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

Resubmission

ranibizumab, 10mg/mL solution for injection (Lucentis®) SMC No. (732/11)

Novartis Pharmaceuticals UK Ltd

05 April 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 resubmission

ranibizumab (Lucentis®) is accepted for 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. This resubmission relates to branch RVO only.

Ranibizumab was associated with significant improvements in visual acuity during 6-month sham-controlled treatment in a phase III randomised double-blind study in patients with branch retinal vein occlusion.

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.

SMC has previously accepted ranibizumab for use in macular oedema secondary to central retinal vein occlusion (CRVO). This advice now extends its use to patients with branch retinal vein occlusion (BRVO).

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 May 2013

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. In macular oedema secondary to BRVO, 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 (MO), 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.

For the above indication, the Scottish Medicines Consortium (SMC) has previously accepted ranibizumab for restricted use in patients with macular oedema secondary to central retinal vein occlusion (CRVO). In this resubmission, the submitting company has requested that SMC considers the use of ranibizumab when positioned for use in the treatment of visual impairment due to MO secondary to branch BRVO.

Evidence supporting this positioning is from a phase III, sham-controlled, 12 month study (BRAVO) in adults with foveal centre-involved macular oedema secondary to BRVO diagnosed within the previous 12 months, 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 and mean central subfield thickness ≥250micrometres.[1] 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 six months. Rescue laser therapy was allowed in all patients after three months. This was followed by a six-month observational period during which patients were evaluated monthly and ranibizumab was administered on an as required basis; only when patients met pre-specified criteria did they receive further treatment with their original dose. Patients in the sham group crossed over to ranibizumab 0.5mg. 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.

The primary outcome was the mean change from baseline in the BCVA letter score at six 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. Results are presented in the table for ranibizumab 0.5mg only, the licensed dose.

Table: Mean change from baseline to 6 months in BCVA score

	Ranibizumab 0.5mg (n=131)	**Sham (n=132)**
Baseline BVCA score: mean (range)	53.0 (22 to 79)	54.7 (16 to 73)
Mean change in BCVA score at 6 months (standard deviation [SD])	18.3 (13.2)	7.3 (13.0)
Difference in means ranibizumab versus sham (95% confidence interval [CI])	11.0 (7.8 to 14.2)	-
p-value for difference	<0.0001	

The mean number of injections during the six month treatment period in the ranibizumab 0.5mg group was 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 12 months, with sham assigned patients eligible to receive ranibizumab 0.5mg after month six, the mean changes in BCVA were 18.3 (14.6) and 12.1 (14.4) in the ranibizumab/ranibizumab and ranibizumab/sham groups respectively. In the 6 to 11 month period, patients received a mean number of 2.7 injections in the 0.5mg ranibizumab group, while patients treated with sham injection for the first six months then ranibizumab 0.5mg in the 6 to 11 month period received a mean of 3.6 injections.[2]

The difference between ranibizumab and sham injections was significant at day 7 and maintained to 6 months. More ranibizumab patients had a clinically significant improvement in visual acuity, with the proportion of patients experiencing a gain in BCVA of ≥15 letters at six months being 61% in the ranibizumab group and 29% in the sham group.[1]

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 were significantly greater in patients treated with ranibizumab compared with sham (10.4 versus 5.4 points).[1]

Following the end of the study, 201 patients treated with either ranibizumab 0.5mg or sham/ranibizumab 0.5mg enrolled in a further 12-month open-label, single-arm, extension study (HORIZON), during which they received a mean of 2.0 and 2.1 ranibizumab injections respectively. In total, 139 of the 201 patients received a ranibizumab injection during the HORIZON study and 18 patients received rescue laser therapy. Over 12 months, BCVA remained stable with mean change from baseline of -0.7 in the ranibizumab 0.5mg group and 0.9 in the sham/ranibizumab group.

However, due to marketing authorisation being granted, the study was stopped early and there was considerable variation in the length of patient follow up.[3]

Summary of evidence on comparative safety

No new or unexpected safety issues were identified. At six months, ocular adverse events were reported in 5.4% (7/130) of ranibizumab 0.5mg patients and 13% (17/131) of sham patients. In the ranibizumab 0.5mg group, one patient developed endophthalmitis (a complication of intraocular injection), and cataract was reported in four patients in both the sham and ranibizumab groups.[1]

In pooled safety data from the BRAVO study in combination with the phase lll study in the CRVO population, 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 six 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.[4]

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 six 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.

In the HORIZON extension study, the most commonly reported adverse events were retinal haemorrhage and conjunctival haemorrhage with the incidence of conjunctival haemorrhage being higher in the ranibizumab 0.5mg group compared with sham (21% versus 12%). The overall rate of cataract was low but was twice as high in the ranibizumab 0.5mg group than the sham group (6.7% versus 3.2%).[3]

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. SMC has previously accepted ranibizumab for restricted use in patients with macular oedema secondary to CRVO. This resubmission reconsiders the use of ranibizumab in patients with BRVO. The steroid preparation, dexamethasone intravitreal implant (Ozurdex®), is licensed for the treatment of macular oedema following BRVO or CRVO, and was recently accepted for restricted use by SMC in patients with CRVO and in patients with BRVO who are not clinically suitable for laser treatment including patients with dense macular haemorrhage or patients who have received and failed on previous laser treatment. The incidence of BRVO is two to three times higher than CRVO.[6]

Scottish experts contacted by SMC suggest that when treatment is required, grid laser photocoagulation is commonly used, dexamethasone intravitreal implant may be used in suitable patients and there is some use of ranibizumab and unlicensed bevacizumab. An unmet need was highlighted in patients with vein occlusion and secondary macular oedema who are unsuitable for dexamethasone intravitreal implant e.g. due to pre-existing glaucoma.

The key, 12 month, phase lll, BRAVO study demonstrated a clinically significant improvement in visual acuity for ranibizumab 0.5mg injection compared with sham injection at six months in patients with a diagnosis of BRVO of less then 12 months. Significant improvements were evident from day 7 onwards.[1] The primary outcome was assessed after six months but the study was still considered controlled at 12 months since the randomised population and blinding were maintained.[4]

Study inclusion and exclusion criteria may limit the generalisablity of the results to clinical practice. BRVO can be further classified as non-ischaemic or ischaemic, the latter having poorer visual prognosis. The majority of patients in the BRAVO study had non-ischaemic RVO; patients with prior episodes of RVO were excluded; patients with evidence of age-related macular degeneration (AMD) or diabetic retinopathy which may also be present in patients with RVO in clinical practice were excluded; and enrolled patients had to have had BRVO diagnosed within the previous 12 months with the mean time to diagnosis of 3.5 months, so there is little experience in patients with chronic disease.

Other limitations include the monthly dosing for six months used in the study, which 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. Feedback from clinical experts suggests that in most patients there would be an initial observation period of around two to three months to allow for spontaneous resolution before initiating treatment.

BRVO can improve or resolve spontaneously over time. It has been reported that in untreated eyes mean visual acuity can in some cases improve by one letter at three months to 15 letters at 18 months, but that clinically significant improvement beyond 20/40 is uncommon.[5] In the BRAVO study, the contribution of spontaneous improvement to the treatment effect is unknown. In a post hoc analysis presented in this resubmission, around 40% of patients who were randomised to sham treatment and did not receive any laser treatment to six months gained ≥15 letters.

Patients in both groups were allowed to receive rescue laser treatment after month three and this was used in more sham than ranibizumab treated patients (54% versus 20%). In a post hoc analysis of BRAVO patients, laser was not found to have influenced the primary outcome of visual acuity. In patients with BRVO, laser treatment is not recommended until three to six months after absorption of the majority of the haemorrhage, and is not associated with short term benefits in visual acuity. Ranibizumab can be used immediately after diagnosis with the potential to achieve rapid improvement in visual acuity maintained for over 12 months. However, in some patients, deferred treatment is not a disadvantage and provides time for any spontaneous improvement.

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 six months.

Ranibizumab requires monthly intravitreal injection which may lack acceptability for some patients. It must be injected under aseptic conditions and patients should be monitored during the following week to permit early treatment if an infection occurs. 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.

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.

There are no comparative data for ranibizumab versus dexamethasone implants. An exploratory Bayesian indirect comparison of ranibizumab 0.5mg intravitreal injection versus dexamethasone 0.7mg intravitreal implant in macular oedema secondary to BRVO was included in the company's

resubmission. The endpoint, percentage of patients reaching different levels of change in BCVA at one month, was used because it was the earliest time point at which a response was measured in all studies, and was prior to the time point when patients were offered laser photocoagulation (in the ranibizumab study). Dexamethasone study outcomes were fitted using a multinomial model, in ranges compatible with those for ranibizumab, and these were used in the indirect comparison. Patient level data were used for ranibizumab. The results of the indirect comparison suggest no significant difference between ranibizumab and dexamethasone. Limitations of the indirect comparison are: the small number of studies included, heterogeneity between studies, and uncertainty whether the results at one month may be extrapolated to longer duration time points.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis to investigate the cost-effectiveness of ranibizumab in patients with BRVO. A Markov model was used with the health states based on levels of visual acuity, and the base case model assumed that the relative proportions of patients treated in their better seeing eye (BSE) or worse seeing eye (WSE) was as per the BRAVO study. The comparator treatments were grid laser therapy or dexamethasone intravitreal implants. A lifetime horizon was used.

For the comparison with grid laser, the clinical data for the first two years of the model were derived from the pivotal studies in BRVO combined with assumptions where necessary (e.g. an equal probability of gaining or losing vision between the treatments from month 7 of the model onwards). For the comparison with dexamethasone intravitreal injections, estimates of relative efficacy were derived from an indirect comparison, the outputs of which demonstrated non-significant differences in favour of ranibizumab. All treatments were assumed to be given only in years one and two of the model. From year 3 onwards of the model, it was assumed that there would be a common 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, which was then adjusted by assumption in order to arrive at utility values related to utility changes in the worse seeing eye. Background mortality in the model was adjusted to take account of the higher mortality rates associated with visual impairment.

In terms of resource use, it was assumed that BRVO patients received a mean of 8 injections of ranibizumab in year 1, and 1.9 injections in year 2. Grid laser patients received 1.5 and 1 treatments in years 1 and 2, and the figures for dexamethasone were 2 treatments in each year. Other costs in the model related to the administration costs associated with giving ranibizumab and associated follow-up visits. The model also included costs associated with patients who moved into the blindness states of the model. The NHS and social work costs of blindness were taken from a standard published source, and were estimated at approximately £12,000 per year.

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 simple discount was given on the price of the medicine. Incorporating the PAS, the results of the model indicated a cost per quality adjusted life year (QALY) in BRVO patients of £13,330. compared to grid laser. In the comparison with dexamethasone implants, the with-PAS results were £2,555 per QALY.

Extensive sensitivity analysis was provided. This indicated that the results were sensitive to changes in key parameters, as summarised in the table below.

Variable	With PAS ICER versus grid laser	With PAS ICER versus dexamethasone
12 injections of ranibizumab in year 1 (i.e. one per month)	£19,010	£10,290
6 ranibizumab injections in year 2	£19,140	£10,466
Use of 1 ranibizumab injection in year 3	£16,596	£7,020
Ranibizumab administration cost £402	£19,516	£10,976
Ranibizumab follow up cost £161	£18,873	£10,104
6 ranibizumab visits in years 3+	£24,261	£17,402
0.1 overall gain for WSE (0.3 assumed in the base case)	£25,406	£2,858
100% treated in WSE	£24,264	£4,047

The company also provided graphs to show the impact of changes to the assumed relative efficacy advantage with ranibizumab. These demonstrated that the cost-effectiveness ratios had the potential to rise fairly sharply if the clinical advantages with ranibizumab were less than assumed in the base case analysis. For example, if ranibizumab was about 20% to 30% less effective from months 7 to 12, the ICER rose to around £20,000 per QALY. Similarly, if the effectiveness of laser improved in months 7-12 by around 25%, the ICER may rise to around £30,000.

There were a number of issues with the analysis.

- The efficacy data in the comparison with dexamethasone used non-significant differences from an indirect comparison. The company provided additional analysis to show the impact of removing the numerical differences between ranibizumab and dexamethasone. This resulted in a cost per QALY with the PAS of £5,174. A QALY gain remained in this analysis due to differences in cataracts between the treatments but this finding showed some sensitivity to the percentage of patients who were then assumed to go on to have a cataract removal procedure. The figure of £5174 assumed that all patients had the procedure but if this fell to 58% or 35% of affected patients, the ICER rose to £11,709 and £23,874 respectively.
- While the resubmission has addressed the issue of patients being treated in their worse seeing eye, with the resultant smaller utility gains that this brings, the sensitivity analysis showed that the results were sensitive to the utility difference assumed for the worse seeing eye. This remains a source of uncertainty.
- There are some limitations in terms of the trial data providing useful information for the economic model. In the analysis versus grid laser, the trial reflects the use of laser in a proportion of the ranibizumab patients and it is not clear that this would happen in clinical practice. In the trials, after 6 months patients in the sham arm could receive ranibizumab, making it difficult to be certain on the true benefits over the longer term. The submitting company did make some assumptions to allow for this latter situation, but the true level of benefit is still associated with some uncertainty.

Despite these uncertainties, the economic case was 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 is unable to publish the estimated QALY gain.

*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.[6] 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 three to six months, after absorption of the majority of haemorrhage. However patients with severe vision loss and with symptoms persisting for more than one year are unlikely to benefit.

Additional information: comparators

The relevant comparators are laser photocoagulation and dexamethasone implants (Ozurdex®). There is some use of bevacizumab 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	4453
Dexamethasone intravitreal Implant	700 micrograms intravitreally	870

Doses are for general comparison and do not imply therapeutic equivalence. Costs were from MIMS online 15 Jan 13. 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 population eligible for treatment to be 1,188 in Year 1 rising to 2,376 in Year 5, with an estimated uptake rate of 4% in year 1 and 30% in year 5. The company has also estimated that there will be a discontinuation rate of 20.5% in all years.

Without PAS: The gross impact on the medicines budget was estimated to be £224k in year 1 and £1.988m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £216k in year 1 and £1.823m in year 5.

The estimated savings in displaced medicines may be understated and therefore the budget impact may not be as high in practice.

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

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

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

2. 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

3. Heier JS, Campochiaro PA, Yau L et al. Ranibizumab for macular edema due to retinal vein occlusions. Long-term follow-up in the Horizon trial. Ophthalmology 2012 in press.

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

5. Rogers SL, McIntosh RL, Lim L et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2010;117:1094-1101

6. The Royal College of Ophthalmologists. Interim Guidelines for Management of Retinal Vein Occlusion. , December 2010.

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