NICE National Institute for Health and Care Excellence

NICE guidance

Ranibizumab for treating choroidal neovascularisation associated with pathological myopia

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia only if the manufacturers of ranibizumab (branded or biosimilar) provide it at a discount level no lower than the discount agreed in the patient access scheme.

2 The technology

2.1 Ranibizumab (Lucentis, Novartis) belongs to a class of drugs that blocks the action of vascular endothelial growth factor (VEGF)-A. By blocking the action of VEGF-A, ranibizumab prevents abnormal blood vessels developing, thereby limiting visual loss and improving vision. Ranibizumab has a marketing authorisation for 'the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia'.

2.2 Ranibizumab The summary of product characteristics states that monitoring is recommended monthly for the first 2 months and at least every 3 months thereafter during the first year. If monitoring reveals signs of disease activity, for example, reduced visual acuity and/or signs of lesion activity, further treatment is recommended.

2.3 Adverse reactions to treatment are mostly limited to the eye. Those commonly reported in clinical trials include vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, sensation of a foreign body in the eye, increased production of tears, blepharitis, dry eye, ocular hyperaemia, itching of the eye and increased intraocular pressure. Nasopharyngitis, arthralgia and headaches are also commonly reported. Contraindications to ranibizumab include known hypersensitivity to the active substance or to any of its excipients, active or suspected ocular or periocular infections, and active severe intraocular inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The manufacturer of branded ranibizumab (Lucentis, Novartis) has agreed a patient access scheme with the Department of Health, revised in the context of NICE's technology appraisal guidance on ranibizumab for treating diabetic macular oedema, which makes ranibizumab available with a discount applied to all invoices. The level of the discount is commercial in confidence. The manufacturer has agreed that the patient access scheme will remain in place until any review of this technology by NICE is published. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. NHS England has completed a national

procurement for medical retinal vascular medicines, which includes the biosimilar versions of ranibizumab. Prices paid for the originator or biosimilar ranibizumab should be in line with the national procurement outcome and should be no higher than that provided through the original PAS.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of ranibizumab and a review of this submission by the Evidence Review Group (ERG).

Clinical effectiveness

3.1 The manufacturer submitted evidence of clinical and cost effectiveness for ranibizumab compared with verteporfin photodynamic therapy (vPDT) in people with choroidal neovascularisation associated with pathological myopia. Pathological myopia is a chronic condition characterised by excessive lengthening of the eye and degenerative changes at the back of the eye. These changes to the eye can cause blood vessels to leak or bleed into the retina in a process known as choroidal neovascularisation. This can result in visual impairment, in particular a loss of central vision. The manufacturer did not provide a comparison with bevacizumab, which is listed as a comparator in the scope for this appraisal. It did not consider bevacizumab to be a valid comparator because it is unlicensed for this condition and not routinely used.

3.2 The main sources of evidence presented in the manufacturer's submission came from a Novartis phase 3 trial (RADIANCE) and 2 other randomised trials (Gharbiya 2010; Iacono 2012). Gharbiya (2010) and Iacono (2012) compared ranibizumab with bevacizumab. However, the manufacturer did not present data from the bevacizumab arm of these trials.

3.3 RADIANCE compared ranibizumab with vPDT in people with visual impairment caused by choroidal neovascularisation secondary to pathological myopia. The trial was a randomised, double-blind, multicentre study conducted in 20 countries, which compared 2 groups of patients using ranibizumab (n=222) with 1 group using vPDT (n=55). On day 1 of treatment, patients in the ranibizumab groups received 0.5 mg of ranibizumab and patients in the vPDT group were given 6 mg/m^2 of verteporfin intravenously, followed by a light dose of 50 J/cm^2 at an intensity of 600 mW/cm^2 for 83 seconds. In the ranibizumab disease activity group (n=116) and the vPDT group, patients were re-treated if visual impairment caused by intra or subretinal fluid, or active leakage secondary

to pathological myopia, was seen. Treatment was continued until these effects were no longer seen. In the ranibizumab disease stabilisation group (n=106), patients were re-treated if there was a loss of best corrected visual acuity (BCVA) because of disease activity. Treatment was continued until BCVA was stable for 3 consecutive monthly assessments.

3.4 The primary end point of RADIANCE was the mean average change in BCVA between baseline and months 1 to 3, measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart, in which a score of 85 letters corresponds to normal visual acuity. Gains in BCVA (reported as mean±standard deviation [SD]) were statistically significantly greater in both ranibizumab groups (disease activity group; 10.6±7.3 letters, $p<0.0001$ compared with vPDT, disease stabilisation group; 10.5±8.2 letters, $p<0.0001$ compared with vPDT) than in the vPDT group (2.2±9.5 letters). The secondary end points included the proportion of patients gaining 10 or more or 15 or more letters, mean change in BCVA, and changes in central retinal thickness from baseline. Both of the ranibizumab groups had statistically significantly more patients gaining 10 or more letters or 15 or more letters than the vPDT group. There was no statistically significant difference between either of the ranibizumab groups compared with the vPDT group in mean change in BCVA or in mean change in central retinal thickness. The length of follow-up was 12 months for the 2 ranibizumab groups. After 3 months, 72% of the patients in the vPDT group received ranibizumab. Therefore, the manufacturer did not compare the results of the vPDT group with the results of the ranibizumab groups after the initial 3-month period.

3.5 The 2 other randomised trials (Gharbiya 2010; Iacono 2012) were single-centre trials conducted in Italy comparing ranibizumab with bevacizumab. The manufacturer did not present the data for the bevacizumab arm for either trial. The Iacono (2012) study was a double-blind clinical trial in people with subfoveal choroidal neovascularisation secondary to pathological myopia (55 eyes; ranibizumab=27, bevacizumab=28) with a follow-up period of 18 months. Gharbiya (2010) was an interventional study in people with subfoveal or juxtafoveal choroidal neovascularisation secondary to pathological myopia and evidence of leakage from the choroidal neovascularisation lesion (32 eyes; ranibizumab=16, bevacizumab=16) with a follow-up period of 6 months. The mean (±SD) change in BCVA was 9±NR (not reported) letters in the ranibizumab arm of the Iacono (2012) study and 17.3±11.1 letters in the ranibizumab arm of the

Gharbiya (2010) study. It was not reported how many patients gained 10 or more letters in the Iacono study, although 7 (30%) gained 15 or more letters in the ranibizumab arm. In the ranibizumab arm of the Gharbiya (2010) study, 12 (75%) patients gained 10 letters or more and 9 (56%) gained 15 letters or more. The mean change in retinal thickness was not reported in the Iacono (2012) study. In the ranibizumab arm of the Gharbiya (2010) study, the mean change in retinal thickness was -45±NR micrometres.

3.6 The manufacturer identified 6 non-randomised studies relevant to the decision problem. All 6 studies investigated the use of ranibizumab in patients with choroidal neovascularisation secondary to pathological myopia, with follow-up times ranging from a mean of 8 months to a median of 17 months. One study was a multicentre phase 2 study (the REPAIR study) and the other 5 studies were prospective case-series (Calvo-Gonzalez 2011; Lalloum 2010; Ouhadj 2010; Silva 2010; Vadala 2011). A statistically significant change in BCVA from baseline to time of assessment was shown in 4 of the 6 studies. The number of patients who gained 15 or more letters at follow-up ranged from 24% to 47%.

3.7 Adverse effects of ranibizumab were reported in RADIANCE. Ocular adverse events in the ranibizumab disease activity group were 16 (14%, 0 severe), 31 (26%, 1 severe), and 44 (37%, 1 severe) and in the ranibizumab disease stabilisation group were 29 (27%, 0 severe), 38 (36%, 0 severe), and 46 (43%, 1 severe) by 3, 6, and 12 months respectively. There were 5 (9%) ocular adverse events in the vPDT group by 3 months, of which none were severe. Non-ocular adverse events in the ranibizumab disease activity group were 30 (25%, 1 severe), 42 (36%, 3 severe), and 51 (43%, 6 severe) and in the ranibizumab disease stabilisation group were 27 (26%, 0 severe), 38 (36%, 1 severe), and 48 (45%, 3 severe) by 3, 6, and 12 months respectively. There were 6 (11%) non-ocular adverse events in the vPDT group by 3 months, of which none were severe. There were no systemic or significant ocular adverse events in the Iacono (2012) or Gharbiya (2010) trials. REPAIR reported adverse events that occurred in 2 or more patients. Ocular adverse events occurred in 29 (45%) patients and non-ocular adverse events in 39 (60%) patients over 12 months. Calvo-Gonzalez (2011) reported that 2 eyes developed anterior uveitis over a mean follow-up of 16 months. The other 4 non-randomised studies (Lalloum 2010; Ouhadj 2010; Silva 2010; Vadala 2011) reported that no systemic or ocular adverse events were observed, with the mean follow-up ranging from 8 to 17 months.

3.8 Impact on health-related quality of life was measured in RADIANCE. The change in National Eye Institute Visual Functioning Questionnaire 25 item (NEI VFQ-25) composite score from baseline to 3 months (reported as mean±SD) was statistically significantly higher for the 2 ranibizumab groups (disease activity group; 4.3±10.1, $p<0.05$ compared with vPDT, disease stabilisation group; 5.3±14.0, $p<0.05$ compared with vPDT) compared with the vPDT group (0.3±12.6). The mean (±SD) change in the EQ-5D questionnaire from baseline to 3 months was 2.3±55.0, 4.2±NR, and 2.1±NR for the ranibizumab disease activity, ranibizumab disease stabilisation, and vPDT groups respectively. The mean (±SD) reduction in Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH) score from baseline to 3 months was 22.0±55.0, 21.9±75.2, and 10.2±59.9 for the ranibizumab disease activity, ranibizumab disease stabilisation, and vPDT groups respectively. The statistical significance of the differences between the groups for the EQ-5D and WPAI-GH scores were not reported.

Cost effectiveness

3.9 The manufacturer developed a cost–utility Markov model that evaluated the cost effectiveness of ranibizumab compared with vPDT in people with choroidal neovascularisation associated with pathological myopia. There were 8 health states in the model, defined by the BCVA in the treated eye in addition to the absorbing health state of death. The health states were defined by a 10-letter range in BCVA. The model had 3-monthly cycles and a lifetime time horizon.

3.10 The transition probabilities for the first cycle of the model (baseline to month 3) for both ranibizumab and vPDT were based on RADIANCE. For the next 3 cycles (months 4 to 12), the transition probabilities between health states were derived from RADIANCE for ranibizumab and from the Verteporfin in Photodynamic Therapy (VIP) trial for vPDT. VIP compared vPDT with photodynamic therapy in 120 patients with subfoveal choroidal neovascularisation secondary to pathological myopia. For cycles 5 onwards (1 year onwards), a slow worsening of visual acuity was assumed, based on natural disease progression reported in Yoshida (2002) for the base case and an additional 6 natural history studies for the other transition probabilities. The model included crossover from the better-seeing eye to the worse-seeing eye and vice versa as patients changed

health states.

3.11 A baseline rate of bilateral involvement (that is, both eyes affected by choroidal neovascularisation) of 15% was derived from 2 published studies (Cohen 1996; Hampton 1983) and the model assumed no incidence of choroidal neovascularisation secondary to pathological myopia after baseline measurement. Based on expert opinion, the manufacturer estimated a recurrence of choroidal neovascularisation in 6% of patients each year after the first 2 years of modelling. The manufacturer assumed an indefinite duration of treatment benefit, based on the treatment benefit seen at year 1.

3.12 Base-case utility values for the better-seeing eye were taken from a published study of the UK general population in which BCVA health states were simulated with contact lenses that created the effects of age-related macular degeneration (Czoski-Murray et al. 2009). They ranged from 0.850 in patients with a BCVA of 86 to 100 letters to 0.353 for those with a BCVA of less than 25 letters. Base-case utility values for the worse-seeing eye were calculated from the values for the better-seeing eye, with the assumption that the maximum utility gain in the worse-seeing eye was 0.1. These utilities therefore ranged from 0.850 for a BCVA of 86 to 100 letters, to 0.750 for a BCVA of less than 25 letters.

3.13 Disutilities were defined as adverse events that occurred in more than 5 patients and were suspected to be related to the study drug or ocular injection in RADIANCE (for ranibizumab) or VIP (for vPDT). Disutilities were conjunctival haemorrhage (ranibizumab; 8.5%, vPDT; 0%), increased intraocular pressure (ranibizumab; 4.2%, vPDT; 0%), visual disturbance (ranibizumab; 0%, vPDT; 14.8%), and injection site adverse events (ranibizumab; 0%, vPDT; 9.9%).

3.14 Total costs for treatment were calculated from the unit costs, administration costs, and the cost of a monitoring visit multiplied by the total number of treatment visits and monitoring visits needed. The cost of blindness was calculated as £17,326 in the first year and £17,245 in each year after.

3.15 The manufacturer's base-case deterministic cost-effectiveness analysis results showed that ranibizumab dominated vPDT (that is, it was more effective and less costly), resulting in more QALYs (13.18 compared with 12.75) and lower costs (£9,694 compared with £12,455). The manufacturer similarly presented

base-case probabilistic results which showed that ranibizumab dominated vPDT.

3.16 The manufacturer conducted one-way sensitivity analyses using a net monetary benefit approach (calculated by multiplying the incremental QALYs by £20,000 and then subtracting the incremental costs) because ranibizumab dominated vPDT in the base-case analysis. The sensitivity analysis showed that the model was sensitive to changes in the unit cost of ranibizumab and vPDT, the number of ranibizumab injections in the first and second year, the starting age of the patient group, the discount rate for benefits and the maximum utility gain in the worse-seeing eye. The results of the manufacturer's sensitivity analysis showed that ranibizumab remained dominant up to a unit cost of £783 (range £0 to £3,750) and when up to 12 injections were needed in either year 1 or year 2 (range 0 to 12, with vPDT given 3.4 times per year). Scenario analyses showed that ranibizumab remained dominant when other methods for calculating transition probabilities, such as keeping transition probabilities constant across all visual acuity levels, and other sources of natural history data (Bottoni et al. 2001; Hampton et al. 1983; Hotchkiss et al. 1981; Kojima et al. 2006; Secretan et al. 1997; Tabandeh et al. 1999; Yoshida et al. 2002), were used, and when the maximum gain in utility for the worse-seeing eye is 0.2 or 0.3. The sensitivity analysis showed that there was a 100% probability of ranibizumab being cost effective if the maximum acceptable ICER was £20,000 or £30,000 per QALY gained.

3.17 The manufacturer conducted 3 scenario analyses. The first scenario analysis involved calculating the transition probabilities from patient-level data using 3 different methods. The base-case method used probabilities that were dependent on the current BCVA level and assumed the patient could move from any health state to any other health state in each cycle. The second method used probabilities that were dependent on the patients' current BCVA level for the top 2 health states only, so that a patient could only gain or lose up to 2 health states in each cycle. The third method used a constant probability across all BCVA levels, regardless of the patient's current BCVA level, and assumed that patients could only gain or lose up to 2 health states each cycle. The second scenario analysis involved using different sources for calculating transition probabilities beyond year 1. The third scenario analysis involved using different values for the maximum utility gains for the worse-seeing eye. Ranibizumab continued to dominate vPDT in all of the scenario analyses.

ERG critique of the manufacturer's submission

3.18 The ERG commented that the manufacturer did not include bevacizumab as a comparator even though it was included in the NICE appraisal scope. The ERG noted that the manufacturer stated that bevacizumab is unlicensed for use in the UK for choroidal neovascularisation associated with pathological myopia and that use of bevacizumab is not established practice in the UK for this indication. The ERG stated that although vPDT has a UK marketing authorisation for treatment of choroidal neovascularisation, it is rarely used in clinical practice.

3.19 The ERG found 2 head-to-head trials of bevacizumab and ranibizumab. The ERG noted that the manufacturer had included these 2 trials in their submission, but had only presented data from the ranibizumab arms. The ERG stated that neither of these studies showed statistically significant differences between the ranibizumab and bevacizumab arms in mean change from baseline in BCVA, mean change in central retinal thickness, or in the number of patients gaining 10 or more or 15 or more letters.

3.20 The ERG noted that in RADIANCE the primary end point was at 3 months, and the ERG's clinical specialist thought that 12 months should be the minimum to assess longer-term efficacy of treatment. The ERG stated that in VIP, the statistically significant difference between the vPDT and photodynamic therapy groups in the primary end point at 3 months was no longer seen at 24 months, and that this could also be true for ranibizumab. The ERG believed that it was unlikely that a 3-month follow-up period would provide adequate information about potential adverse effects of the anti-VEGF treatment.

3.21 The ERG noted that geographic atrophy, which is an advanced form of dry age-related macular degeneration in which the rods and cones of the retina degenerate, is a common feature in patients with pathological myopia. It stated that the development of geographic atrophy or extension of pre-existing geographic atrophy has been recognised as a potential side effect in patients with age-related macular degeneration having anti-VEGF treatment. The ERG was concerned that geographic atrophy was not assessed in RADIANCE because it can affect long-term visual outcomes.

3.22 The ERG noted that there was a difference between the patient populations in

the RADIANCE and VIP trials. It was concerned that RADIANCE included a greater proportion of patients with non-subfoveal involvement. The ERG stated that this may affect the comparability of the trials, because patients with subfoveal involvement tend to have a worse prognosis. The ERG suggested that the difference in the number of patients with subfoveal involvement in the 2 trials may overestimate the benefit of ranibizumab.

3.23 The ERG noted that the model accounted for the possibility of the better-seeing eye becoming the worse-seeing eye, and vice versa, as patients change health states. The ERG stated that the method used by the manufacturer may underestimate the net quality-adjusted life year (QALY) gains and costs of blindness that may arise from the more effective treatment.

3.24 The ERG questioned whether an appropriate source had been used for the health-related quality-of-life data in the model. The ERG identified the Brown et al. (1999) study, which measured health-related quality of life directly from patients with impaired vision in at least 1 eye, producing a narrower range of utility values than the study by Czoski-Murray et al. (2009).

3.25 The ERG noted that the number of ranibizumab injections needed in years 2 and 3 may have been underestimated. It described a study by Franqueira et al. (2012) that reported results of a 3-year retrospective study of 40 eyes with choroidal neovascularisation associated with pathological myopia. The mean number of injections in the study was 2.4 in year 2. The ERG suggested that 1.7 injections in year 2 would be a more reasonable assumption than the 1 injection in year 2 assumed in the manufacturer's model.

3.26 The ERG commented that the costs of blindness may have been overestimated. This was driven by the different costs of residential care calculated by the ERG and the manufacturer. The ERG suggested that a cost of blindness of £7,510 in the first year and £7,429 in each subsequent year, based on 2011 Personal and Social Services Research Unit costs and 30% of people being privately funded, was a more reasonable assumption.

3.27 The ERG noted that there were health state probabilities included in the manufacturer's model that were populated by relatively few patients. It was unsure whether the trials provided sufficient patient-level data to be able to

sensibly populate a model with 8 health states and a 64 cell transition probability matrix. Therefore the ERG was concerned about the reliability of the manufacturer's probability modelling.

3.28 The ERG noted some uncertainty about the use of mortality multipliers in the manufacturer's model. It stated that the definition of visual impairment in Christ et al. (2008), which was used by the manufacturer as a source of the multipliers, was ambiguous.

3.29 The ERG noted that EQ-5D data were collected in RADIANCE but were not included in the manufacturer's submission. The ERG requested the EQ-5D data during the clarification process and these were provided by the manufacturer. The ERG commented that the data indicated that changes in the BCVA of the worse-seeing eye had no impact on patients' health-related quality of life.

3.30 The ERG stated that the manufacturer's assumption that treatment benefit would continue indefinitely was optimistic. The ERG performed exploratory analyses that incorporated alternative durations of treatment benefit of 1, 5, 10 and 20 years. This caused the net savings, QALYs and health benefits to decrease compared with those in the manufacturer's model. Ranibizumab remained dominant compared with vPDT even for a 1-year duration of treatment benefit.

3.31 The ERG highlighted minor errors in the manufacturer's model, in the calculation of the quarterly proportion of patients worsening, derived from natural history data. These errors were acknowledged in the manufacturer's clarification responses. The ERG corrected the errors in their exploratory analysis of the manufacturer's model.

3.32 The ERG conducted an exploratory analysis which involved the following modifications to the manufacturer's model:

- Brown et al. (1999) as a source of utility values in addition to Czoski-Murray et al. (2009)
- changed the dose of ranibizumab in year 2 from 1 to 1.7
- changed the costs of blindness from £17,326 in year 1 and £17,245 in each subsequent year to £7,510 and £7,429 respectively

- changed the mortality multiplier for blindness (BCVA of 35 letters or less) from 1.54 to 1.48
- corrected the calculation of the quarterly proportion of patients worsening.

3.33 In the ERG's exploratory analysis, ranibizumab dominated vPDT. The total cost of ranibizumab was £10,055 and of vPDT was £12,529 (incremental cost -£2,474). Using utility values from Brown et al. (1999), the total QALYs were 14.514 for ranibizumab and 14.170 for vPDT (incremental QALYs 0.344). Using utility values from Czoski-Murray et al. (2009), the total QALYs were 13.105 for ranibizumab and 12.838 for vPDT (incremental QALYs 0.266).

3.34 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ranibizumab, having considered evidence on the nature of choroidal neovascularisation associated with pathological myopia and the value placed on the benefits of ranibizumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the current management of visual impairment caused by choroidal neovascularisation associated with pathological myopia. The clinical specialist stated that verteporfin photodynamic therapy (vPDT) has been used since 2005, and before this, no treatment was available. It heard from the clinical specialist that vPDT is not effective in most patients. The Committee discussed the use of vPDT and noted that its use is now diminishing because of the anti-vascular endothelial growth factor (anti-VEGF) treatments, such as ranibizumab and bevacizumab. It noted that bevacizumab is used outside of its marketing authorisation and has to be formulated under a 'specials' licence. It concluded that a licensed alternative treatment to vPDT for visual impairment caused by choroidal neovascularisation with pathological myopia would be welcomed by clinicians and patients.

4.3 The Committee considered the impact of visual impairment caused by choroidal neovascularisation with pathological myopia on the everyday life of patients. The Committee understood from the patient expert that the condition affects a younger group of patients compared with other eye conditions and so affects the ability to work, drive, and care for children or other dependents. It heard from the patient expert that loss of vision has a significant effect on the independence of people with the condition and can lead to depression. The Committee agreed that loss of vision caused by choroidal neovascularisation seriously impairs quality of life.

4.4 The Committee considered the comparators for this appraisal. The Committee expressed concern that the manufacturer had not included bevacizumab as a comparator. It noted that the scope listed vPDT and bevacizumab as comparators, although it was aware that bevacizumab does not have a marketing

authorisation for treating visual impairment caused by choroidal neovascularisation associated with pathological myopia. The Committee noted that appropriate comparators should be established practice in England. This is not intended to be restrictive, but to emphasise the need for comparison with all relevant comparators; any drug in routine use or considered to be best practice should be considered a potential comparator. The Committee heard from the manufacturer that it considered that bevacizumab was not an appropriate comparator because its use in the NHS is not routine or best practice. The Committee heard from the patient expert and clinical specialist that bevacizumab is used in some patients, but only after some delay to agreement for funding. The Committee noted that the written statements submitted by the Royal College of Ophthalmologists, the Royal College of Pathologists, and the Macular Society suggested considerable use of bevacizumab in the NHS for this indication. The Committee also noted that there are 2 trials (see section 4.7) that compared ranibizumab with bevacizumab in choroidal neovascularisation associated with pathological myopia. However, both of these had a small number of patients. The Committee heard from the clinical specialist that there are some residual safety concerns with the use of bevacizumab, but considered these to be minor. It was aware of the conclusions of NICE's Decision Support Unit report on bevacizumab in eye conditions, which stated that adverse event rates were low in all bevacizumab and comparator groups. However, the Committee also noted that the use of bevacizumab in the eye had not been assessed by the regulatory agencies. It agreed that bevacizumab was a legitimate potential comparator with respect to its use in the NHS. The Committee concluded that because the available evidence for bevacizumab in this indication was limited to 2 small trials, there was currently insufficient evidence to allow bevacizumab to be included with confidence in a clinical and cost-effectiveness analysis, but it did not rule out the possibility of future evidence providing that confidence.

Clinical effectiveness

4.5 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of ranibizumab. The Committee acknowledged that the evidence was primarily from RADIANCE, which compared ranibizumab with vPDT, and was complemented by evidence from 2 other randomised trials that compared ranibizumab with bevacizumab, even though the manufacturer did not

present the data for the bevacizumab arms of these trials in its submission. The Committee noted that ranibizumab was associated with a greater improvement than vPDT in best corrected visual acuity (BCVA) between baseline and months 1 to 3. The Committee concluded that ranibizumab is a clinically effective treatment option for visual impairment caused by choroidal neovascularisation associated with pathological myopia.

4.6 The Committee discussed the primary end point of RADIANCE, which was the mean average change in BCVA between baseline and months 1 to 3. The Committee heard from the clinical specialist that 3 months was not a long time period to assess the longer-term benefits of ranibizumab. However, the other studies of ranibizumab and the long-term follow-up of its use in other eye conditions suggest a sustained effect. The Committee concluded that, because the clinical effectiveness of ranibizumab was not compared with vPDT after 3 months in RADIANCE, there is uncertainty about the long-term efficacy of ranibizumab for visual impairment caused by choroidal neovascularisation associated with pathological myopia.

4.7 The Committee considered the 2 trials presented in the manufacturer's submission that compared the use of ranibizumab and bevacizumab in choroidal neovascularisation associated with pathological myopia. The Committee noted that this was in line with the scope, in which bevacizumab was included as a comparator. The Committee heard from the clinical specialist that the 2 trials, although small, showed ranibizumab and bevacizumab to be equally effective. It was aware that the manufacturer presented only the results from the ranibizumab arms of these trials in their submission and that the Evidence Review Group (ERG) had presented the results from the bevacizumab arms in their report (see section 3.19). The Committee concluded that ranibizumab is likely to be as clinically effective as bevacizumab in patients with visual impairment caused by choroidal neovascularisation associated with pathological myopia.

4.8 The Committee considered the trial evidence for adverse events associated with ranibizumab. The Committee discussed whether geographic atrophy was under-reported because markers of this effect were not measured in RADIANCE. The clinical specialist argued that there was no particular reason to expect geographic atrophy as a side effect of ranibizumab treatment. The Committee was aware that the main adverse events listed in the summary of product

characteristics were eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, and vitreous detachment. The Committee agreed that the evidence suggested manageable adverse events with ranibizumab, and concluded that ranibizumab was safe and well tolerated in patients with visual impairment caused by choroidal neovascularisation associated with pathological myopia.

Cost effectiveness

4.9 The Committee considered the cost-effectiveness evidence presented in the manufacturer's submission, including the base-case results, the sensitivity and scenario analyses and the ERG's critique of the manufacturer's evidence. It noted that the manufacturer had not included bevacizumab as a comparator in its economic model. The Committee understood that the manufacturer's base-case analysis showed that ranibizumab dominated vPDT (that is, it was more effective and less costly), resulting in more quality-adjusted life years (QALYs; 13.18 compared with 12.75) and lower costs (£9,694 compared with £12,455).

4.10 The Committee accepted the model structure, but was concerned by some of the uncertainties about the assumptions used by the manufacturer. In particular, the Committee queried:

- the larger proportion of patients with subfoveal involvement at baseline in the VIP trial than in the RADIANCE trial
- the assumption of an indefinite duration of benefit of ranibizumab treatment
- the low number of ranibizumab injections needed in year 2 of treatment
- the high estimated costs of blindness
- the low estimated costs of ranibizumab and vPDT administration
- the lack of clarity about the source of the mortality multipliers used in the model
- the underestimated changes in net QALY gains and the cost of blindness resulting from the method used to account for the possibility of the treated eye changing from being the better-seeing eye to being the worse-seeing

eye

- the use of Czoski-Murray et al. (2009) as a source of utility values, rather than the EQ-5D data collected in RADIANCE.

The Committee considered each of these issues in turn, as detailed below.

4.11 The Committee considered the clinical-effectiveness data that were used in the manufacturer's economic model. It recognised that the clinical-effectiveness data for ranibizumab were derived from RADIANCE and the data for vPDT after 3 months were derived from the VIP trial. The Committee noted that there was a larger proportion of patients at baseline with subfoveal involvement in VIP compared with RADIANCE and it was concerned that this might have had an impact on the model. The Committee heard from the clinical specialist that an imbalance would only be clinically relevant if it was in the number of patients with extra-foveal involvement, and that this did not appear to be the case. The Committee concluded that the imbalance in the number of patients with subfoveal involvement in RADIANCE and VIP was unlikely to have a large impact on the manufacturer's model.

4.12 The Committee discussed the manufacturer's assumption that the average BCVA gain at the end of year 1 would continue indefinitely. The Committee heard from the clinical specialist that data collected at the 3 time points in RADIANCE showed that the benefit of ranibizumab was maintained for at least 12 months. The Committee noted that the ERG's sensitivity analyses included different durations of treatment benefit, and that ranibizumab dominated vPDT even when the duration of treatment benefit was reduced to 1 year. The Committee concluded that the duration of treatment benefit was likely to be less than the manufacturer's assumption of an indefinite duration, and that ranibizumab dominated vPDT when the duration of effect was reduced.

4.13 The Committee discussed the manufacturer's assumption about the number of ranibizumab injections that people would receive in clinical practice. The Committee heard from the clinical specialist that, on average, patients only need ranibizumab injections in the first 3 months of their first year of treatment. The clinical specialist also stated that patients in the REPAIR trial had well-preserved eyesight after 18 months and did not need further treatment. The Committee

noted that the ERG had increased the number of ranibizumab injections in the second year of ranibizumab treatment from 1.0 to 1.7 in its exploratory analysis. Based on experience with patients using ranibizumab, the clinical specialist felt that this number could be too high. The Committee concluded that the number of injections included in the manufacturer's base case could be an underestimate and that even if the number of injections was increased, ranibizumab would continue to dominate vPDT.

4.14 The Committee considered the costs of blindness used in the manufacturer's economic model. It noted that the ERG presented lower costs of blindness in their report. The Committee heard from the ERG that the difference in the costs of blindness was mainly related to the way the costs for private residential care were calculated. The Committee noted that the manufacturer's sensitivity analysis showed that the model was not sensitive to changes in the costs of blindness. The Committee concluded that the ERG's assumptions about the costs of blindness were likely to be more realistic than those used by the manufacturer, and that if the ERG's assumptions had been used, ranibizumab would continue to dominate vPDT.

4.15 The Committee discussed the administration costs of ranibizumab used in the manufacturer's economic model. It noted that these costs were likely to be an underestimate of the true costs incurred in the NHS. The Committee recognised that the manufacturer's sensitivity analysis showed that the model was not sensitive to changes in the administration costs. The Committee concluded that although some uncertainty remained about the NHS costs involved in the administration of ranibizumab, the uncertainty was not great enough to affect the dominance of ranibizumab over vPDT.

4.16 The Committee discussed the mortality multipliers that the manufacturer had used in its economic model. It heard from the ERG that the source of some of the mortality multipliers was unclear. The ERG also stated that changing the mortality multipliers to alternative values had little impact on the cost savings or QALYs for ranibizumab. The Committee concluded that the manufacturer's rationale for some of the mortality multipliers used in their model was unclear, and that any changes to them were unlikely to change the dominance of ranibizumab over vPDT.

4.17 The Committee considered the method used in the manufacturer's economic model to account for the possibility of the treated eye changing from being the better-seeing eye to being the worse-seeing eye as patients changed health states. The Committee understood that the way the manufacturer had modelled this seemed to underestimate the changes in net QALY gains and costs of blindness that may arise from the more effective treatment. The Committee noted that it was not possible to quantify the size of the effect on the base-case analysis. The Committee concluded that the modelling of the treated eye changing from being the better-seeing eye to being the worse-seeing eye as patients changed health states may have had an impact on the base-case analysis, which showed that ranibizumab dominated vPDT, although the level of impact remained unclear.

4.18 The Committee discussed the utility values used in the manufacturer's economic model. The Committee noted that the source of utility data used in the base-case analysis (Czoski-Murray et al. 2009) was used in NICE's technology appraisal guidance on ranibizumab for the treatment of diabetic macular oedema, ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and aflibercept solution for injection for treating wet age-related macular degeneration. It was aware that EQ-5D data were also collected in RADIANCE, but these data were not used in the model. The Committee heard from the manufacturer that the EQ-5D data from RADIANCE were not included because the EQ-5D is widely recognised as not being sensitive in studies of eye conditions. The Committee heard from the ERG that using the EQ-5D data collected in RADIANCE did not have a large effect on the model, although the effect for the worse-seeing eye was not clear. The Committee concluded that using the EQ-5D data from RADIANCE was unlikely to change the overall results of the base-case analysis and that ranibizumab would continue to dominate vPDT.

4.19 The Committee noted that the manufacturer's model had not included bevacizumab as a comparator and so the base-case analysis was limited to a comparison of ranibizumab with vPDT. However, because the available evidence for bevacizumab in this indication was limited to 2 small trials (see section 4.4), there was currently insufficient evidence to allow bevacizumab to be included with confidence in a clinical and cost-effectiveness analysis. The Committee considered the uncertainties in the manufacturer's model and noted that they did

not have an effect on the overall results of the base-case analysis, which showed that ranibizumab dominated vPDT. The Committee concluded that ranibizumab was a cost-effective use of NHS resources for treating people with visual impairment caused by choroidal neovascularisation associated with pathological myopia when vPDT was the comparator.

4.20 The Committee discussed how innovative ranibizumab is in its potential to make a significant and substantial impact on health-related benefits. It agreed that anti-VEGF treatments, such as ranibizumab, were a substantial improvement over previous treatments, and considered that this improvement applied to the class of drugs, including bevacizumab. It stated that the innovation was a step forward in providing health-related patient benefits, not the act of licensing. In addition there were no substantial benefits of ranibizumab over its comparators that were not already captured in the QALY estimation in the modelling. The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way. No equality issues were raised during the appraisal process or at the Committee meeting. Therefore, the Committee concluded that no alterations or additions to its recommendations were needed.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has choroidal neovascularisation associated with pathological myopia and the healthcare professional responsible for their care thinks that ranibizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Dr Maria Dyban
General Practitioner, Kings Road Surgery, Cardiff

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Emily Lam
Lay Member

Dr Allyson Lipp
Principal Lecturer, University of South Wales

Dr Claire McKenna
Research Fellow in Health Economics, University of York

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine
Formerly Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Dr Paul Miller
Director, Payer Evidence, AstraZeneca UK Ltd

Dr Anna O'Neill
Deputy Head of Nursing and Healthcare School / Senior Clinical University Teacher, University of Glasgow

Alan Rigby
Academic Reader, University of Hull

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ella Fields
Technical Lead

Sally Doss
Technical Adviser

Lori Farrar
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen HTA Group:

- Cummins E, Fielding S, Cruickshank M et al. Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia, August 2013

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups gave their expert views on ranibizumab by providing a written statement to the Committee. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- Novartis

Professional or specialist and patient or carer groups:

- Fight for Sight
- Macular Society
- Royal National Institute of Blind People (RNIB)
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal of Pathologists

Other consultees:

- Department of Health

- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- Cochrane Eyes and Vision Group
- MRC Clinical Trials Unit
- Aberdeen HTA Group
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on ranibizumab for treating choroidal neovascularisation associated with pathological myopia by providing oral or written evidence to the Committee.

- Clare Bailey, Consultant Ophthalmologist, nominated by The Royal College of Ophthalmologists – clinical specialist (Clare was unable to attend the meeting but provided a clinical statement)
- Sobha Sivaprasad, Consultant Ophthalmologist, nominated by the Royal National Institute of Blind People – clinical specialist
- Clara Eaglen, Policy and Campaigns manager, nominated by the Royal National Institute of Blind People – patient expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis

Update information

May 2024: The wording of the recommendation describing the patient access scheme (see section 1.1), and in sections 2.2 and 2.4, has been updated to include procurement information about ranibizumab biosimilars.

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