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. (732/11)

Novartis Pharmaceuticals UK Ltd

07 October 2011

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 restricted use within NHS Scotland.

Indication under review: for the treatment of visual impairment due to macular oedema (MO) secondary to retinal vein occlusion (RVO) (branch RVO or central RVO) in adults.

SMC restriction: restricted to use in patients with macular oedema secondary to central retinal vein occlusion (CRVO).

Ranibizumab was associated with significant improvements in visual acuity during 6-month sham-controlled treatment in one study in patients with branch retinal vein occlusion and in one study in patients with central retinal vein occlusion. The benefits were considerable in patients with CRVO and there is a lack of alternative treatment options for these patients.

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 PAS in NHS Scotland.

The submitting company did not present a sufficiently robust economic analysis for ranibizumab in the treatment of BRVO to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 November 2011

Indication

Ranibizumab is indicated for the treatment of visual impairment due to macular oedema (MO) secondary to retinal vein occlusion (RVO) (branch [BRVO] or central [CRVO]) in adults.

Dosing Information

The dose is 0.5mg 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. Consequently, if there is no improvement in visual acuity over the course of 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 MO secondary to RVO. 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

27 May 2011

Summary of evidence on comparative efficacy

In patients with retinal vascular disease, retinal vein occlusion (RVO) is the second most common cause of blindness after diabetic retinopathy. There are two main types of RVO, determined by the site of vein occlusion, central (CRVO) or branch (BRVO), and these can be further categorised as non-ischaemic or ischaemic. Macular oedema, a swelling of the central part of the retina, is a complication of RVO which can result in vision loss.

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, which are all thought to be contributing factors in the progression of visual impairment caused by macular oedema. Ranibizumab has previously been accepted by the Scottish Medicines Consortium for use in the treatment of neovascular (wet) age-related macular degeneration and not recommended for use in the treatment of visual impairment due to diabetic macular oedema. This submission relates to a recent extension to the marketing authorisation for ranibizumab to allow its use in the treatment of visual impairment due to macular oedema when this is secondary to RVO.

Evidence supporting this submission is from two very similar, phase III, sham-controlled studies. The key differences between the studies were the patient populations: one enrolled patients with BRVO, and permitted the use of laser therapy in all groups, and the other enrolled patients with CRVO. Eligible patients were at least 18 years old with foveal centre-involved macular oedema secondary to CRVO or BRVO diagnosed within the previous 12 months. They had best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts equivalent to Snellen values of 20/40 to 20/400 in BRVO or 20/40 to 20/320 in CRVO and mean central subfield thickness ≥250µm from two measurements. Patients were randomised to receive monthly ranibizumab 0.3mg or 0.5mg by intravitreal injection or sham treatment (needleless syringe pressed towards the conjunctiva) for 6 months. For each patient one eye was chosen as the study eye. If both eyes met the inclusion criteria the eye with the worst BCVA at baseline was selected as the study eye. In the BRVO study, rescue laser therapy was allowed in all patients after 3 months. This was followed by a further 6-month observational period when patients were evaluated monthly; those meeting pre-specified criteria could receive further treatment and patients in the sham group crossed-over to ranibizumab 0.5mg.

The primary outcome was the mean change from baseline in the BCVA letter score at 6 months assessed in the intention to treat population and using the last observation carried forward (LOCF) approach to impute missing data. Significant improvements in mean change from baseline in BCVA letter score at 6 months were achieved with ranibizumab compared with sham treatment in both studies. Results are presented below for ranibizumab 0.5mg (licensed dose) and sham.

In patients with BRVO, the mean number of injections during the 6 month treatment period was similar in both groups (5.7). Grid laser therapy was used in more patients in the sham group than the ranibizumab 0.5mg group (54% versus 20% respectively). At 6 months, the mean change (standard deviation [SD]) in the BCVA letter score was 18.3 (13.2) in patients treated with ranibizumab 0.5mg (n=131) compared with 7.3 (13.0) in patients treated with sham (n=132), corresponding to a difference of 11.0 (95% confidence interval [CI]: 7.8 to 14.2). At 12 months, with sham assigned patients eligible to receive ranibizumab 0.5mg after month 6, the mean changes were 18.3 (14.6) and 12.1 (14.4) respectively.

In patients with CRVO, the mean number of injections during the 6-month treatment period was similar in both groups (5.7). At 6 months, the mean change (SD) in the BCVA letter score was 14.9 (13.2) in patients treated with ranibizumab 0.5mg (n=130) compared with 0.8 (16.2) in patients treated with sham (n=130), corresponding to a difference of 14.1 (95% CI: 10.5 to 17.7). At 12 months, with sham assigned patients eligible to receive ranibizumab 0.5mg after month 6, the mean changes were 13.9 (14.2) and 7.3 (15.9) respectively.

In both studies, the differences between ranibizumab and sham were significant at day 7 and maintained to 6 months. Ranibizumab produced clinically significant improvements in visual acuity in more patients than sham, with the proportions of patients experiencing a gain in BCVA of ≥15 letters at 6 months being 61% in the ranibizumab group and 29% in the sham group in the BRVO study, and 48% and 17% respectively in the CRVO study.

Vision-related quality of life functioning was measured using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in which a four-point change in composite score is considered to be a small clinically-meaningful difference. After 6 months, the mean improvement from baseline in the NEI VFQ-25 composite scores in the branch and central studies were significantly greater in patients treated with ranibizumab (10.4 and 6.2 points respectively) than in patients treated with sham (5.4 and 2.8 points respectively).

Following the end of the two studies, 608 patients enrolled in a further 12-month open-label, single-arm extension study, during which patients from the BRVO study received a mean of 2.5 ranibizumab injections and those from the CRVO study, a mean of 3.8 injections. Thirty-three BRVO patients also received laser therapy. Over 12 months, BCVA remained stable with mean changes from baseline of ± 2 letters in BRVO patients, but there was a mean BCVA decrease from baseline of 4 to 5 letters in CRVO patients.

Summary of evidence on comparative safety

No new or unexpected safety issues were identified in the studies of ranibizumab in RVO. In the pooled safety population of both studies, any ocular adverse event suspected to be related to study drug or injection procedure was reported in 32% (84/259) ranibizumab 0.5mg patients and 27% (71/260) sham patients at 6 months. The majority of ocular adverse events were related to the injection procedure and included conjunctival haemorrhage (22% versus 19%), eye pain (14% versus 7.3%), increased intraocular pressure (3.5% versus 1.5%) as well as maculopathy, myodesopsia (floaters in the eye), ocular hyperaemia, ocular vascular disorder, retinal depigmentation, retinal exudates and retinal vascular disorder. Serious ocular adverse events were reported in 1.5% (4/259) ranibizumab and 3.1% (8/260) sham patients but these were considered to be related to the disease.

The incidence of non-ocular adverse events suspected to be related to study drug or injection procedure was 1.5% (4/259) in patients treated with ranibizumab 0.5mg and 1.2% (3/260) in patients treated with sham at 6 months. Serious non-ocular adverse events were uncommon and there appeared to be no difference between ranibizumab and sham treatments with most events occurring in a single patient.

Summary of clinical effectiveness issues

Ranibizumab is the first VEGF inhibitor to be licensed for the treatment of visual impairment due to macular oedema secondary to RVO. The steroid preparation, dexamethasone intravitreal implant (Ozurdex®), is licensed for the treatment of macular oedema following BRVO or CRVO, but is not recommended for use by SMC.

The two clinical studies described above have demonstrated clinically significant improvements in visual acuity compared to sham at 6 months. Significant improvements were evident from day 7 onwards. The primary outcomes were assessed after only 6 months despite the European Medicines Agency (EMA) recommending that 12 month data versus standard care should be provided. However, the studies were still considered controlled at 12 months since the randomised population and blinding were maintained.

There are a number of limitations relating to the generalisability of the study population to patients with RVO in clinical practice. In the clinical studies ranibizumab injections were given monthly for six months. This differs from the licensed treatment regimen of monthly administration continued until maximum visual acuity is achieved i.e. visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment.

Both BRVO and CRVO can be further classified as non-ischaemic or ischaemic, the latter having poorer visual prognosis. The majority of RVOs in both studies were non-ischaemic. In addition the studies excluded patients with prior episodes of RVO. These limitations are highlighted in the SPC: "There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischaemic BRVO and CRVO. In patients with RVO presenting with clinical signs of irreversible ischaemic visual function loss, treatment is not recommended." The studies also excluded patients with evidence of AMD or diabetic retinopathy which may also be present in patients with RVO in clinical practice. In enrolled patients, RVO had been diagnosed within the previous 12 months (after a mean of 3.5 months and 3.3 months in the BRVO and CRVO studies respectively) so there is little experience in patients with chronic disease.

Although RVO is usually unilateral, with normal vision maintained in the non-affected eye, the patient-reported outcomes assessing vision-related quality of life found statistically significant improvements with ranibizumab over sham at 6 months.

BRVO can improve or resolve spontaneously over time. A recent systematic review of untreated eyes suggested that mean visual acuity improved by one letter at 3 months to 15 letters at 18 months, but that clinically significant improvement beyond 20/40 were uncommon. Since the study in BRVO was not sham-controlled between months 6 and 12, the contribution of spontaneous improvement to the treatment effect is unknown. The BRVO study also allowed patients in both groups to receive laser treatment. This was permitted once during the 6-month treatment phase after month 3 and was used in more sham than ranibizumab treated patients (54% versus 20%). The effects of this deferred treatment are difficult to assess. The EMA noted that this study does not confirm that ranibizumab offers a sustained advantage over standard care in the long term management of BRVO. However, it concluded that the effect of ranibizumab had been demonstrated and that the effect of these factors on the magnitude of the additive effect of ranibizumab was of minor concern.

CRVO is more severe than BRVO and is not associated with spontaneous improvement. Laser therapy has not been proven to be effective in CRVO so there is a greater clinical need in this patient population. The improvement in visual acuity in the CRVO population in the studies was considerable therefore the benefits of ranibizumab in these patients are likely to be greater.

Ranibizumab can be used immediately after diagnosis with the potential to achieve rapid improvement in visual acuity maintained for over 12 months. In patients with BRVO, laser treatment is not recommended until 3 to 6 months after the initial event and after absorption of the majority of the haemorrhage, and is not associated with short term benefits in visual acuity. However, in some patients, deferred treatment is not a disadvantage and provides time to allow for any spontaneous improvement. Ranibizumab requires monthly intravitreal injection which may lack acceptability for some patients. It also has a higher immediate risk, associated with the injections, than laser therapy which has a longer-term risk, associated with destruction of retinal vessels and resulting scar tissue.

There are no comparative data for ranibizumab versus dexamethasone implants or laser therapy.

SMC clinical experts have advised that laser treatment is currently the predominant treatment for macular oedema secondary to BRVO and that macular oedema secondary to CRVO is generally untreated. Experts advise that there is limited intraocular use of unlicensed preparations of triamcinolone and bevacizumab in macular oedema secondary to RVO in Scotland. The National Institute for Health and Clinical Excellence (NICE) has been asked to consider the feasibility of undertaking an appraisal of the clinical and cost effectiveness of intravitreal bevacizumab in eye conditions. SMC policy precludes consideration of unlicensed medicines as a comparator.

Ranibizumab must be injected under aseptic conditions. Patients should self-administer antimicrobial drops for three days before and after each injection and should be monitored during the week following the injection to permit early treatment if an infection occurs. The EMA notes that due to the major risks of incorrect injection procedure, there will be a need for a continuous education of physicians in this field. The requirement for monthly monitoring visits, while receiving ranibizumab treatment and also after its discontinuation to determine need for treatment, is expected to have significant implications for service delivery.

Summary of comparative health economic evidence

The submitting company provided two cost-utility analyses to investigate the cost-effectiveness of ranibizumab in patients with BRVO and CRVO. Markov models were used for both analyses and in each case the health states related to differing levels of visual acuity. In the BRVO model, the comparator treatment was grid laser therapy. In the CRVO model, the comparator was observation alone. These comparators were appropriate. For both models, health states were defined according to the best corrected visual acuity (BCVA) in the treated eye. The analyses assumed that the treated eye was the better seeing eye (BSE) although in the clinical trials the treated eye was predominantly the worse seeing eye (WSE). The time horizon for both models was 15 years.

The clinical data for the first 2 years of the model were derived from the two pivotal studies in BRVO and CRVO patients, combined with assumptions where necessary (e.g. to adjust for the fact that in both trials patients in both the ranibizumab and comparator arms could receive ranibizumab after 6 months). Ranibizumab was assumed to be given only in years 1 and 2 of the model. From year 3 of the model onwards, it was assumed that there would be a natural worsening of BCVA for all patients, and this was based on data from a published study in a general population.

Quality of life values associated with each of the visual acuity states were estimated from a published study and related to utility changes in the BSE. This study was conducted in people with vision loss, of whom 7% had RVO.

In terms of resource use, it was assumed that BRVO patients received a mean of 8 injections of ranibizumab in year 1 and 2.5 injections in year 2. For CRVO patients the figures were 9 and 3.8 respectively. Other costs in the model related to the administration costs associated with ranibizumab and associated follow-up visits. The model also included costs associated with

patients who moved into the blindness states of the model. The costs of blindness were taken from a standard published source.

A patient access scheme 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 simple discount was offered on the list price of ranibizumab. Based on the PAS the results of the base case economic analyses indicated that in patients with BRVO the estimated ICER was £21,300 per QALY and in CRVO, the estimated ICER was £9,425.

Extensive sensitivity analysis was provided. This indicated that the results were sensitive to changes in key parameters. Assuming a higher cost associated with ranibizumab administration increased the with-PAS cost per QALY estimates to £24,682 and £11,742 for BRVO and CRVO patients respectively. If it was assumed that one ranibizumab injection would be given in year 3, the incremental cost-effectiveness ratios (ICERs) increased to £23,908 and £10,876 for BRVO and CRVO patients respectively. Making differential, but relatively extreme, assumptions about the transition probabilities used in the first few years of the model caused the ICERs to rise sharply in some cases.

There were a number of issues with the analyses:

- It was assumed that the BSE was treated, with utility values relating to the BSE. However, the majority of patients have RVO in their WSE and it is likely that cost-effectiveness would be poorer when treating the WSE as the quality of life gain would be less. The submitting company provided analyses to show the impact of assuming a reduced level of quality of life gain associated with treating the WSE. In the NICE appraisal of wet AMD it was assumed that treatment in the WSE would result in a 30% lower utility gain. If this level of utility decrement was factored into the analyses, the with-PAS cost per QALY figures increased to £24k in CRVO and to £27k in BRVO. It should be noted, however, that these estimates for BRVO were based on a post-hoc subgroup analysis of patients with more severe disease (less than 50% of the sample used in the base case) and included a stopping rule at 3 months. When the 30% lower utility gain was applied to the whole base case population in the BRVO analysis the cost per QALY increased to £38k.
- The results were sensitive to the continued use of ranibizumab in the third year of the model. While SMC clinical experts gave mixed views on the likelihood of treatment after year 2, the results showed some sensitivity to this assumption. With respect to the sensitivity analysis on this variable, the analysis assumed a cost for continued treatment but this was conservative in that it did not impute any additional benefit associated with the injection.
- The cost of administration used in the base case may be too low, therefore underestimating the true opportunity cost of administering ranibizumab in practice due to capacity issues within NHS Scotland to deliver treatment. Sensitivity analysis showed that the results were sensitive to the use of a higher administration cost.
- While changes to some variables (e.g. injection in year 3, administration costs) produced only a small impact on the ICER individually, the combined effect of changes was more marked. For example, a pessimistic sensitivity analysis to show the combined impact of assuming an additional injection in year 3, higher treatment administration costs and the 30% adjustment to the utility gain for the WSE increased the with- PAS ICER in the BRVO case to £33,287 per QALY (based on the subgroup analysis) and £29,538 per QALY for CRVO.
- The results were sensitive to the source of utility values used. The submitting company

provided some additional analyses using other utility values from the literature. While the advantages and disadvantages with each source of utility values differ, this highlights that the results show some sensitivity to the source of data used.

- SMC clinical experts suggest that the natural rate of worsening in visual acuity used in the model may be low given the comorbidities of the population concerned. Sensitivity analysis suggested that increasing the rate of decline raised the cost-effectiveness ratios.

For the CRVO analysis the key uncertainty related to the use of BSE utility data. While the ICER was sensitive to the assumed reduction in utility gain, the SMC considered that in view of the lack of alternative treatments in this patient group and the lower base case ICER which allows for some uncertainty in the model assumptions, the economic case in CRVO was demonstrated.

For the BRVO analysis, additional weaknesses were:

- There are some limitations in relation to the application of the study data to the economic model. The BRVO study reflects the use of laser in a proportion of the ranibizumab treated patients. While the model made adjustments to the data to allow for this, it remains a source of uncertainty.
- As the base case ICER in the BRVO analysis is relatively high the cumulative uncertainty is such that the true ICER in this patient group is likely to be above acceptable limits when the model is adjusted to account for the lower utility gain in the WSE and the weaknesses with the clinical data.

Given these uncertainties the economic case for use in BRVO was not demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was received from RNIB Scotland.

Additional information: guidelines and protocols

The Royal College of Ophthalmologists published Interim Guidelines for the Management of Retinal Vein Occlusion in December 2010. These guidelines provide separate recommendations for central RVO and branch RVO. In central RVO there are recommendations for dexamethasone and ranibizumab (although unlicensed for the indication at the time of publication). In branch RVO there are recommendations for laser photocoagulation, dexamethasone and ranibizumab. It is noted that laser photocoagulation is beneficial only after 3 to 6 months, after absorption of the majority of haemorrhage. However patients with severe vision loss and with symptoms persisting for more than 1 year are unlikely to benefit.

Additional information: comparators

The relevant comparators are laser photocoagulation (BRVO only) and dexamethasone implants (Ozurdex®, which is not recommended by SMC). Bevacizumab is also being used to treat RVO but this use is unlicensed.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 6 months(£)
Ranibizumab	0.5mg intravitreally once monthly	4,567
Dexamethasone intravitreal implant	700 micrograms intravitreally	870

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs August 2011. The cost for ranibizumab is based on six monthly injections. The cost for dexamethasone implant is based on one implant.

Additional information: budget impact

The submitting company estimated the budget impact based on BRVO and CRVO patient groups but advised that estimates of market uptake should remain commercial in confidence.

For BRVO, the company estimated there would be 1157 patients eligible for treatment each year. The net impact on the medicines budget was estimated at £218k in year 1 and £2.03m in year 5 without the PAS.

For CRVO, the company estimated there would be 556 patients eligible for treatment each year. The net impact on the medicines budget was estimated at £217k in year 1 and £2.0m in year 5 without the PAS.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

Campochiaro P, Heier J, Feiner L et al. Ranibizumab for macular edema following branch retinal vein occlusion. Ophthalmology 2010;117:1102-1112.

Brown D, Campochiaro P, Singh R et al Ranibizumab for macular edema following central retinal vein occlusion. Ophthalmology 2010;117:1124-1133.

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Brown DM, Campochiaro PA, Bhisitkul RB et al. Sustained benefits from ranibizumab for macual edema follwing branch retinal vein occlusion: 12 month outcomes of a phase III study. Ophthalmology 2011;118:1594-1602

The European Medicines Agency (EMA). European Public Assessment Report for ranibizumab (Lucentis®), www.ema.europa.eu Procedure No : EMEA/H/C/000715/II/0022

Campochiaro PA, Brown DM, Awh CC et al. Sustained benefits from ranibizumab for macual edema follwing central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology in press, available online 29 June 2011

**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*

This assessment is based on data submitted by the applicant company up to and including 16 September 2011.

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.