynamic therapy with verteporfin (V-PDT) and other 'rescue' AMD therapies. Patients were withdrawn when non-study AMD therapy, other than V-PDT, was started.

The primary objective was to investigate loss of vision within the first year measured using visual acuity charts where the patient is asked to read rows of letters (five per row) reducing in size in a geometrical progression. The primary end-point was a response defined as loss of <3 lines (15 letters) of visual acuity from baseline to week 54.

In an intention-to-treat analysis with last observation carried forward, the response rates at 54 weeks were 206/294 (70%) for the group receiving pegaptanib 0.3 mg (licensed dose) and 164/296 (55%) in the control group,  $p < 0.001$ . Mean visual acuity scores declined in all groups, but the rate of decline was significantly less in the pegaptanib 0.3 mg group than in the control group ( $p = 0.0059$ ). There were also significant advantages for pegaptanib 0.3 mg over control in the proportion of patients experiencing severe vision loss, progression to legal blindness and maintenance or gain in vision. There was an increase in lesion size in all groups, but this was less for the 0.3 mg pegaptanib group than for the controls. Subgroup analysis did not reveal any factor which would predict a better response.

At the end of the first year (week 54), approximately 1053 patients who gave consent for a second year's study were re-randomised for treatment up to week 102. Patients assigned to an active treatment in the first year were re-randomised to continue at the same dose or discontinue. Those assigned to sham therapy in the first year were re-randomised to continue or discontinue sham injection or to be switched to one of the three doses of pegaptanib. Patients who discontinued active treatment could re-start pegaptanib at the investigator's discretion if their visual acuity declined in the second year.

On average, the treatment benefit was maintained at 102 weeks with continuing preservation of visual acuity for patients re-randomised to continue pegaptanib. Patients who were re-randomised to discontinue pegaptanib after one year lost visual acuity during the second year.

### **Summary of evidence on comparative safety**

In the pegaptanib 0.3mg group, 84% of patients experienced an adverse event considered to be related to the procedure, and these were serious in 3% of patients. Twenty-seven percent (27%) of patients had an adverse event considered to be related to the study drug and these were serious in 0.7%. The rate of discontinuation because of adverse events during the first year was 1% in both the pegaptanib 0.3 mg group and the sham injection group. Ocular adverse events were the most common in both the active treatment and control groups. Serious adverse events associated with the injection procedure in the active treatment groups included intra-ocular infection, traumatic cataract and retinal detachment, each of which occurred with an incidence of <0.2 events per 100 injections.

### **Summary of clinical effectiveness issues**

Entry criteria defined subfoveal neovascular AMD, implying that patients with extrafoveal or juxtafoveal disease were excluded from the trials. Subfoveal is the most common form of neovascular disease but the licence does not distinguish between sub-types on the basis of this classification.

All angiographic sub-types were included and the patient population comprised predominantly classic (26%), occult with no classic (38%) and minimally classic (36%). There was no

evidence that any angiographic subtype, lesion size or baseline visual acuity precluded a response.

The studies were designed primarily to assess pegaptanib within the first 12 months, and all protocol specified objectives and endpoints were related to the first 54 weeks of therapy. The supporting clinical study reports acknowledge that several features inherent in the design of the follow-up study could limit the analysis of efficacy in the second year including the reduced number of patients in each group compared with the first year, particularly in the sham injection group.

Patients who discontinued active therapy in the second year could be re-started at the investigator's discretion. This could have improved the response in this group, and reduced the relative advantage for patients who continued treatment compared with discontinuation had no further therapy been allowed.

Compared with the 0.3 mg dose, which has been licensed, there were no further advantages for the higher doses of pegaptanib assessed in the trials.

Verteporfin was administered to about 20% of patients in the pivotal studies and it is not entirely clear how this affected the results. There are no comparative data against verteporfin making it difficult to determine relative efficacies in the patients who could be treated with either agent. Verteporfin offers the advantage of an intravenous infusion, as opposed to intravitreal injection and up to 4 treatments per year compared to nine with pegaptanib. Verteporfin, however requires photodynamic activation.

## **Summary of comparative health economic evidence**

The manufacturer presented a cost-utility analysis comparing pegaptanib used over 2 years with usual care for patients with neovascular age-related macular degeneration. A 13 state Markov model was used to predict the costs and benefits of the treatment over a 10 year time horizon. The main data source used in the economic evaluation was the VISION trial. Different treatment scenarios are presented by the manufacturer. One targeted option involved treatment with pegaptanib for patients with best-corrected visual acuity (VA) of 6/12 to 6/60 (inclusive). In addition, pegaptanib is discontinued for patients when VA falls below 6/60 during treatment and for those who have experienced severe visual loss (loss of 6 Snellen lines from their pre-treatment level). This option was considered to be most like way that pegaptanib would be used in practice and gave a cost per QALY of £15,000 after 2 years of treatment.

The economic evaluation uses "usual care" (management of vision loss through provision of aids) as the comparator, which is appropriate for around 94% of patients with this illness. In addition, the correct model and cycle length have been used to capture the health states of the patients. However, the Markov model contains 13 health states, which appears somewhat complex. A weakness is that photodynamic therapy was not considered as an alternative comparator. Treatment duration was assumed to be for 2 years but restriction to 1 year is likely to increase cost-effectiveness; the "targeted treatment option" described in the paragraph above would help in this respect.

The key strength of the clinical evidence is that the manufacturer has provided a targeted treatment option based on clinical opinion regarding what is likely to happen in practice in Scotland. In addition, the manufacturer has justified the extrapolation beyond the 2 year trial data to a 10 year time horizon. Resource use estimates were based on clinical opinion and Scottish data have been incorporated where appropriate.

The main strengths of the results are that QALYs were calculated and a number of treatment options were presented in the submission. In addition, sub-group analysis was performed and the effect of reducing the time horizon was also included to allow further analysis of how this impacts the results.

## **Patient and public involvement**

A Patient Interest Group Submission was not made.

## **Budget impact**

The manufacturer estimated a net NHS budget impact for the base-case treatment option of £92,000 in year 1, rising to £1 million in year 5 for 1 year of treatment. Budget impact for 2 years treatment would be £100,000 in year 1 rising to £1.8 m in year 5. This estimate is based on 20 patients in 2006 rising to 236 by 2010.

## **Guidelines and protocols**

The National Institute for clinical excellence (NICE) has published the scope for a review to appraise the clinical and cost effectiveness of ranibizumab and pegaptanib within their licensed indications for age-related macular degeneration, and to provide guidance to the NHS in England and Wales. Expected publication, August 2007.

NICE Appraisal Guidance No.68 (September 2003) recommends photodynamic treatment with verteporfin (VPDT) only for those patients with 'wet' AMD, a confirmed diagnosis of classic (no occult) disease and best corrected visual acuity (BCVA)  $\geq 6/60$ . It is not recommended for predominantly classic, but partly occult neovascular AMD except in clinical studies.

The Royal College of Ophthalmologists has published proposals for a cohort study for patients receiving V-PDT according to NICE recommendations including, but not confined to, patients with predominantly classic but partly occult neovascular AMD.

## **Additional information**

Verteporfin is licensed for use in the photodynamic treatment (PDT) of patients with AMD and predominantly classic subfoveal choroidal neovascularisation (CNV) or occult subfoveal CNV with evidence of recent or ongoing disease progression. It is also licensed for CNV secondary to pathologic myopia. In clinical trials, verteporfin with PDT was used in addition to pegaptanib.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including **16 June 2006**.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*The under noted reference was supplied with the submission.*

Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004; 351:2805-16.