

**ranibizumab 10mg/ml solution for intravitreal injection  
(Lucentis®) No. (381/07)**

**Novartis Pharmaceuticals UK Ltd**

4 May 2007

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

**ADVICE:** following a full submission.

**ranibizumab (Lucentis®)** is accepted for use within NHS Scotland for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Ranibizumab reduces the rate of visual acuity loss and increases visual acuity. It should be stopped if visual acuity falls persistently below 6/60 during treatment.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Indication**

Treatment of neovascular (wet) age-related macular degeneration (AMD).

**Dosing information**

The recommended dose is 0.5mg by intravitreal injection, carried out under aseptic conditions. Ranibizumab is initiated with a loading phase of one injection per month for three consecutive months followed by a maintenance phase in which patients should be monitored for visual acuity every month. If the patient experiences a loss of greater than 5 letters in visual acuity (EDTRS) or one Snellen line equivalent, ranibizumab should be administered.

**Product availability date**

12 February 2007

**Summary of evidence on comparative efficacy**

Ranibizumab targets human vascular endothelial growth factor A (VEGF-A) which is associated with choroidal neovascularisation (CNV), endothelial cell proliferation and vascular leakage - all of which are thought to contribute to the progression of the neovascular ('wet') form of age-related macular degeneration (AMD). The disease primarily affects central vision in patients over 50 years of age and is a common cause of blindness. It is classified according to the extent to which the lesions meet criteria for 'classic' CNV and according to their position relative to the fovea.

Two phase III multicentre, randomised, double-masked clinical trials have adopted similar designs to assess monthly intravitreal injections of ranibizumab 0.3mg or 0.5mg in different patient populations. The first trial enrolled patients with minimally classic or occult subfoveal CNV, and the control group received sham injection (to simulate placebo). The second trial compared ranibizumab to photodynamic therapy with verteporfin (V-PDT) in patients with predominantly classic subfoveal CNV. One eye was designated the study eye and the other eye was not treated with trial medication. Trials are intended to run for two years but the primary analyses were at 12 months. A third trial with a similar design was established to assess an alternative dosing regimen whereby patients received ranibizumab 0.3mg or 0.5mg for each of the first three months of the trial and then once every three months. The comparator was sham injection.

In all trials, patients were randomised to each of three groups in a 1:1:1 ratio. Stratification was performed according to visual acuity scores at baseline and study centre in all studies, and by CNV classification in the first and third studies. Analyses were performed for all randomised patients and missing data were imputed with last observation carried forward.

The primary outcomes in all trials were based on best corrected visual acuity (BCVA) scores measured as the number of letters (arranged in lines of five letters) which the patient could read on an ETDRS chart at 2 metres in the first two trials and 4 metres in the third. The ETDRS differs from the more usual Snellen vision chart in that the size of the letters reduce in size in a geometrical progression, but scores could be converted to a Snellen equivalent where, for example, a score of 6/60 was classified as legal blindness for the purposes of the trials.

In the first two trials the primary end-point was the proportion of patients who lost less than 15 letters (moderate vision loss) between baseline and 12 months. Secondary end-points included mean change in BCVA from baseline, the proportion of patients gaining  $\geq 15$  letters and the proportion with a Snellen equivalent VA score of 6/60 or worse at 12 months. There was a significant difference in favour of ranibizumab compared with control for all those end-points in both studies and there were also significant advantages in end-points assessing anatomical changes related to CNV. Table 1 gives the results for VA end-points at 12 months for ranibizumab at the 0.5mg dose and for the control group in each trial. Data at 24 months are available from the first trial and confirm the efficacy findings at 12 months.

**Table 1. Results for primary\* and secondary\* visual acuity end-points in trials involving monthly administration of ranibizumab**

End point at 12 months	Sham-injection-controlled study		Comparative study with V-PDT	
	0.5mg R	Sham	0.5mg R	V-PDT
Proportion of patients losing $<15$ letters BCVA <sup>†</sup>	95% (92,90%)	62% (56, 68%)	96% (93, 100%)	64% (56, 72%)
Proportion of patients gaining $\geq 15$ letters BCVA <sup>†</sup>	34% (28, 40%)	4.6% (2.0, 7.3%)	40% (32, 48%)	5.6% (1.8, 9.4%)
Proportion of patients with Snellen equivalent VA 6/60 or worse <sup>†</sup>	12% (8, 16%)	43% (37, 49%)	16% (10, 23%)	60% (52, 68%)

Figures in brackets are 95% Confidence Intervals

R= ranibizumab V-PDT= verteporfin with photodynamic therapy BCVA= best corrected visual acuity at 2 metres

*Other data were also assessed but remain commercially confidential.\**

## Summary of evidence on comparative safety

For the trial involving comparison of ranibizumab and verteporfin PDT, safety issues are summarised as follows:

The frequency of reported ocular serious adverse events in the study eye was similar among the verteporfin PDT (4.2%), ranibizumab 0.3 mg (4.4%), and 0.5 mg (5.7%) groups. Non-serious ocular adverse events reported  $\geq 10\%$  more frequently in either of the ranibizumab groups compared with the verteporfin PDT group in the study eye were conjunctival haemorrhage (in 45.5% of subjects in the verteporfin PDT group, 67.2% of subjects in the 0.3 mg ranibizumab group, and 62.1% of subjects in the 0.5 mg ranibizumab group), and vitreous floaters (4.2%, 11.7%, and 17.9%, respectively). No such imbalance was observed in the untreated eye.

The frequency of reported intraocular inflammatory adverse events in the study eye was higher in the ranibizumab groups (10.2% in the 0.3 mg group and 15.0% in the 0.5 mg group) than in the verteporfin PDT group (2.8%). Serious intraocular inflammatory adverse events were reported only in the 0.5 mg ranibizumab group and were uncommon ( $<1\%$ ).

No non-ocular adverse events were reported  $\geq 5\%$  more frequently in either of the ranibizumab groups compared with the verteporfin PDT group. Seven deaths were reported during year 1 of the study, with two deaths reported in the verteporfin PDT group, three deaths in the ranibizumab 0.3 mg group, and two deaths in the 0.5 mg group.

With regard to side-effects potentially related to systemic VEGF inhibition, no imbalance was observed for arterial thromboembolic events overall, hypertension or other potentially associated events. However, modest increases in the frequency of non-ocular haemorrhage were noted in the ranibizumab groups. A small trend toward a higher rate was observed in

the ranibizumab 0.5 mg group for APTC arterial thromboembolic events (vascular deaths, non-fatal myocardial infarctions, non-fatal ischaemic strokes, and non-fatal haemorrhagic strokes - Antiplatelet Trialists' Collaboration 1994), which were observed in 2.1% of verteporfin PDT-treated subjects, 2.2% of subjects treated with 0.3 mg ranibizumab, and 4.3% of subjects treated with 0.5 mg ranibizumab.

## Summary of clinical effectiveness issues

With monthly dosing in the first two trials, the greater part of the vision gain with ranibizumab was seen in the first three months, after which vision remained stable in ranibizumab-treated patients and declined in the comparator groups.

The licensed dosing regimen allows for flexible dosing. This regimen has not been assessed in a clinical trial but is based on a drug and disease model which predicted that individualised dosing after a three-month loading phase would maintain visual acuity at a stable level (<5 letters lost). The licensing authorities have accepted this as the basis for the licensed regimen.

The methodology for the trial comparing ranibizumab with verteporfin and PDT includes a non-inferiority analysis; however the results as presented show a statistically significant advantage for ranibizumab for both primary and secondary end points.

## Summary of comparative health economic evidence

The manufacturer presented a cost-utility Markov model based upon three-monthly cycles over a ten year time horizon, with health states being defined by visual acuity scores. This Markov model was implemented for the results of the clinical trials programme for different types of age related macular degeneration (AMD):

- ranibizumab against photodynamic therapy + verteporfin in primarily classic AMD patients
- ranibizumab against best supportive care in primarily classic AMD patients
- ranibizumab against best supportive care in all AMD patients
- ranibizumab against best supportive care in occult AMD patients
- ranibizumab against best supportive care in minimally classic AMD patients

Clinical effectiveness estimates were drawn from the initial efficacy studies, which mainly used monthly dosing. Dosing for ranibizumab for all the models drew heavily upon the trial assessing the efficacy of a reduced dosing frequency which through further pooled disease modelling enabled a reduced frequency flexible dosing to be assumed. Patients were assumed to receive therapy for the duration of the trial period then to cease treatment. Some continued efficacy for the six months after cessation of treatment was also assumed for ranibizumab based upon the disease modelling.

Resource use was drawn mainly from expert opinion, which differentiated costs principally by treatment but also to a degree by visual acuity. Costs of legal blindness were drawn from the literature.

Utility values for visual acuity health states were drawn from a separate time trade off exercise among members of the general public. The average age of respondents was 32, in contrast to an average age within the clinical trials programme of 77. The results from the time trade off exercise were noted as differing from some others within the literature, but did not appear unreasonable.

For modelling based upon the initial efficacy trials, among those with primarily classic AMD receiving photodynamic therapy a move to one year of treatment with ranibizumab was anticipated to result in an additional 0.20 QALYs over the ten year modelling horizon at a cost of £917 to give an ICER of £4,489 per QALY. If these patients were receiving only best supportive care, the additional benefit rose to 0.28 QALYs but at an additional cost of £4,068 to give an ICER estimate of £14,781 per QALY. For those with minimally classic or occult AMD a move to two years of treatment with ranibizumab saw a patient benefit of around 0.33 QALYs over the ten year modelling horizon, at an additional cost of between £8,494 and £9,125 to give an ICER of around £26,000 per QALY.

Modelling based upon the reduced dosing trial estimated an additional average benefit of 0.26 QALYs across all AMD types when compared with best supportive care, at an additional cost of £3,120, to give an ICER estimate of £12,050 per QALY.

## **Summary of patient and public involvement**

Patient Interest Group Submission: Royal National Institute of the Blind Scotland/Macular Disease Society

## **Additional information: 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; September 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. Review of this guidance is anticipated to coincide with publication of the results of the on-going UK cohort study but currently no timelines are available

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.

The Royal College of Ophthalmologists has also published interim recommendations for the management of patients with AMD (November 2006) and recommends the use of anti-VEGF agents as second-line therapy in predominantly classic subfoveal/juxtafoveal CNV and occult subfoveal/juxtafoveal CNV and as first-line in minimally classic subfoveal/juxtafoveal CNV. It adds that 'although there have been no direct comparisons of the different anti-VEGFs it seems that ranibizumab is the more efficacious of the two products currently available.'

## **Additional information: previous SMC advice**

In July 2006 following a full submission the Scottish Medicines Consortium advised:

Pegaptanib for intravitreal injection (Macugen®) 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.

### **Additional information: comparators**

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 pathological myopia.

### **Additional information: costs**

<b>Drug</b>	<b>Dose regimen</b>	<b>Cost per year (£)</b>
<b>Ranibizumab</b>	<b>0.5mg by intravitreal injection 6-12 times a year*</b>	<b>4567-9134</b>
Verteporfin	6mg/m <sup>2</sup> by intravenous infusion repeated up to four times a year+	850-3400 plus cost of photodynamic therapy (PDT)
Pegaptanib	0.3 mg by intravitreal injection every 6 weeks (9 times a year)	4626

Costs are taken from eVadis database on March 12th 2007.

\*Some patients may require fewer doses

+assumes 1 vial per dose

### **Additional information: budget impact**

The manufacturer estimated a gross drug budget impact of £2.4 million in year 1 rising to £7.1 million by year 5. This was based upon an annual incidence of around 2,300 patients of whom around 620 present for treatment and are assessed as suitable, coupled with a treatment duration of two years.

Expert advice suggests that there is likely to be a much faster rise in drug budget impact from that which the manufacturer presented due to a large number of prevalent patients. Given this, the manufacturer's estimated year five gross drug cost of £7.1 million could be reached or exceeded by year two.

An additional £1.3 million in year 1 rising to £4.0 million in year 5 of hospital costs were anticipated, to give an overall gross cost of £3.7 million in year 1 rising to £11.1 million in year 5. Expert advice suggests that the hospital costs will vary across health boards and may not be as high as suggested by the manufacturer.

The manufacturer also estimated the net costs of ranibizumab after taking account of the potential savings that would arise from reduced photodynamic therapy usage. These savings would arise from year three onwards given that patients currently on photodynamic therapy would not switch treatment. On this basis the year one cost remained at £3.7 million but the year five cost changed to £8.7 million.

It is unclear whether the cost would stabilise at year two. It is not certain that, in clinical practice, therapy would cease after 2 years if vision were being maintained. If not, the number of patients receiving on-going treatment could be considerably greater than anticipated with a corresponding increase in the budget impact.

**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 13 April 2007.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*\* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

*The undernoted references, shaded grey, are additional to information supplied with the submission.*

Rosenfield PJ, Brown DM, Heier JS et al. Ranibizumab for neovascular age-related macular degeneration. NEJM 2006;355:1419-31

Brown DM, Kaiser PK, Michels M et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. NEJM 2006;355:1432-44.