Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

ranibizumab, 10mg/mL, solution for injection (Lucentis®) SMC No. (907/13)

Novartis Pharmaceuticals UK Ltd

04 October 2013

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.

Indication under review: Treatment for visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults.

In patients with choroidal neovascularisation secondary to pathologic myopia, ranibizumab intravitreal injection was associated with a significant improvement in visual acuity of 8.4 Early Treatment Diabetic Retinopathy Study letters at three months compared with photodynamic therapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of ranibizumab. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 November 2013

Indication

Treatment for visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults.

Dosing Information

Treatment is initiated with a single injection. If monitoring reveals signs of disease activity, e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, optical coherence tomography or fluorescein angiography. While many patients may only need one or two injections during the first year, some patients may need more frequent treatment. Therefore monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month.

There is no experience of concomitant administration of ranibizumab and verteporfin.

Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Product availability date

04 July 2013

Summary of evidence on comparative efficacy

Ranibizumab is a humanised recombinant monoclonal antibody fragment that inhibits the binding of vascular endothelial growth factor A (VEGF-A) to its receptors thereby preventing endothelial cell proliferation, neovascularisation and vascular leakage. It is licensed for a range of ophthalmic indications; the marketing authorisation has recently been extended to allow its use in the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults. There is no agreed definition of pathologic myopia but at least one of the following characteristics should be present: a refractive error of at least -6 dioptres; an axial length of at least 26.5mm; or fundus changes consistent with pathological myopia, such as lacquer cracks and chorioretinal atrophy. The condition often affects both eyes. An estimated 5 to 11% of patients with pathologic myopia will develop choroidal neovascularisation (CNV) which leads to loss of vision. Ranibizumab is the first licensed exclusively pharmacological therapy for the treatment of visual impairment due to CNV secondary to pathologic myopia.

The main evidence supporting the marketing authorisation application for this new indication is from a phase III, randomised, double-masked study.[1,2] RADIANCE evaluated the efficacy and safety of two different dosing regimens of intravitreal ranibizumab 0.5mg versus verteporfin photodynamic therapy (vPDT) in 277 adults with:

- visual impairment due to CNV secondary to pathologic myopia
- best corrected visual acuity (BCVA) in the study eye >24 and <78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters

- high (pathologic) myopia (more severe than -6 dioptres)
- anterio-posterior elongation >26mm
- posterior changes compatible with pathologic myopia
- subfoveal, juxtafoveal or extrafoveal lesions in the study eye.[2]

Patients were randomised in a 2:2:1 ratio as follows:

- ranibizumab disease activity group (n=116) received at least one intravitreal injection of ranibizumab 0.5mg with subsequent retreatment only if monthly assessments showed disease activity (defined as vision impairment, attributable to intra- or subretinal fluid or active leakage secondary to pathological myopia as assessed by optical coherent tomography or fluorescein angiography).
- ranibizumab stabilisation group (n=106) received at least two ranibizumab injections (one month apart) with subsequent retreatment only if BCVA changed compared with the two previous monthly visits. Once restarted, ranibizumab was administered monthly until stable visual acuity was reached again for three consecutive monthly assessments.
- vPDT group (n=55) received vPDT treatment on day 1. From months 3 to 11, patients were eligible to receive ranibizumab 0.5mg or vPDT (licensed dose) or both according to disease activity criteria (as defined above) at the investigator's discretion.[1,2]

Masking was carried out using sham treatments for the full duration of the study.[3] The mean number of ranibizumab injections administered over 12 months in the ranibizumab (disease activity), ranibizumab (stabilisation) and vPDT groups were 3.5, 4.6 and 3.2, respectively. In the vPDT group, 72% (38/53) of patients received an injection of ranibizumab. Two of the 15 patients who did not receive ranibizumab after month 3 received a second dose of vPDT.[1,2]

The primary outcome of difference between the mean of BCVA assessed at months 1, 2 and 3 and mean baseline BCVA was significantly better for ranibizumab than vPDT: 10.6, 10.5 and 2.2 ETDRS letters for the ranibizumab (disease activity), ranibizumab (stabilisation) and vPDT groups, respectively. Non-inferiority of the ranibizumab treatment regimens for the primary endpoint was also demonstrated.[1,2]

At month 12, mean BCVA gain from baseline in the ranibizumab (disease activity), ranibizumab (stabilisation) and vPDT groups was 14.4, 13.8 and 9.3 ETDRS letters, respectively. In the respective groups, 69%, 70% and 49% gained ≥10 letters (or reached 84 letters). The proportion of patients with CNV leakage and intraretinal oedema reduced by >70% in all three groups from baseline to month 12.[1,2,3]

Health related quality of life was measured by the National Eye Institute Visual Functioning questionnaire (NEI VFQ)-25, a self-administered questionnaire, (with scores ranging from 1 to 100 and higher scores indicating better health), which includes a general health composite score and 11 subscales. At three months, there was a clinically and statistically significant improvement in NEI VFQ-25 composite score for both ranibizumab groups over vPDT.

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

Summary of evidence on comparative safety

Ranibizumab treatment was generally well tolerated and there were no new adverse events (ocular or non-ocular). Ocular adverse events (in at least three patients in any group) over the 12 month study were reported in 37% to 43% of patients who received ranibizumab compared with 27% in patients who received vPDT alone. Non-ocular adverse events (in at least three patients in any group) were reported in 43% to 50% of patients who received ranibizumab compared with 33% of patients who received vPDT alone.[2]

The following ocular adverse events were reported (in at least three patients in any group) for the ranibizumab (disease activity, n=118), ranibizumab (stabilisation, n=106), vPDT with ranibizumab (n=38) and vPDT without ranibizumab (n=15) groups: conjunctival haemorrhage 10%, 11%, 5.3% and 0; increased intraocular pressure 5.9%, 2.8%, 10% and 0; allergic conjunctivitis 4.2%, 0.9%, 2.6% and 0; eye pain 3.4%, 3.8%, 2.6% and 6.7%; punctate keratitis 2.5%, 7.5%, 5.3% and 0; retinal haemorrhage 2.5%, 0.9%, 0 and 0; metamorphopsia 2.5%, 0, 0 and 0; injection site haemorrhage 2.5%, 2.8%, 5.3% and 0; dry eye 1.7%, 3.8%, 0 and 6.7%; vitreous floaters 0.8%, 4.7%, 0 and 0. There were only two reported serious ocular adverse events: retinoschisis in the ranibizumab (disease activity) group; and corneal erosion in the ranibizumab stabilisation group. No patients in the vPDT groups reported any serious ocular adverse events.[2]

The following non-ocular adverse events were reported (in at least three patients in any group) for the ranibizumab (disease activity), ranibizumab (stabilisation), vPDT with ranibizumab and vPDT without ranibizumab groups: nasopharyngitis 10%, 11%, 2.6% and 13%; headache 9.3%, 7.5%, 2.6% and 0; hypertension 4.2%, 2.8%, 7.9%, and 0; upper respiratory tract infection 3.4%, 2.8%, 2.6%, and 0; influenza 3.4%, 1.9%, 2.6% and 0; bronchitis 3.4%, 0.9%, 2.6% and 0; back pain 3.4%, 1.9%, 0 and 0; urinary tract infection 2.5%, 2.8%, 0 and 0; abdominal pain 0.8%, 2.8%, 0 and 0, upper respiratory tract infection, 3.4%, 2.8%, 2.6% and 0. Non-ocular serious adverse events were reported in 4.2% (5/118) patients in the ranibizumab (disease activity) group (one each of atrial tachycardia, subdural haematoma, spinal column stenosis, lung adenocarcinoma and chronic renal failure) and in 5.7% (6/106) patients in the ranibizumab (stabilisation) group (one each of myocarditis, erosive gastritis/gastrointestinal haemorrhage, hepatic function, joint dislocation, breast cancer and depression). No patients in the vPDT groups reported any serious non-ocular adverse events.[2]

Summary of clinical effectiveness issues

Typically, patients with myopic CNV may present with a sudden decrease in vision that then stabilises over several months, possibly due to absorption of blood and exudates. It has been suggested that CNV itself may not be a major influence on long-term poor visual outcome but the development and continual increase in chorioretinal atrophy around regressed CNV is known to be an important factor in loss of vision.[4] CNV following pathologic myopia usually has its onset in patients younger than 50 years.[5] Factors that increase the probability of a poor visual outcome include older age at onset, higher degree of myopia, a larger area of myopic CNV and proximity to the fovea, severity of leakage and baseline visual acuity. Older myopic patients may show signs of both clinical and pathophysiological age-related macular degeneration and pathologic myopia. CNV secondary to pathologic myopia is more common in women than men and in Asians compared with Caucasians.[4]

The licensed dosing schedule reflects the disease activity criteria dose regimen in the pivotal RADIANCE study which demonstrated a mean average improvement in BCVA of 8.4 EDTRS letters for ranibizumab compared with vPDT after three months.[1] This is a statistically, although not clinically, significant difference; the company submission states that a difference of 10 letters is considered to be clinically significant. At three months, there was a clinically and statistically significant improvement for ranibizumab over vPDT in the quality of life NEI VFQ-25 composite score and in three of 11 subscales. [3,4]

The study had several limitations. The head to head comparison between ranibizumab and vPDT lasted only three months. After that, patients in the vPDT group could continue to receive vPDT monotherapy, switch to ranibizumab monotherapy or receive combination treatment at the discretion of the unmasked investigator. As the natural history of this condition may include a period of stabilisation after an initial visual loss, this may be insufficient time to determine treatment efficacy.[5] Study inclusion criteria allowed patients with reasonably good vision (up to 78 letters) to participate so the primary outcome of change in visual acuity may have been compromised in some patients because of limited potential for improvement. Due to the short follow up, there is no evidence about the long term safety and efficacy of ranibizumab versus vPDT.

vPDT is the only other approved treatment for this condition, although it is not specifically indicated for the treatment of the associated visual impairment. As there was only a three month head to head comparison of ranibizumab and vPDT, the submitting company used a naïve indirect comparison in the economic case to provide clinical effectiveness and adverse events data from months 4 to 12. A formal indirect comparison would have been more appropriate.

SMC clinical experts have advised that use of vPDT is reducing in Scotland and that there is some use of intravitreal VEGF-A inhibitors.

Patients should self-administer antimicrobial drops (four times daily for three days before and after each injection). Ranibizumab must be injected under aseptic conditions, which has service implications, and patients should be monitored during the following week to permit early treatment if an infection occurs. Monitoring for disease activity is required for one year after the initial injection of ranibizumab; monthly for the first three months and then every three months.[1]

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

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ranibizumab to vPDT in patients with visual impairment due to CNV secondary to PM. Although SMC clinical experts noted that vPDT is no longer used routinely in this indication it was considered to be the appropriate comparator. Treatment consisted of 3.5 injections of ranibizumab in year 1 and 1 injection in year 2. For vPDT, 3.4 treatments were assumed for year 1 and 1.7 in year 2. A lifetime horizon was used for the analysis and the mean age of patients at the start of the analysis was 55.

A Markov model was used with health states based on levels of visual acuity, and was similar in structure to other analyses in this area. 15% of patients were assumed to have bilateral eye disease and the distribution of treated eyes according to better seeing eye/worse seeing eye (BSE/WSE) status was taken from the main clinical study. For the ranibizumab patients,

transition probabilities for the first year of treatment were taken from the ranibizumab disease activity arm of the main clinical study. For the vPDT arm, efficacy results for the first 3 months of treatment were taken from the vPDT arm of the main clinical study, and for months 4 to 12, data were taken from the vPDT arm of the VIP study.[6] As such, for this period, a naive indirect comparison was used. After year 1, patients in both arms of the model were assumed to have a common natural history rate of decline in BCVA, based on a published paper.

Quality of life values were estimated from a published paper, which were then adjusted to derive values for patients treated in their worse seeing eye. This resulted in a maximum utility gain in the WSE of 0.1. Resource use in the model related to treatment administration and monitoring, and for patients who progress to the worst visual acuity states of the model, a cost associated with blindness (£17,325 in the first year, £17,244 per annum thereafter).

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a confidential discount was offered on the price of the medicine. With the PAS, ranibizumab was the dominant treatment (cost saving and more effective).

A good range of sensitivity analyses was provided. This indicated that dominance was maintained unless the cost of a ranibizumab monitoring visit was increased to around 8 times the base case value of £175.

A number of issues were noted with the analysis:

- Data for months 4 to 12 for vPDT are based on a naive indirect comparison, which introduces uncertainty into the analyses. The company did however provide additional analysis where it was assumed that the effectiveness of vPDT was the same as ranibizumab for this period. This resulted in ranibizumab remaining the dominant treatment. The finding of an increased level of saving under this (pessimistic) scenario was surprising as it would have been anticipated that the assumption would have led to fewer patients entering the high cost blindness states. The company clarified that this was a function of small sample sizes within the data set for the model. Further extra analysis was provided to adjust for this and to set the blindness cost to zero and the dominant result remained.
- vPDT does not appear to be commonly used according to SMC clinical experts and it was recognised that there is some unlicensed use of intravitreal VEGF-A inhibitors. .
- As with previous submissions in this area, the true opportunity cost of clinic time to administer and monitor ranibizumab (given capacity constraints) may not be fully reflected in the unit costs used in the base case result. However, even if the cost was increased to around £1400, the with-PAS result remains dominant.
- The cost associated with blindness is particularly high in this submission compared to a recent ranibizumab submission for BRVO. However, the company provided additional sensitivity analysis using lower values and the findings were still robust.

Given the robustness of the dominance result to changes in all relevant parameters, the economic case was demonstrated when compared to vPDT.

It is SMC policy to include the incremental costs and the estimated QALY gain in the detailed advice document for all submissions. The PAS for ranibizumab includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the

QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason SMC is unable to publish the incremental costs and estimated QALY gain for ranibizumab in choroidal neovascularisation secondary to pathologic myopia in adults.

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

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

vPDT is the only other approved treatment for choroidal neovascularisation (marketing authorisation specifies subfoveal only) secondary to pathological myopia in adults.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)*
Ranibizumab	**Initially one 0.5mg intravitreal injection, then monthly if required for disease activity**	**2,227 to 2,969**
Verteporfin	6mg/m^2 body surface area by intravenous infusion	2,250 to 3,400**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from dm+d on 11 July 13. *Costs are based on a range of 3 to 4 ranibizumab doses (mean in RADIANCE study [disease activity group] was 3.5) and 3 to 4 verteporfin treatments in an adult with body surface area 1.8m^2 (mean number of treatments in first year was 3.5 according to the Visudyne summary of product characteristics). Costs are based on treatment of one eye. **Cost of photodynamic therapy is not included.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 500 in year 1 rising to 509 in year 5, with an estimated uptake rate of 7% in year 1 and 32% in year 5. A discontinuation rate of 3.6% per year was assumed. The budget impact figures provided were stated to be commercial in confidence.

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

References

The undernoted references were supplied with the submission.

1. Summary of product characteristics for ranibizumab solution for injection (Lucentis®). Novartis Pharmaceuticals UK Limited.

2. Bandello F. Twelve-month efficacy and safety of ranibizumab 0.5 mg(RBZ) versus verteporfin photodynamic therapy (vPDT) in the treatment of visual impairment(VI) due to choroidal neovascularization(CNV) secondary to pathologic myopia(PM). Oral presentation presented at the annual meeting of the Association for Vision Research and Ophthalmology. 5-9 May 2013 Seattle, Washington, USA. Abstract 1247. 2013.

3. Novartis. Data on file. Phase III study (CRFB002F2301) 12-month Clinical study report. Dec 2012.

4. Neelam K, Cheung CM, Ohno-Matsui K et al. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res 2012.

5. Tufail A, Patel PJ, Sivaprasad S et al. Ranibizumab for the treatment of choroidal neovascularisation secondary to pathological myopia: interim analysis of the REPAIR study. Eye 2013; 1:8.

6. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial--VIP report no. 1. Ophthalmology 2001;108:841-52.

This assessment is based on data submitted by the applicant company up to and including 13 September 2013.

**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/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the

basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.