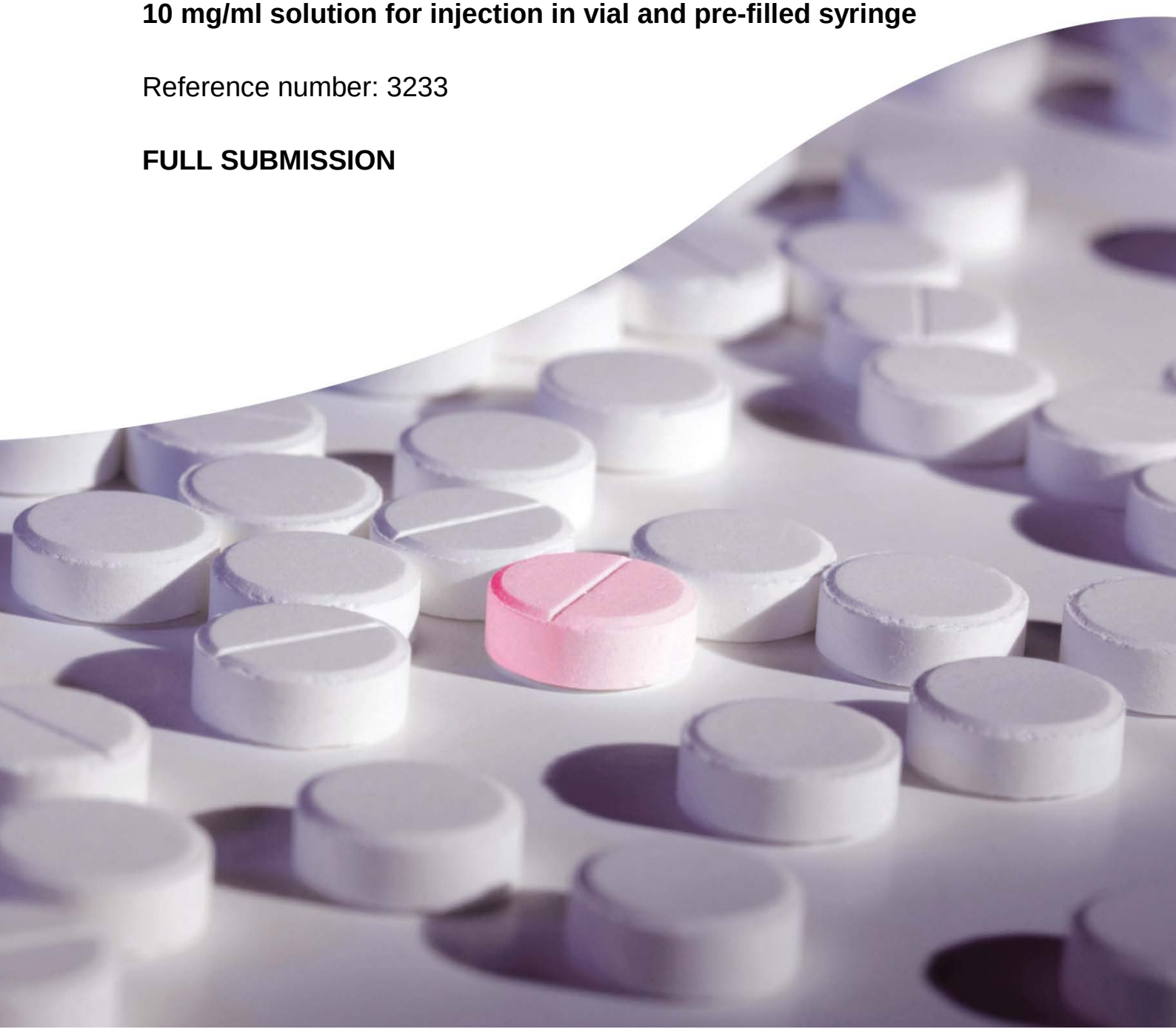
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ranibizumab (Lucentis®)
10 mg/ml solution for injection in vial and pre-filled syringe

Reference number: 3233

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Ranibizumab (Lucentis®) 10 mg/ml solution for injection in vial and pre-filled syringe

1.0 SUMMARY

Product information	This is an assessment of a licence extension for ranibizumab (Lucentis®) for the treatment of visual impairment in adults due to choroidal neovascularisation (CNV) not due to pathologic myopia or neovascular (wet) age-related macular degeneration.
Current clinical practice	There are currently no other licensed medicines available for the treatment of CNV due to uncommon causes and the company has used best supportive care as the comparator. Welsh clinical expert opinion suggests that off-label or unlicensed anti-vascular endothelial growth factor agents are currently used in clinical practice. All ranibizumab indications other than rare CNV are covered by National Institute for Health and Care Excellence technology appraisal guidance.
Clinical effectiveness evidence	Evidence from one pivotal randomised controlled trial showed that at Month 2, ranibizumab was significantly superior in inducing and sustaining an improvement in visual acuity in adults with CNV due to uncommon causes. Ranibizumab also improved health-related quality of life. The overall safety profile of ranibizumab is well characterised and no new safety findings were detected.
Cost effectiveness evidence	A simple Department of Health Patient Access Scheme is included in the submission. The company used a cost-utility analysis comparing ranibizumab to best supportive care. Results of the base case analysis show that ranibizumab is less costly and more effective than best supportive care. The incremental cost-effectiveness ratio (ICER) shows ranibizumab to be [commercial in confidence information removed]. Scenario analyses describe ICERs ranging from [commercial in confidence information removed].
Estimated budget impact	The budget impact assumes that 244 patients in Wales will be eligible for treatment. The company estimates that 35% will be treated in Year 1 (i.e. 80 patients) and that uptake will increase by 10% each year until reaching 65% in Year 4 (i.e. 149 patients). Ranibizumab treatment is predicted to cost [commercial in confidence figure removed] in Year 1. Due to an assumed 10% increase in uptake and a decrease in the treatment costs after the first year, costs amount to [commercial in confidence figures removed]. The total cumulative budget impact (including administration costs) for the introduction of ranibizumab into NHS Wales is estimated to be [commercial in confidence figures removed].

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd and an evidence search conducted by AWTTC on 11 January 2018, 12 January 2018 and 12 March 2018.

2.0 DECISION CONTEXT

2.1 The condition and current treatment

Choroidal neovascularisation (CNV), characterised by the abnormal growth of new blood vessels below the sub-retinal pigment epithelium or into the sub-retinal space[1], is a major cause of vision loss[2,3]. Without effective treatment, people might experience further deterioration and progression of the CNV lesion, leading to irreversible and rapid vision loss[4], a worsening quality of life[3] and an increased mortality risk[5]. Although most commonly associated with neovascular (wet) age-related macular degeneration (nAMD) and pathologic myopia, other inherited and acquired conditions can also lead to CNV, including angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic CNV, and other miscellaneous diseases[1] (see Glossary). The applicant company therefore refers to CNV due to uncommon causes as rare CNV[6], which usually occurs in adults younger than 50 years old[7].

The company submission highlights current non-pharmacological treatment options for CNV, including surgical approaches, laser photocoagulation, photodynamic therapy with or without verteporfin, transpupillary thermotherapy, and radiation therapy, but states the efficacy of these are limited[6]. AWTTC-sought clinical experts have highlighted that in clinical practice, some people with rare CNV are treated with off-label medicines (such as aflibercept, another anti-vascular endothelial growth factor [VEGF] inhibitor agent).

2.2 The appraised medicine

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human VEGF-A[8,9]; by blocking the action of VEGF-A, ranibizumab decreases vascular permeability and prevents abnormal blood vessels developing, thereby limiting visual loss and improving vision[1,10]. The recommended dose of ranibizumab is 0.5 mg given as a single intravitreal injection[8,9].

This assessment considers ranibizumab for the treatment of visual impairment in adults due to rare CNV[6]. In 2013, ranibizumab was approved for CNV due to pathologic myopia and in 2016, this indication was updated to cover the treatment of visual impairment due to CNV[8,9]. Ranibizumab is also licensed for the treatment of nAMD, visual impairment due to diabetic macular oedema, and visual impairment due to macular oedema secondary to branch or central retinal vein occlusion[8,9]. All ranibizumab indications other than rare CNV are covered by National Institute for Health and Care Excellence (NICE) technology appraisal guidance[10-13].

2.3 Comparators

The comparator included in the company submission is best supportive care (BSC), defined as no treatment or 'watch and wait'[6].

2.4 Guidance and related advice

- NICE technology appraisal (TA) guidance 486 (TA486). Aflibercept for treating choroidal neovascularisation (2017)[14].
- NICE TA298. Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (2013)[10].
- NICE TA155. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (2012)[11].

There are no available guidelines that are specific to rare CNV. NICE guidance applies in NHS Wales for all other ranibizumab indications[10-13]. It should be noted that the NICE Horizon Scanning, Topic Selection and Scoping team concluded that the licence extension for rare CNV did not warrant a further submission in the foreseeable future.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The applicant company provided evidence from the pivotal MINERVA study, which compared the efficacy and safety of ranibizumab with sham (empty vial) treatment in adult patients with visual impairment due to rare CNV[6]. MINERVA also included a non-randomised, open-label group of five adolescent patients (age 12 to < 18 years)[4], but this population is not relevant to the submission and will not be discussed further.

The applicant company conducted a systematic review, with search dates between 1974 and 24 May 2017[6]. The aim of this review was to collate evidence on the comparative clinical efficacy and safety of interventions potentially utilised for the treatment of visual impairment due to rare CNV. However, an indirect comparison or mixed treatment comparison was not considered feasible based on the lack of evidence identified (outside of the MINERVA study)[6].

3.1 MINERVA study

MINERVA was a phase III, 12-month, double-masked, sham-controlled, head-to-head, prospective, multicentre study in 178 patients, who were randomised 2:1 to receive either ranibizumab 0.5 mg intravitreal injections or sham[4]. The randomisation was stratified by type of underlying categories of ocular pathophysiologic mechanisms (angioid streaks versus others)[4].

All patients were aged ≥ 18 years, with a confirmed diagnosis of at least one CNV lesion in the study eye with involvement of the central macular area, and best-corrected visual acuity between ≥ 24 and ≤ 83 Early Treatment Diabetic Retinopathy Study letters[4] (see Glossary).

Patients started the study treatment with 0.5 mg intravitreal injection of ranibizumab or sham at baseline[4]. This was followed by an individualised treatment regimen based on evidence of disease activity from Month 1. Use of rescue medication, either thermal laser photocoagulation or verteporfin photodynamic therapy, was allowed at Month 1 at the investigator's discretion and if the patient had a visual acuity loss of more than five letters due to disease activity from baseline to Month 1; these patients continued in the study[4].

At Month 2, all except seven patients randomised into the sham arm were switched to as-needed treatment with open-label ranibizumab[4]. At Month 12, the mean number of ranibizumab injections was 5.8 of a possible 12 injections in the ranibizumab group and 5.4 of a possible 10 injections in the group who had received sham and then ranibizumab. All patients were monitored monthly for disease activity, for consideration of retreatment. The last possible treatment was administered at Month 11 and the last assessment was performed at Month 12. In total, 167 patients (93.8%) completed the study[4].

The primary efficacy endpoint was the change in best-corrected visual acuity from baseline to the second month[4]. Statistical superiority of ranibizumab compared to sham was shown (95% confidence interval, one-sided p-value < 0.001), with a between-treatment difference (treatment effect) of 9.94 letters (deemed clinically relevant by the Committee for Medicinal Products for Human Use [CHMP]). The secondary endpoints support the superiority of ranibizumab compared to sham treatment (see Table 1)[4].

Table 1. Endpoints from MINERVA[1,4]

MINERVA	Ranibizumab N = 119	Sham N = 59	Treatment effect, p-value < 0.001*
Primary endpoint			
LS mean change in BCVA at Month 2, letters (95% CI)†	9.5 (7.6 to 11.4)	−0.4 (−2.8 to 1.9)	9.94 (6.97 to 12.91)
Secondary endpoints			
Mean change in BCVA Month 12, letters (95% CI)§	11.0 (8.5 to 13.6)	9.3 (5.7 to 12.9)¶	NR
Patients with ≥ 15 BCVA letter gain at Month 2, % (95% CI)§	31.4 (23.13 to 40.54)	12.3 (5.08 to 23.68)	NR
Mean change in CSFT at Month 2, micrometres (95% CI)**	−77.0 (−94.5 to −59.5)	9.8 (−25.6 to 45.2)	−86.8 (−126.1 to −47.5)
*Analysed using MMRM (see Glossary) †n ranibizumab = 118; n sham = 57 §n ranibizumab = 119; n sham = 59 ¶Data are for sham with ranibizumab rather than sham alone **n ranibizumab = 115; n sham = 57			
BCVA: best-corrected visual acuity; CI: confidence interval; CSFT: central subfield foveal thickness; LS: least squares; MMRM: mixed-effect model repeated measure; N: total number of patients; n: number of patients with data available; NR: not reported			

Subgroup analyses in adults were carried out on the primary efficacy endpoint for the following groups: baseline best-corrected visual acuity (≤ 60 and ≥ 60 letters), baseline CNV aetiology, and baseline age (≤ 60 and > 60 years)[4]. A consistent positive treatment effect in favour of ranibizumab was observed throughout the analyses. The magnitude of the treatment effect (least squares adjusted means) across the five different CNV aetiology subgroups ranged from a gain of 5.0 to 14.6 letters. Patients with a lower baseline best-corrected visual acuity score, as well as patients ≤ 60 years, had a larger treatment effect with ranibizumab at Month 2 (see Table 2)[4].

Table 2. Change in best-corrected visual acuity from baseline to Month 2 in each of the specified subgroups in the study eye from the MINERVA study (full analysis set observed)[4]

	n (%)	Ranibizumab (letters)	Sham (letters)	Treatment effect, letters (95% CI)	p-value*
Age of patient					< 0.001
≤ 60 years	105 (60.0)	13.0	−0.2	13.17 (9.17 to 17.17)	
> 60 years	70 (40.0)	4.2	−0.8	5.04 (0.78 to 9.30)	
Baseline BCVA					0.271
≤ 60 letters	76 (43.4)	12.9	0.8	12.17 (6.95 to 17.39)	
> 60 letters	99 (56.6)	6.9	−1.2	8.11 (4.56 to 11.67)	
Baseline CNV aetiology					0.648
Idiopathic	62 (35.4)	12.5	1.1	11.44 (6.76 to 16.12)	
Angioid streaks	27 (15.4)	11.0	−3.5	14.57 (6.13 to 23.01)	
Post-inflammatory retinochoroidopathy	27 (15.4)	7.0	0.4	6.53 (−2.34 to 15.40)	
CSC	23 (13.1)	6.6	1.6	5.02 (−3.12 to 13.16)	
Miscellaneous†	36 (20.6)	7.5	−3.0	10.57 (−0.34 to 21.47)	

*p-value is the interaction between the subgroup and treatment; p-values > 0.05 are consistent with an equal treatment effect across the subgroup categories
†Aetiologies that did not fit into the other CNV aetiology subgroups and were insufficiently frequent to form a separate subgroup (see Glossary for Miscellaneous definition)

BCVA: Best-corrected visual acuity; CI: confidence interval; CNV: choroidal neovascularisation; CSC: central serous chorioretinopathy; n: number of patients

Health-related quality of life was measured using the National Eye Institute Visual Function Questionnaire-25 ([NEI-VFQ-25]; see Glossary)[1]. At Month 2, mean change improvement (95% confidence interval) in the NEI-VFQ-25 composite score from baseline was 2.7 (1.24 to 4.26) in the ranibizumab arm versus −0.1 (−3.41 to 3.13) in the sham arm. Further improvements in the composite score with ranibizumab were observed at Month 6 (5.4 [3.51 to 7.31]) and at Month 12 (4.6 [2.47 to 6.70])[1].

3.3 Safety

The safety population in MINERVA comprised 119 patients receiving ranibizumab and 59 patients receiving sham from baseline to the second month[4]. Of the latter, 52 patients then received at least one ranibizumab injection in the study eye during the open-label phase of the study[4].

CHMP deemed that no new safety concerns were detected and that the safety profile of ranibizumab in people with CNV appeared to be broadly in line with that reported in previously approved indications[1]. No serious adverse events were suspected to be related to ranibizumab or the ocular injection[4]. There were no reports of deaths or endophthalmitis in the study[4]. Generally, the adverse events reported in the MINERVA study were few and mild in severity[1].

The Summary of Product Characteristics includes a warning concerning risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for nAMD[8,9]. CHMP concludes that the risk factor applicable to nAMD might also be valid to other CNV indications and that the warning should be updated accordingly[1]. Furthermore, in light of the low prevalence of some of the conditions in rare CNV, CHMP is of the view that the safety profile of ranibizumab should continue to be monitored in future periodic safety update reports[1].

3.4 AWTTC critique

- There is no established standard of care for many of the rare conditions associated with CNV. Ranibizumab is the only licensed treatment for visual impairment due to rare CNV in the UK[4].
- CHMP accepts that there is already substantial experience gained with ranibizumab in people with CNV (although mainly from people with nAMD), and that VEGF plays a key role in the pathophysiology of CNV[1].
- In their submission, the applicant company uses BSC as the comparator; the company states that there is no licensed active comparator in current Welsh practice[6]. Clinical expert opinion sought by AWTTC indicates that other anti-VEGF agents by intravitreal injection may be given, although this use would be off-label.
- The primary endpoint in the MINERVA study was evaluated at Month 2. Although a longer double-blind, controlled study would be desirable, CHMP recognises that previous studies showed the onset of action of ranibizumab to be rapid, and data for previously approved CNV-associated conditions did not suggest that the effect would be of limited durability[1]. In addition to the MINERVA study, CHMP was provided with supportive safety data from an observational study (PIXEL) in patients with ocular complications secondary to a pseudoxanthoma elasticum (with CNV being one of them) on treatment for up to four years[1].
- The majority of patients were on open-label ranibizumab from Month 2 to Month 12 in the MINERVA study; it is therefore not possible to make a meaningful comparison between the two groups after two months due to the cross-over from sham to active treatment[1].
- After Month 2, the gain in best-corrected visual acuity essentially plateaued in the ranibizumab treatment group, and was maintained up to the end of the study at 12 months[1].
- The MINERVA study demonstrated that ranibizumab was effective in treating CNV associated with various aetiologies, with subgroup analyses demonstrating that ranibizumab had a clinically meaningful change in vision in younger adults (≤ 60 years)[4]. There were no new safety findings[4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) comparing ranibizumab 0.5 mg intravitreal injection to BSC in adult patients with visual impairment due to CNV associated with causes other than nAMD or pathologic myopia[6].

The CUA takes the form of a patient-level simulation model, comprising of one-month cycles over a lifetime horizon of 50 years. Costs and outcomes are discounted at an annual rate of 3.5% and the model adopts an NHS and Personal Social Services perspective. The submission incorporates a simple Department of Health Patient Access Scheme discount for ranibizumab.

The model samples the patient's baseline characteristics individually based on the patient cohort of the MINERVA study and determines whether the patients are to receive

unilateral or bilateral treatment along the pathway[4]. The probability of having bilateral disease at baseline and treatment discontinuation were taken from the MINERVA study[4]. The probability of developing bilateral disease was sourced from the literature[3], whilst disease re-occurrence was informed by company-sought expert opinion[15]. Patients might be as young as 18 years at the start of the model, with a mean age of 54.6 years, and approximately 10% of simulated patients still alive at the end of the modelled time horizon. The model simulates treatment with ranibizumab and BSC independently and follows the patient through a maximum of 600 cycles. The progression of each eye is modelled individually, with a combination of both eyes' best-corrected visual acuity offering health-related quality of life values.

Clinical effectiveness values for ranibizumab are derived from regression models based on the MINERVA study data, which include a 12-month follow-up for the ranibizumab group and two-month follow-up for the sham injection group. The same data are then applied to the BSC group for two years until transitioning to natural history data[16-19]. Continued effectiveness of ranibizumab is assumed constant throughout the treatment period. Ranibizumab patients progress through the clinical effectiveness pathway for a maximum of four years of treatment and then follow the natural history progression. BSC patients follow the MINERVA data for 12 months and then follow the visual acuity progression of natural history. Disease recurrence might occur at any time throughout the model process at an annual rate of 6%, based on company-sought expert opinion[6]. Mortality is based on statistics from the Office for National Statistics survival data and includes a modifier attached to the degree of vision loss. Higher levels of visual impairment are associated with increased mortality through a range of health pathways[5]. The only adverse event included is conjunctival haemorrhage at a monthly probability of 0.49% in the ranibizumab arm[4]. No adverse events were assumed for the BSC arm. Costs and health outcomes of adverse events were both estimated to be zero, as the condition is assumed to require no treatment and to settle down by itself within one or two weeks[20].

The model includes the costs of ranibizumab, administration, monitoring and blindness. The unit cost of ranibizumab, with a single prefilled syringe, is [commercial in confidence figure removed], including the current confidential simple Department of Health Patient Access Scheme discount. Each individual receives initial treatment followed by a monthly probability of receiving treatment throughout the first year. On average, each patient receives 5.8 treatments over the first 12 month period. After 12 months, the probability of treatment decreases to an average of 1.7 treatments per year. In addition to the medicine cost of ranibizumab, patients incur £101.72 per procedure for treatment administration and £55.14 for optical coherence tomography[21]. BSC was assumed to not incur direct costs aside from monitoring. Monitoring costs consist of an ophthalmologist consultation visit and the cost of an optical coherence tomography, totalling £172.17[21]. The ranibizumab patients incurred 8.5 monitoring visits in Year 1 and four monitoring visits in subsequent years, and the BSC group received four monitoring visits each year throughout the model pathway. Cost of blindness is based on a weighted cost approach and includes an initial cost of £144.96 for being registered blind[22] and a yearly mean cost of £6,947.03[22,23], both adjusted to 2016 British Pound rates.

Health-related quality of life is estimated through the use of regression analysis of real-world data[24,25]. The visual acuity to health-related quality of life data is collected through a time trade-off exercise, which develops EQ-5D scores relative to visual impairment levels simulated via the use of contact lenses. Analysis was utilised within the economic model; this estimated utlity as a function of the logarithm of the minimal angle of resolution for visual acuity (logMAR VA) for both eyes with the inclusion of an interaction term[25]. The regression model results in a valuation of health-related quality of life, which decreases with lower levels of visual acuity. The health-related quality of life valuation of visual acuity is applied in the same way for both arms of the model.

One-way deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. The range of inputs varied within the sensitivity analysis and include alterations to the discount rate, the utility levels attached to visual acuity, the clinical effectiveness of ranibizumab and the structure of monitoring. The impact of structural uncertainty was investigated using a range of scenario analyses. The scenarios focussed on variations which would result in the most substantial impact on the cost-utility of ranibizumab.

4.1.2 Results

The results of the base case analysis are detailed in Table 3. When compared with BSC, ranibizumab is associated with an increase of 1.06 quality-adjusted life-years (QALYs) and an incremental decrease in costs of [commercial in confidence figure removed]. The base case results for ranibizumab are therefore considered [commercial in confidence information removed] when compared to BSC. Furthermore, the model estimates an extension of life expectancy of 0.25 years.

Table 3. Results of the base case analysis

	Ranibizumab	Best supportive care	Difference
Cost-utility analysis			
Medicine costs	¶¶	¶¶	¶¶
Administration costs	£1,373	£0	£1,373
Monitoring	£5,060	£4,153	£907
Blindness	£11,272	£20,651	–£9,379
Adverse events	£0	£0	£0
Total cost per patient	¶¶	¶¶	¶¶
Total life-years	28.09	27.84	0.25
Total QALYs per patient	10.59	9.53	1.06
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence data removed.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Table 4 summarises the results of the deterministic scenario analyses. The clinical and QALY outcomes throughout these scenarios remain positive for ranibizumab. The cost impact of ranibizumab shifts from cost saving to marginally higher costs under certain conditions, but ranibizumab remains cost-effective at the £20,000 per QALY gained threshold. The different scenarios offered in this sensitivity analysis range from [commercial in confidence information removed]. The highest ICER offered by the deterministic sensitivity analysis occurs under the condition of higher use of ranibizumab in the second year (5.8 per year for two years).

Table 4. Results of scenario analyses

Scenarios	ICER/Cost difference	Plausibility
Scenario 1: Limit the maximum treatment duration to 1 year	Cost difference: ¶¶ QALY difference: 0.54 ICER: ¶¶	Plausible – dependent upon clinical appropriateness
Scenario 2: Ranibizumab treatment extended to 2 years (5.8 per year)	Cost difference: ¶¶ QALY difference: 1.02 ICER: ¶¶	A plausible approach given the variability in usage levels and recommendation guidelines
Scenario 3: Best corrected visual acuity for 1 year (from MINERVA study) then natural history	Cost difference: ¶¶ QALY difference: 1.25 ¶¶	A plausible alternative approach to valuing HRQoL; this includes a greater level of natural history data and less trial data
Scenario 4: Czoski-Murray[24] model of QoL from NICE AMD guidelines used	Cost difference: ¶¶ QALY difference: 1.42 ¶¶	Plausible alternative valuation of QoL, which focuses only on the BSE score
Scenario 5: 12 monitoring visits per year following the first year	Cost difference: ¶¶ QALY difference: 1.06 ¶¶	The plausibility of this conservative approach to monitoring is unclear
¶¶: commercial in confidence data removed. AMD: age-related macular degeneration; BSE: best-seeing eye; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life-year; QoL: quality of life		

The results of the scenario analyses show that the ICER was most sensitive to changes in treatment frequency, maximum duration of treatment and the choice of health-related quality of life valuation approach. When limiting the treatment duration or increasing treatment frequency, variations in structural assumptions produce ICERs exceeding the baseline level. Probabilistic sensitivity analyses show that ranibizumab has a 99% chance of being the most cost-effective treatment at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained.

4.1.3 AWTTC critique

The results of the base case CUA indicate that the use of ranibizumab produces increased life years and QALYs compared to BSC, in adults with CNV associated with causes other than nAMD or pathologic myopia. Despite the initial medicine cost associated with ranibizumab, the long-term model estimates the intervention to be cost saving. The broad range of sensitivity analyses findings corroborate the base case.

The submission is characterised by both strengths and limitations. Reasonable justifications are provided for the assumptions applied to the model.

Strengths of the economic analysis:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- In the absence of other licensed treatments in Wales for the patient population, BSC appears to be the appropriate comparator for the CUA for this patient group. While other anti-VEGF inhibitors might be used under certain circumstances in routine practice, their use is off-label or unlicensed. Furthermore, the lack of available efficacy data would severely limit the usefulness of any comparison.
- A range of sensitivity analyses are reported that enable assessment of uncertainty surrounding the parameter and structural uncertainty.
- The clinical inputs reflect the best available data and have been implemented in a transparent and well supported way.

Limitations of the economic analysis:

- No utility data were collected as part of the MINERVA study. Utility values are therefore calculated using a regression analysis based on time trade-off techniques and real-world published data, whereby utility is a function of visual acuity in both the best-seeing eye and the worst-seeing eye, including an interaction term. While this approach was previously used in NICE technology appraisals, the amount of data manipulation required will introduce bias and could affect results.
- Conjunctival haemorrhage is the only adverse event included in the analysis and is assumed to not affect patient health-related quality of life. Considering the increased likelihood of this adverse event as a result of intravitreal injection, any valuation which views this adverse event as detrimental to health-related quality of life would decrease the expected QALYs for the ranibizumab arm and increase the ICER.
- Follow-up in the MINERVA study was limited to 12 months in the ranibizumab arm. After 12 months, if patients were still on treatment, it was assumed that effectiveness observed in the trial period between 3 and 12 months would continue beyond that point until treatment was discontinued. Once treatment was stopped, best-corrected visual acuity was assumed to change according to the natural history of the disease. No longer-term data are available to verify this assumption.
- Clinical effectiveness data for the BSC arm were derived from the control group in the MINERVA study, which is limited to two months due to a crossover of the patients in the sham group to the ranibizumab group after this time.
- A model time horizon of 50 years is used to reflect patients' lifetime based on the mean age of 54.6 years observed in the MINERVA study. Considering that patients as young as 18 years were included in the trial and the condition has a small impact on mortality, approximately 10% of the model population are still alive at the end of the 50 year horizon. The company states that the additional computational time required would have outweighed the overall impact on results. However, this will introduce bias as not all downstream costs and effects are considered for the entire patient population.
- Data for the probability of development of bilateral disease post-baseline were not available from the MINERVA study for development of active disease in the fellow eye over time, and literature sources were used as an alternative. This will introduce bias due to potential heterogeneity between study populations and methods.
- Recurrence rates were not available from the MINERVA study and were based on expert opinion. This might result in an over- or underestimation of costs and effects in the ranibizumab arm.
- Discontinuation figures might have diminished the overall cost of the ranibizumab arm as the reduction in diagnostic and monitoring costs cannot be achieved in the BSC comparator arm. This approach might underestimate net cost and not factor in the benefits of monitoring.
- The model assumes that treatment is equally effective for the study and fellow eyes. While this is consistent with previous appraisals, no data are available to verify the assumption, which might cause bias.
- The MINERVA study was conducted in 20 countries, including 14 European countries. However, there were no UK or Welsh centres included in the trial. It is therefore assumed that the results can be generalised to the Welsh population and context.

4.2 Review of published evidence on cost-effectiveness

A literature search by AWTTC did not identify any studies relevant to the cost-effectiveness of ranibizumab compared to BSC in adults with visual impairment due to CNV associated with causes other than nAMD or pathologic myopia.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The prevalence of rare CNV within Wales is estimated to be 244 people based on company-sought expert opinion and published rates[6,26-29]. Taking into account the Welsh population size and reported incidence rate of 0.57 per 100,000[30], an estimated two new cases per year are assumed. The submission highlights that neither Welsh nor UK clinicians feel that this estimate of new cases per year is an accurate figure. Therefore, the figure used for the budget impact model is assumed static at 244 people with rare CNV. Currently there are reports that patients might have access to ranibizumab through off-label treatment via treatment for additional conditions[31].

Estimated market share for ranibizumab begins at 35% per year and increases by 10% each year to a top limit of 65%. The coverage assumption comes from expert opinion and the acknowledgment that higher levels might be unrealistic. For each patient that is treated, the assumed first year acquisition cost (5.8 treatments) is [commercial in confidence figure removed]. Following the first year, in line with the economic model, patients would receive fewer treatments and the cost would fall to between [commercial in confidence figures removed]. No costs are assumed for BSC. A scenario analysis is performed based on the assumption of two additional patients each year with no reduction in patient base due to mortality.

5.1.2 Results

The estimated net budget impact is shown in Table 5. The cumulative direct costs associated with ranibizumab are [commercial in confidence figures removed].

Analysis of the impact on NHS resource use suggests a cumulative cost of £76,733 in Year 1 rising to £150,009 for the five-year duration. These extra costs result from the administration costs associated with ranibizumab.

Table 5. Company-reported costs associated with the use of ranibizumab for the treatment of rare CNV (based on a Patient Access Scheme price)

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Number of eligible patients (indication covered in this submission)	244	244	244	244	244
Uptake of ranibizumab (%)	35	45	55	65	65
Number of patients receiving ranibizumab, allowing for discontinuations	80	103	126	149	149
Medicine acquisition costs in a market without ranibizumab	£0	£0	£0	£0	£0
Medicine acquisition costs in a market with ranibizumab	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Cumulative net costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figures removed					

Varying the uptake of ranibizumab by 10% intervals to assess the influence of the input parameter offered a medicine-only cost of [commercial in confidence figure removed] with a 10% reduction, and a value of [commercial in confidence figure removed] with a 10% increase (excluding administration costs).

Administration costs, which include diagnostic and monitoring costs, total £76,733 in Year 1, £23,070 in Year 2, £24,720 in Year 3, £24,087 in Year 4 and £1,399 in Year 5.

The scenario analysis which includes the incidence rate of two new cases per year increases the cumulative budget impact to [commercial in confidence figures removed].

5.1.3 AWTTC critique

- The budget impact calculations and attached workings were of a high standard and offered a transparent and realistic estimate of costs.
- Workings are based upon a static patient base of 244. The reported incidence has not been used to factor in scenarios of new cases. If new incidence increases the number of newly treated patients, the current budget impact model figures would underestimate the financial outlay, as illustrated by the scenario analysis.
- Uptake rates are estimates and any changes to the uptake rate will affect the budget impact of ranibizumab.

5.2 Comparative unit costs

Acquisition costs for ranibizumab for adult patients with visual impairment due to CNV associated with causes other than nAMD or pathologic myopia are given in Table 6.

Table 6. Examples of medicine acquisition costs

Regimen	Example doses	Approximate costs per patient per year
Ranibizumab (Lucentis®) 10 mg/ml	0.5 mg (0.05 ml) as a single intravitreal dose	An average of 5.8 treatments totalling £3,196 (¶¶ with DoH PAS)

¶¶: commercial in confidence figure removed.
No other regimens are recommended for use in Wales for this patient population.
See relevant Summaries of Product Characteristics for full licensed indications and dosing details[8,9].
Costs are based on Monthly Index of Medical Specialities list prices as of 5 February 2018, assuming vial wastage[32].
Costs of administration are not included.
DoH PAS: Department of Health Patient Access Scheme

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, ranibizumab (Lucentis®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

LUMINOUS (NCT01318941) is a global, five-year, multicentre, observational study to evaluate the long-term effectiveness, safety and treatment patterns associated with ranibizumab 0.5 mg in routine clinical practice for patients with CNV due to nAMD, CNV due to pathologic myopia, diabetic macular oedema and retinal vein occlusion. The primary manuscript for LUMINOUS is still in development, with anticipated publication stated to be Quarter 4 of 2018.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

GLOSSARY

Early Treatment Diabetic Retinopathy Study (ETDRS)
A measure of visual acuity. The ETDRS chart, the gold standard tool for measuring visual acuity, uses letters printed in lines of decreasing size, which are read from a fixed distance; usually 6 metres (20 feet) for distance acuity[33]. The ETDRS visual acuity is written as a number; for example, 70 letters is equivalent to 6/24 Snellen. ETDRS letter score is often represented as a Snellen equivalent for ease of comprehension[33].

Miscellaneous aetiologies of CNV
Aetiologies that do not fit into the other CNV aetiology subgroups and are insufficiently frequent to form a separate subgroup[1]. They include retinal angiomatous proliferation, Morbus Stargardt, choroidal nevus, macular/juxtafoveal telangiectasia type 2, chorioretinitis by toxoplasma, pattern dystrophy of retinal pigment epithelium, adult pseudovitelliform macular dystrophy, polypoidal choroidal vasculopathy, trauma/scar (e.g. post laser), familial dominant drusen, Best's disease, choroidal rupture, haemangioma chorioideae[1].

Mixed-Effect Model Repeated Measure (MMRM)
MMRM contains scheduled visit, the type of underlying pathophysiologic mechanism (angioid streaks versus others) and treatment group as fixed effect factors, centred baseline best-corrected visual acuity as a continuous covariate and treatment group by visit, and visit by centred baseline best-corrected visual acuity interactions[1].

National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)
A survey that measures the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases[34]. The survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. It also includes an appendix of additional items from the 51-item version that researchers can use to expand the scales up to 39 total items[34].

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