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

Re-submission

ranibizumab, 10mg/mL solution for injection (Lucentis®) SMC No. (711/11)

Novartis Pharmaceuticals UK Ltd

09 November 2012

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 Scotland. The advice is summarised as follows:

ADVICE: following a full resubmission

ranibizumab (Lucentis®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of visual impairment due to diabetic macular oedema (DMO) in adults.

SMC restriction: treatment of visual impairment due to DMO in adults with best corrected visual acuity (BCVA) 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or less at baseline.

Ranibizumab significantly improved visual acuity over 12 months compared with standard laser photocoagulation treatment. Open label extension results up to 3 years suggest maintenance of effect.

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 or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Ranibizumab is indicated for the treatment of visual impairment due to diabetic macular oedema (DMO) in adults.

Dosing Information

Ranibizumab 0.5mg is administered as a single intravitreal injection. Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DMO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than one month.

There is some experience of ranibizumab administered concomitantly with laser photocoagulation. When given on the same day, ranibizumab should be administered at least 30 minutes after laser photocoagulation. Ranibizumab can be administered in patients who have received previous laser photocoagulation.

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

Product availability date

January 2011

Summary of evidence on comparative efficacy

Diabetic retinopathy is a complication of diabetes mellitus and diabetic macular oedema (DMO) is one of the main causes of visual impairment in diabetic retinopathy. DMO is caused by breakdown of the blood retinal barrier, leading to leakage of fluid and plasma resulting in oedema and swelling of the central part of the retina, the macula. The macula mediates high-resolution visual acuity and if DMO is left untreated loss of visual acuity equivalent to at least two lines (Early Treatment Diabetic Retinopathy Study [ETDRS] ≥ 10 letters) within two years can occur in approximately 50% of patients. Vascular endothelial growth factor (VEGF) levels are raised in the vitreous humour of patients with diabetic retinopathy leading to endothelial cell proliferation, neovascularisation, and vascular leakage. Ranibizumab is a humanised recombinant monoclonal antibody fragment that inhibits the binding of VEGF-A to its receptors.[1,2]

In this resubmission, the submitting company has requested that the Scottish Medicines Consortium (SMC) considers ranibizumab when positioned for use in the treatment of visual impairment due to DMO in adults with best corrected visual acuity (BCVA) 75 ETDRS letters or less at baseline.

Evidence is from two phase III studies, RESTORE[2] and DRCRnet[3] comparing ranibizumab with the current standard treatment, grid laser photocoagulation, (hereafter referred to as laser).

The pivotal 12 month, randomised, double-masked, RESTORE study recruited 345 adults with type 1 or 2 diabetes mellitus; HbA1c ≤ 10.0%; on diet, exercise, and/or diabetic medication which had been stable for the previous three months; with visual impairment due to focal or diffuse DMO and BCVA of 78 to 39 ETDRS letters. Only one eye was treated but if both eyes were eligible the worse seeing eye was treated unless otherwise determined by the investigator.[2]

Patients were randomised to monthly intravitreal ranibizumab 0.5mg injection (n=116), monthly intravitreal ranibizumab 0.5mg injection plus laser (n=118) or laser monotherapy (n=111) initially for three months. If after three months stable vision was not reached, monthly injections continued until there was no further improvement in vision or BCVA reached >84 letters (approximately 20/20 Snellen equivalent) for two visits and then stopped. Monthly assessments continued and treatment was re-started if there was a decrease in BCVA due to progression of DMO. Laser treatment was administered at baseline and then as required at intervals of at least three months.

The primary outcome was mean average change from baseline in BCVA letter score over all monthly post-baseline assessments from month 1 to month 12 in the full analysis set, defined as all patients who received any study treatment and had at least one post-baseline assessment for BCVA. Missing data were imputed using the last observation carried forward (LOCF) approach. Significant improvements in mean average BCVA change for month 1 to month 12 were achieved with ranibizumab (+6.1 letters, standard deviation [SD] 6.4), and ranibizumab plus laser (+5.9 letters, SD 7.9), compared with laser alone (+0.8 letters, SD 8.6). Treatment difference versus laser in least squares mean values was 5.3 letters (95% confidence interval [CI]: 3.5 to 7.3) for ranibizumab and 4.9 letters (95% CI: 2.8 to 7.0) for ranibizumab plus laser. The mean number of injections and laser treatments was similar for all groups.[2]

Secondary outcomes were consistent with the primary outcome and included the mean change ± SD in BCVA letter score from baseline to month 12 was 6.8 ± 8.3 in the ranibizumab group, 6.4 ±11.8 in the ranibizumab plus laser group and 0.9 ± 11.4 in the laser group; the proportion of patients with a gain in BCVA of 2 lines (≥10 letters), 37% (43/115) in the ranibizumab group, 43% (51/118) in the ranibizumab plus laser group and 16% (17/110) in the laser group; and the proportion of patients gaining at least 3 lines (≥15 letters), 23% (26/115 and 27/118) in both ranibizumab groups compared with 8% (9/110) in the laser group. However in over half of patients the changes ranged between a deterioration of up to 10 letters and an improvement of less than 10 letters.[1,2]

Quality of life measures showed no significant difference in the European Quality of Life EQ-5D mean scores, however vision-related quality of life functioning measured using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) showed significant improvements in the NEI VFQ-25 composite score in the ranibizumab groups at 12 months, 5.0 points in the ranibizumab group, 5.4 in the ranibizumab plus laser group and 0.6 in the laser group. Both ranibizumab groups provided significant improvements on the general vision, near activities and distance activities subscales compared with laser alone.[2]

In an extension to the RESTORE study, 240 patients received open-label ranibizumab 0.5mg intravitreal injection as required. Laser photocoagulation was allowed at the investigator's discretion. The primary outcome was the incidence of ocular and non ocular adverse events, with secondary outcomes including mean change in BCVA and VFQ-25. Interim data at two years indicate that in 166 patients originally randomised to ranibizumab with or without laser, the mean BCVA letter score gained at 12 months was maintained at 24 months, at +7.9 letters in

the ranibizumab group and +5.4 letters in the ranibizumab plus laser group. In 74 patients previously treated with laser alone the mean change in BCVA from baseline to 24 months was +5.4 letters.[4]

The supportive, randomised, double-masked DRCRnet[3] study evaluated laser photocoagulation, ranibizumab plus prompt laser (within 3 to 10 days) or ranibizumab plus deferred laser (≥ 24 weeks) or triamcinolone plus prompt laser for DMO. The study included 691 adults with type 1 or 2 diabetes mellitus; BCVA 24 to 78 electronic ETDRS letters; and definite retinal thickening due to DMO involving the centre of the macula at a retinal thickness ≥ 250 micrometres. If eligible, both eyes were treated, comprising a total of 854 study eyes. The number of eyes randomised to each treatment was: sham intravitreal injection plus prompt laser (n=293), ranibizumab 0.5mg intravitreal injection plus prompt laser (n=187), ranibizumab 0.5mg intravitreal injection plus deferred laser (n=188) or triamcinolone 4mg intravitreal injection plus prompt laser (n=186). Triamcinolone outcomes are not relevant to the assessment and will not be discussed further.

Ranibizumab/sham injection was administered every four weeks. At week 16, depending on success or failure criteria, continued treatment was as per retreatment algorithm or investigator's discretion. Laser treatments had to be at least 13 weeks apart. Patients in the three prompt laser groups were masked to treatment until the primary outcome visit at one year, however the ranibizumab plus deferred laser group was not masked.

The primary outcome was mean change in BCVA letter score from baseline to one year using the intention to treat principle for all randomised eyes. Missing values were imputed using LOCF. Significantly greater mean improvements in BCVA were achieved in the ranibizumab plus laser group (+9 letters with either prompt or deferred laser; SD 11 and 12 respectively) than with laser alone (+3 letters SD 13). The estimated treatment difference between the ranibizumab groups and laser alone was 5.8 letters (95% CI: 3.2 to 8.5) and 6.0 letters (95% CI: 3.4 to 8.6) for prompt and deferred laser, respectively. Patients in the ranibizumab groups received a median of eight to nine injections over the year.

The proportions of patients who achieved ≥10 letters improvement in BCVA were 47% (88/188) for ranibizumab plus deferred laser, 51% (95/187) for ranibizumab plus prompt laser and 28% (81/293) for laser.

In a two-year follow-up report to study DRCRnet, data were available for 642 eyes. Visual acuity outcomes at one year were largely sustained through to the two-year visit in both ranibizumab groups. Between years one and two the median number of ranibizumab injections was 2 and 3 and the median number of visits seven and 10, for the prompt and deferred laser groups, respectively.[5]

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

Summary of evidence on comparative safety

In the RESTORE study 43% of patients in the ranibizumab groups experienced ocular adverse events (AE) compared with 39% with laser alone. The most common ocular AEs in the ranibizumab groups were eye pain, conjunctival hyperaemia, conjunctival haemorrhage and foreign body sensation. Approximately half of AEs were due to the ocular injection with only a small percentage related to ranibizumab; ranibizumab (2.6%), ranibizumab with laser (5.8%) and laser alone (2.7%). The incidence of ocular serious adverse events (SAEs) was low and none were considered to be treatment-related.

The proportion of patients experiencing non-ocular drug related AEs in each group was ranibizumab monotherapy (5.2%), ranibizumab plus laser (0.8%) and laser alone (1.8%). Three patients in the ranibizumab monotherapy group and one patient in the ranibizumab plus laser combination therapy group had a cardiovascular or cerebrovascular AE. In the RESTORE extension study, no new ocular or non ocular AEs were reported at 24 months.[2,4]

In the DRCRnet study there was a low incidence of major ocular AEs, with ranibizumab plus laser therapy similar to laser alone. Retinal vein occlusion was reported in one patient in each group, increased intraocular pressure between 6 to 9% in all groups and there were three reports of endophthalmitis in ranibizumab patients. There were no reported systemic AEs over two years.[3]

Summary of clinical effectiveness issues

The current standard of care for DMO is grid laser photocoagulation which can reduce the risk of a severe decrease of visual acuity (≥15 letters) by 50% over 2 to 3 years. However, there is a group of patients who are unresponsive or unsuitable for laser treatment; patients with macular ischaemia, generalised oedema or involvement of the fovea. In these patients loss of central vision cannot be prevented by laser. Ranibizumab is the first medicine licensed to treat DMO.

In this resubmission, the submitting company has requested that SMC considers ranibizumab when positioned for the treatment of visual impairment due to DMO in adults with BCVA 75 ETDRS letters or less at baseline. This subgroup included the majority of the patients in the pivotal studies but excluded those patients with less severe vision impairment who gained less benefit from ranibizumab treatment

In the two pivotal phase lll studies, RESTORE and DRCRnet, ranibizumab significantly improved visual acuity over 12 months compared with standard laser photocoagulation. Follow up reports in both studies suggest that the gains in BCVA letter scores achieved at 12 months were maintained at 24 and 36 months.[2-5]

There are a number of factors impacting the evidence base.

- Ranibizumab was compared with grid laser photocoagulation, the current standard of treatment, but the aims of these two interventions differ with laser treatment preserving rather than improving visual acuity.

- In the RESTORE study, patients were stratified by visual acuity at baseline, ≤60, 61-73 and >73 EDTRS letters. Patients in the >73 letter group did not gain the same magnitude of benefit as the rest of the population.
- In the RESTORE study, while many patients had a significant improvement in visual acuity, in over half the patients the change in BCVA was small, ranging between a deterioration of less than 10 letters and an improvement of less than 10 letters.
- Data up to 24 months suggest that the number of ranibizumab injections in the second year is much reduced compared with year one but there is still uncertainty as to the duration of treatment and the need for continued monitoring.
- The NEI VFQ-25 composite score demonstrated at least a five point improvement, which is considered clinically significant, in both ranibizumab groups compared with laser. However no benefit was demonstrated using EQ-5D mean scores.
- Around 48% of patients in the RESTORE study had previously received laser treatment. Previous response was not reported in the published paper, but subgroup analysis would suggest that patients who previously received laser did better on ranibizumab alone while patients who had not received laser had better outcomes when treated with ranibizumab plus laser. This suggests that the optimum combination of these two interventions has not been fully established.

Safety data in patients with DMO is limited with respect to less common adverse events and long-term treatment.

Ranibizumab must be injected under aseptic conditions and patients monitored the week following the injection to permit early treatment if an infection occurs. The requirement for monthly monitoring visits, including after discontinuation to determine need for retreatment, may have substantial implications for the service.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ranibizumab with grid laser in patients with visual impairment due to DMO. Expert responses indicated grid laser is the appropriate comparator. The patient population included in the economic analysis was described as patients with DMO due to type 1 or type 2 diabetes mellitus with BCVA of 36 – 75 letters and an average age of 63 years.

A Markov model was used which modeled changes in visual acuity over a 15-year time horizon. The model was based on a cohort of 1,000 patients and used eight BCVA health states to capture disease progression over time based on monthly cycles. A key change to the model in the resubmission is the inclusion of patients treated in their worse seeing eye and patients treated in both eyes. The company assumed 55% of patients would be treated only in their worse seeing eye, 15% would be treated only in their better seeing eye and 30% would be treated in both eyes.

Patient level data relating to the proportion of patients with a 2 or 3 line (10 or 15 letter) change in BCVA from the RESTORE study were used to derive monthly transition probabilities between health states for the first year of the model. For years 2 and 3 extension study data were used for the ranibizumab arm. For the grid laser arm, in the absence of longer term trial data, the transition probabilities beyond year 1 were derived based on a weighted average of the transition probabilities from months 10, 11 and 12 of grid laser treated patients in the RESTORE

study. For years 4 onwards it was assumed there was a 3.5% probability of vision deteriorating and a 2.5% probability of improving over a 3 month period, based on a combination of literature sources.

The utility values relating to the better seeing eye were derived using an algorithm from the literature which was used in the NICE wet age-related macular degeneration cost-effectiveness model. The utility values were estimated using the time trade-off method to elicit values from members of the public. For the worse seeing eye the company assumed the maximum benefit from treatment was a utility gain of 0.3. This equated to a 40% lower utility gain from treating the worse seeing eye compared to the better seeing eye. The company argued this assumption was reasonable as in the RESTORE study there was a reduction in benefit of 30%, as defined by the VFQ-25, when the worse seeing eye was treated.

Resource use included administration and monitoring costs, with a higher administration cost applied in the ranibizumab arm of the model (£157 versus £137). Based on the clinical study patients in the model were assumed to receive 7, 4 and 3 injections in years 1, 2 and 3 respectively. The cost of monitoring was assumed to involve a consultant-led outpatient visit with 12, 8 and 6 monitoring visits included in treatment years 1, 2 and 3 respectively based on clinical opinion. The cost of severe vision loss was included based on a weighted average of different resources, including residential care, and was consistent with previous SMC submissions for vision loss treatments.

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. The PAS offered a simple discount on the list price of ranibizumab. With the PAS, the cost per QALY was estimated to be £14,759.

The following limitations were noted:

- The mean change in BCVA letter score predicted by the model appears to slightly overestimate the gain from ranibizumab treatment in comparison with the study results. The company argued that the mean change in BCVA letter score was not the key driver of the model and subsequently provided additional data to show that the distribution of patients across the health states estimated by the model was similar to the distribution of patients in the study at various time points.
- The utility values used for both the better seeing eye and worse seeing eye may be overestimating the quality of life gains from treatment in comparison with the values used in other submissions in this disease area. Using alternative utility values resulted in the cost per QALY increasing to £22k with the PAS. Additional sensitivity analysis provided by the company showed the cost per QALY increased to £18k when the maximum utility gain from treating the better seeing eye was reduced from 0.516 in the base case to 0.35. When the maximum utility gain from treating the worse seeing eye was reduced from 0.3 in the base case to 0.1 the cost per QALY increased to £20k.
- The benefits of ranibizumab treatment were assumed to continue for the duration of the model and this assumption was not specifically tested in the sensitivity analysis. When the benefits of treatment were truncated using a 10-year time horizon the cost per QALY increased to £20k with the PAS.

- The administration cost in the ranibizumab arm is higher than the laser arm to proxy the true marginal cost of delivering this treatment in practice when there are capacity issues. Whether this cost is sufficiently high to fully address this issue is unclear. It should also be noted that the results were sensitive to the number of ranibizumab monitoring visits required per annum.

Despite these limitations, the economic case was considered to be demonstrated.

It is SMC policy to include 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 has agreed not to publish the estimated QALY gain for ranibizumab in visual impairment due to diabetic macular oedema.

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

Summary of patient and public involvement

A Patient Interest Group Submission was received from the Royal National Institute of the Blind Scotland (RNIB).

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published (SIGN) 116 Management of diabetes in March 2010. This recommends that modified ETDRS grid laser photocoagulation should be used for patients with clinically significant macular oedema in the absence of significant macular ischaemia.

The Royal College of Ophthalmologists Preferred Practice Guidance Diabetic Retinopathy Screening (DRS) and the Ophthalmology Clinic set up in England September 2010. Laser photocoagulation is the standard of care for diabetic maculopathy and proliferative retinopathy. It is shown that timely, appropriate laser treatment can reduce the risk of vision loss in these patients by 50%. Evidence of new treatment options for both diabetic maculopathy and proliferative diabetic retinopathy is gathering pace. Intravitreal therapy, using steroid preparations as well as anti-VEGF agents is increasingly finding its way in clinical practice. Currently no licensed products are available for diabetic retinopathy per se, however, clinical use of intravitreal triamcinolone, dexamethasone, bevacizumab, pegaptanib and ranibizumab have been shown to be promising. It is therefore important that the hospital eye service considers implications of such treatment options in the care of DR patients and services are planned so as to accommodate such therapeutic advances.

Additional information: comparators

The relevant comparator is laser photocoagulation.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
ranibizumab	**0.5mg intravitreally every month until maximum visual acuity is achieved**	**5,195***

Doses are for general comparison and do not imply therapeutic equivalence. Cost from MIMS August 2012 * Annual cost based on mean of seven injections used in pivotal study over the first 12 months. Data reporting follow up to 2 years suggest that the number of injections in the second 12 months is much lower, approximately three to four injections.

Additional information: budget impact

Without PAS:
The submitting company estimated the population eligible for treatment to be 4,295 in Year 1 rising to 6,203 in Year 5 with an estimated uptake rate of 10% in year 1 and 20% in year 5. The gross impact on the medicines budget was estimated to be £1.3m in year 1 and £3.7m in year 5. As no other drugs were assumed to be displaced the net medicines budget impact is expected to remain as £1.3m in year 1 and £3.7m in year 5.

The committee noted that the company's estimated uptake rate may be conservative and therefore the corresponding medicines budget impact could be considerably greater when Health Boards have services in place to deliver treatments. The submitting company assumed that the service implications associated with introducing ranibizumab in the treatment of diabetic macular oedema would be minimal but this is not borne out by advice from SMC clinical experts.

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

References

The undernoted references were supplied with the submission.

1. The European Medicines Agency (EMA) European Public Assessment Report for Ranibizumab (Lucentis®) 21/10/2010, EMEA/H/C/000715/II/0020 www.emea.europa.eu

2. Mitchell P, Bandello F, Schmidt-Erfurth U et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011; 118: 615-25.

3. Elman MJ, Aiello LP, Beck RW et al. for the Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010; 117: 1064-77

4. Mitchell P, group Res. 2-year Safety And Efficacy Outcome Of Ranibizumab 0.5 mg In Patients With Visual Impairment Due To Diabetic Macular Edema (DME): An Interim Analysis Of The Restore Extension Study ARVO, May 09, 2012. 2012:Poster #4667

5. Elman MJ, Bressler NM, Qin H et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011; 118: 609-14.

This assessment is based on data submitted by the applicant company up to and including 12 October 2012.

**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. These have been confirmed from the eVadis drug database. 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.