



**Lucentis™ (ranibizumab) Therapy for the
Treatment of wet Age-related Macular Degeneration**

**Evidence Submitted to the
National Institute for Clinical Excellence
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All available and relevant evidence in the possession of
Novartis Pharmaceuticals UK Ltd is included in this dossier

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Executive Summary – CIC Data Removed

Lucentis™ (ranibizumab) is the first intervention to improve vision in a significant proportion of people with wet AMD (regardless of lesion subtype, lesion size or visual acuity (VA) at presentation)^{Error! Bookmark not defined.}.

The treatment goal for active wet AMD is to maintain or improve vision in order to maintain the highest possible level of visual and physical functioning and independent living. Lucentis meets this goal. A licence for the treatment of wet AMD is expected during the course of the appraisal. Lucentis is a humanised recombinant monoclonal antibody fragment that binds all isoforms of human vascular endothelial growth factor A (VEGF-A). As such, it targets the biological processes underlying wet AMD because VEGF-A promotes the angiogenesis and increased permeability that produce the abnormal ‘leaky’ blood vessel growth (choroidal neovascularisation – CNV) that result in loss of vision. Lucentis is an outpatient treatment involving a 3 month loading phase of monthly intravitreal injections of 0.5mg (0.05ml) Lucentis, followed by a maintenance phase of further injections as required (*i.e.* if there is a loss of 5 letters or more on monthly visual acuity assessment).

Evidence for the benefits of Lucentis™ is derived from a global phase III programme of rigorously conducted, randomised, controlled trials involving more than 1300 patients with all subtypes of wet AMD (predominantly classic, minimally classic and occult) for treatment periods of up to two years. The pivotal studies are MARINA^{Error! Bookmark not defined.} (a sham controlled study in wet AMD with minimally classic or occult CNV) and ANCHOR^{Error! Bookmark not defined.} (a PDT controlled study in wet AMD with predominantly classic CNV). These studies, show statistically significant benefits in favour of Lucentis™ for all the vision outcomes evaluated. Vision outcomes are corroborated by angiographic and optical coherence tomography evidence that treatment alters disease progression and, in addition, patient-reported improvements in ability to perform vision-related activities of daily living and quality of life provide evidence of effectiveness. The key study outcomes are:-

- Lucentis improves vision in more than 70% of patients treated (*mean VA at 12/24 months is above baseline levels*)
- Lucentis offers clinically meaningful improvement of vision to 33% to 40% of patients treated with the recommended dose of 0.5mg (*15 or more letters VA gained at 12/24 months*)
- Lucentis preserves vision in more than 90% of patients treated, preventing severe vision loss and avoiding progression to legal blindness

(VA gained, maintained or limited to a loss of less than 15 letters with fewer treated patients progressing to a VA of 6/60 or worse compared with untreated patients)

- Lucentis improves contrast sensitivity; this benefit to overall visual function is independent of VA.

(Mean gain in letters compared with untreated patients)

- Lucentis alters anatomical markers of disease progression

(Reduced or stabilised total area of lesion and CNV, reduced area of CNV leakage, reduced retinal thickness)

- Lucentis produces a sustained improvement in key vision-related activities of daily living

(Patient reported improvements in VFQ-25 near activities, distance activities and vision-dependence scores)

Treatment benefits of Lucentis are rapid in onset (seen from the first treatment), sustained for at least two years and are independent of age, race, gender, baseline visual acuity, lesion size and lesion type.

A further Phase III study (PIER)^{Error! Bookmark not defined.}, evaluated a reduced dosing frequency compared with MARINA/ANCHOR, of intravitreal injections at monthly intervals for the first 3 doses, followed by a quarterly regimen up to 12 months. PIER confirmed the efficacy of Lucentis in all subtypes of wet AMD, with visual acuity improvements seen at 3 months. *(CIC data removed)* Taken together, the results of MARINA, ANCHOR and PIER suggest that a fixed dosage regimen may not be appropriate for all patients. A meta-analysis (Drug & Disease Model) of 12-month data from MARINA, ANCHOR and PIER was therefore developed, based on modelling of the vitreous concentration of ranibizumab following an injection, that simulates Lucentis dosing on visual acuity during the maintenance phase of treatment. In this model, a total of 8 injections in the first treatment year (*i.e.* a further 5 injections following the loading phase) and a total of 6 injections in year two were required to stabilise visual acuity at a similar level to that following the loading phase. These data form the basis of the proposed EU and UK Summary of Product Characteristics (SmPC) posology for Lucentis of a 3 dose loading phase followed by a maintenance regimen, with re-treatment based on clinical changes in visual acuity. This proposed dosing has been accepted in principle by the CHMP and has been used in the health economic section to determine the cost-effectiveness of Lucentis.

Cost-effectiveness of Lucentis has been evaluated in a Markov model based on the phase III studies and combining the best available cost data with new utility data estimated by simulating

the visual impairment associated with AMD in the general population. The model adopts an NHS perspective and applies a time horizon of 10 years with an annual discount rate of 3.5% applied to both costs and outcomes. The table below shows the incremental cost per QALY and vision year gained for each lesion type in response to treatment with 0.5 mg Lucentis, and for MC and ONC lesions reflects 8 injections in year 1 and 6 injections in year 2, where as the analysis for PC is based on 8 treatments in year one only, as 2-year data is not yet available from the ANCHOR study for PC lesions. However, the expectations are that the year 2 dosing frequency will be similar for PC as for ONC & MC lesions. Results from the health economic modelling demonstrate that ranibizumab is a cost-effective use of NHS resources compared to the best supportive care (BSC) and photodynamic therapy (PDT).

	PC lesions vs PDT ANCHOR*	PC lesions vs BSC ANCHOR*	All lesion types vs BSC PIER*	ONC lesions vs BSC MARINA**	MC lesions vs BSC MARINA**
Incremental cost/vision year gained	£1,084	£3,994	£4,317	£7,188	£6,638
ICER	£4,489	£14,781	£12,050	£26,454	£25,796
* 1-year treatment data ; ** 2-year treatment data					

(CIC data removed)

In summary, Lucentis is the first and only therapy that maintains or improves vision in virtually all patients, and offers significant clinical improvements to patients and health care professionals. As a result, patients who previously were unable to read, recognise faces and were prevented from driving due to being below the threshold for legal blindness, are now capable of leading a fuller and more independent life.