Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final Protocol

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1. Title of the project:

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration

2. Name of TAR team and 'lead'

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3. Plain English Summary

The macula is the central part of the retina at the back of the eye. As a person ages, changes in this area can occur, causing loss of sight in the central field of vision. The late stage of this condition, age-related macular degeneration (AMD), is the most common form of visual impairment in the UK. Although people retain peripheral vision, activities such as reading, driving, recognizing faces and watching television gradually become impossible.

There are different types of AMD. Geographic atrophy (dry AMD) is a form of extensive atrophy (wasting of cells) which results in patterns of damage that look similar to a map. Wet AMD involves lesions of abnormal blood vessels which grow beneath the retina and leak into it, causing scarring and loss of central vision. Vision deteriorates relatively slowly with geographic atrophy, while the wet form of the disease is associated with much more rapid deterioration of vision. Wet AMD is subdivided into different disease types according to the type of lesions formed and their location in relation to a part of the macula called the fovea. For example, lesions can be described as classic or occult, extrafoveal or subfoveal. The majority of people have subfoveal lesions.

Treatment for dry AMD is limited to vitamin supplementation, which can retard progression. Management for most patients with AMD consists of social support, visual rehabilitation and provision of low-vision aids. Deterioration of vision due to wet AMD with classic, subfoveal lesions can be prevented by using a light sensitive drug in combination with a low-powered laser treatment to seal leaking blood vessels (photodynamic therapy).

Pegaptanib and ranibizumab are two new treatments for wet AMD, administered via intravitreal injection into the eye. A particular protein is essential for forming new blood vessels, increasing the rate at which blood can flow through these, and causing inflammation. Pegaptanib and ranibizumab help to reduce this protein's activity, and so block new blood vessel growth and leaking which would otherwise lead to further deterioration of vision.

The review will summarise the results of clinical trials which compare ranibizumab and pegaptanib with standard treatments for age-related macular degeneration. The report will include an economic evaluation, to give an indication of the cost-effectiveness of these new drugs relative to current practice in the NHS in England and Wales.

4. Decision problem

4.1 Purpose of the decision to be made

Age-related macular degeneration (AMD) is one of the leading causes of irreversible sight loss among adults registered blind.[1] The disease causes loss of central vision resulting in sufferers being unable to read, recognise faces or drive a vehicle, and is associated with a decrease in quality of life and an increased risk of falls. AMD is the late stage of age-related maculopathy,

which is a disorder of the macular area of the retina, most often clinically apparent after 50 years of age.[2] There are different types of late age-related maculopathy, which have different manifestations, prognoses and treatment strategies. Geographic atrophy (dry AMD) is associated with gradual, progressive loss of visual function, while wet (disciform, exudative or neovascular) AMD has a more variable course but can progress much more quickly, sometimes within days or weeks.[3] The majority of patients with legal blindness due to AMD have the neovascular form of the disease.[4] Wet AMD is often associated with choroidal neovascularisation (CNV), which involves the formation of immature blood vessels that grow between the retinal pigment epithelial cells and the photoreceptor cells in the centre of the retina. CNV can be described as 100% classic, predominately classic, minimally classic or occult according to its appearance on fluorescein angiography (a technique for examining blood vessels in the retina). Further subdivisions can be made according to where the lesions occur in relation to the fovea, which is the central part of the macula and the area of highest visual acuity: subfoveal (located behind the middle of the fovea); juxtafoveal (located within 200 μm of the fovea, but not the middle of it); and extrafoveal (located >200 μm outside the fovea).

Treatment options for people with AMD are limited. For most patients with AMD, management consists of social support, visual rehabilitation and provision of low-vision aids. For those with extrafoveal CNV photocoagulation therapy may be used to halt the rapid vision loss caused by the proliferation of blood vessels, however only a small proportion of patients with wet AMD present with extrafoveal lesions.[5] Laser photocoagulation uses high-intensity thermal energy to coagulate CNV, however it does not restore lost vision.[6] The main limitations of photocoagulation are firstly, only 10 to 15% of all neovascular lesions are small enough and sufficiently delineated to be eligible. Secondly, there is at least a 50% chance that leakage will recur during the following two years. Thirdly, at least half of patients have some initial leakage beneath the centre of the fovea, and laser treatment leads to an immediate reduction in central vision.[3]

Photodynamic therapy (PDT) involves intravenous injection of verteporfin, a photosensitive drug that remains in the new blood vessels, before treatment with a low-powered laser that activates the drug.[7] The aim is to destroy CNV lesions without damaging the overlying retina, thereby slowing or halting the progression of vision loss. PDT with verteporfin has been recommended by NICE[8] for the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal CNV. The main disadvantages include: the photosensitive drug remains in the body for

up to 48 hours, therefore patients are required to avoid direct sunlight; adverse events from injection of the drug; long-term effects are unknown; recurrence is common; and over-dose of the drug or laser can result in permanent irreversible vision loss.[7]

The aim of therapy for people with wet AMD is to alter the progression of vision loss and improve vision if possible. The drugs under assessment, pegaptanib and ranibizumab, prevent further development of the disease by inhibiting vascular endothelial growth factor (VEGF), a secreted protein that induces angiogenesis (the formation of new blood vessels), vascular permeability and inflammation.[9] The aim of this report is to assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for the treatment of age-related macular degeneration.

4.2 Definition of the intervention

Pegaptanib (Macugen, Pfizer Ltd) is indicated for the treatment of neovascular (wet) AMD.
Pegaptanib is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular vascular endothelial growth factor (VEGF165) inhibiting its activity. VEGF165 is the VEGF isoform preferentially involved in pathological ocular neovascularisation. It is administered at a dose of 0.3 mg once every six weeks (9 injections per year) by intravitreal injection into the affected eye.[9]

A UK licence for ranibizumab (Lucentis, Genentech / Novartis Pharmaceutical Ltd) for the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal oedema in patients with wet AMD is expected at the end of 2006. Ranibizumab is a humanized therapeutic antibody fragment designed to bind and inhibit VEGF-A. Ranibizumab is designed to block new blood vessel growth and leakiness, which lead to wet AMD disease progression and vision loss. It is administered at a dose of 0.3-0.5 mg as monthly intravitreal injections for as long as the patient benefits.[10]

4.3 Place of the intervention in the treatment pathway(s)

Ranibizumab and pegaptanib would be administered as soon as possible after diagnosis to minimise damage. Guidelines from the American Academy of Ophthalmology report the criteria for treatment with pegaptanib as described in the trial publications.[11] The patients in the pegaptanib trial were required to have subfoveal sites of CNV and a range of best corrected visual acuity of 20/40 to 20/230 in the study eye and of 20/800 or better in the other eye. Lesion sizes of

not more than 12 disc areas were permitted. Patients with minimally classic or occult with no classic CNV were required to have at least one of the following: subretinal haemorrhage associated with CNV, but comprising no more than 50% of the lesion; the presence of lipid; the loss of 15 or more letters (approximately 3 lines on the study eye chart) of visual acuity during the previous 12 weeks.[12] Pegaptanib can be given in combination with PDT with verteporfin,[12] and a change in treatment regimen, for example from PDT with verteporfin to pegaptanib or vice versa may be appropriate depending on the clinical response of a given patient.[11]

4.4 Relevant comparators

Comparators for the interventions under assessment are those suitable for patients with subfoveal wet AMD used in the NHS. These would be best supportive care, or photodynamic therapy for the subgroup of patients with classic no occult subfoveal wet AMD. Best supportive care includes provision of and training with low vision aids, information about support charities (e.g. the Macular Disease Society), registration as visually impaired or blind depending on the level of acuity, and advice about not smoking and vitamin supplementation. Photocoagulation therapy will not be included as a comparator, because although photocoagulation therapy may be considered for new or recurrent subfoveal CNV with poor visual acuity, it is rarely used as the first treatment of choice due to associated loss of vision.[11]

4.5 Population and subgroups

The study population will be adults with the subfoveal CNV associated with wet AMD. Subfoveal lesions are the most common type, accounting for almost 80% of lesions.[5]

Potential subgroups can be described according to the appearance of the lesion (classic no occult, predominately classic, minimally classic or occult no classic), however the interpretation of fluorescein angiography may differ between readers,[13] therefore there may be some uncertainty regarding these diagnoses. Comment will only be made on the effectiveness of pegaptanib and ranibizumab for these patients if appropriate subgroup analyses are presented in the included studies.

4.6 Key factors to be addressed

Clinical outcomes will include visual acuity, contrast sensitivity, adverse effects of treatment, adherence to treatment and health-related quality of life. Direct costs will include estimates of all health care resources consumed in the provision of the interventions – drug acquisition,

administration and monitoring costs – as well as consequences of those interventions, such as treatment of adverse effects.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

- A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify studies reporting clinical-effectiveness, cost-effectiveness, health-related quality of life (HRQOL), resource use / costs, and epidemiology / natural history.
- The draft search strategy for Medline can be seen in Appendix 1.
- A number of electronic databases will be searched including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Ophthalmology conferences will be searched for recent abstracts (from 2004). Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database and will be limited to the English language. The searches will be updated around October 2006.

5.2 Inclusion and exclusion criteria

5.2.1 Patients

- People with the subfoveal choroidal neovascularisation (CNV) associated with wet age-related macular degeneration.
- If appropriate, potential subgroups will be considered according to the composition of the lesion in terms of classic and occult CNV.

5.2.2 Interventions

Studies reporting evaluations of the following interventions will be included:

- Ranibizumab (Lucentis, Genentech/Novartis Pharmaceuticals UK Ltd)

- Pegaptanib sodium (Macugen, Pfizer Ltd)
- Combination of the drugs with photodynamic therapy will be considered where the licensed indication and the evidence allow.

5.2.3 Comparators

- Best supportive care.
- For the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet AMD, photodynamic therapy with verteporfin is also a comparator.
- If insufficient evidence is found using the above comparators, the following comparators will be considered:
    - Sham injection (systematic review of clinical effectiveness only)
    - Photodynamic therapy with verteporfin for patients with subfoveal wet AMD with predominately classic lesions.

5.2.4 Outcomes

Studies reporting one or more of the following outcomes will be included:

- Visual acuity
- Contrast sensitivity
- Adverse effects of treatment
- Adherence to treatment
- Health-related quality of life

5.2.5 Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs will be included. Systematic reviews will be used as a source for RCTs and as a comparator. Indicators of a 'systematic' review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality.
- Studies published only as abstracts or conference presentations will be included in the primary analysis of clinical and cost-effectiveness if sufficient details are presented to allow an appraisal of the methodology and assessment of results.
- Non-English language studies will be excluded.

5.3 Inclusion and data extraction process

- Titles and abstracts of studies identified by the search strategy will be screened by one reviewer based on the above inclusion/exclusion criteria and checked by a second reviewer.
- The full text of relevant papers will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second.
- Data will be extracted by one reviewer using a standard data extraction form (Appendix 2) and checked by a second reviewer.
- At each stage, any discrepancy will be resolved by discussion, with involvement of a third reviewer where necessary.

5.4 Quality assessment

- The quality of included RCTs and systematic reviews will be assessed using NHS CRD (University of York) criteria.
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

5.5 Methods of analysis/synthesis

- Clinical-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed, using appropriate software.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Search strategy

Refer to Appendix 1 for details of the draft search strategy for Medline. The sources to be searched are similar to those used in the clinical-effectiveness review (see Section 5.1). All searches will be limited to the English language.

6.2 Inclusion and exclusion criteria

- Full economic evaluations and systematic reviews of economic evaluations, where relevant, will be included. Inclusion and exclusion criteria will be the same as those applied for the clinical effectiveness review (see section 5.2).

6.3 Inclusion and data extraction process

- Titles and abstracts of studies identified by the search strategy will be screened by one reviewer based on the above inclusion/exclusion criteria and checked by a second reviewer.
- The full text of relevant papers will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second.
- Data will be extracted by one reviewer using a standard data extraction form and checked by a second reviewer.
- Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

6.4 Study quality assessment

The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the International consensus-developed list of criteria developed by Evers and colleagues,[14] and Drummond and colleagues[15]. For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[16]). Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

6.5 Synthesis of evidence on costs and effectiveness

(a) Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations and sponsor submissions to NICE.

(b) Economic Modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. If possible, the incremental cost-effectiveness of the interventions will be estimated in terms of cost per Quality Adjusted Life Year (QALY) gained, as well as the cost per vision year gained i.e. for an additional year of visual function, if data permit. The perspective will be that of the NHS and Personal Social Services. Both cost and outcomes (QALYs) will be discounted at 3.5%.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- The biological disease process (i.e. knowledge of the natural history of the disease);
- The main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events which are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For example, we will need to consider developing a model of vision loss due to wet age-related macular degeneration which could reflect factors such as: patient age, visual acuity, baseline Snellen, time to vision loss, whether previous treatment is received and side effects.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE or experts' clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

To capture health-related quality of life effects, utility values will be sought from the relevant research literature.

Analysis of uncertainty will focus on cost-utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The simulated population will be defined on the basis of both the published evidence about the characteristics of UK population with wet age-related macular degeneration, and the populations for which good quality clinical effectiveness is available. The base case results will be presented for the population of UK with wet age-related macular degeneration. The time horizon for our

analysis will initially be governed by follow-up data available from included clinical trials - we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

7. Handling the company submission(s)

All information submitted by the manufacturers/sponsors as part of the NICE appraisal process will be considered if received by the TAR team no later than 8th August 2006. Information arriving after this date will not be considered.

Industry submissions will be checked for additional studies that meet the inclusion criteria for data on clinical effectiveness, costs and on the current use of ranibizumab and pegaptanib.

Any economic evaluation included in company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Results of cost-effectiveness analyses from industry submissions will be compared with the SHTAC analysis.

Any 'academic in confidence' data or 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

There are no competing interests.

9. Appendices

Appendix 1 Draft search strategy

Appendix 2 Data extraction form

Reference List

1. Evans J, Wormald R. Is the incidence of registrable age related macular degeneration increasing? *Br J Ophthalmol* 1996;80:9-14.

2. Nahta R, Esteva FJ. HER-2-Targeted Therapy: Lessons Learned and Future Directions. *Clinical Cancer Research* 2003;9(14):5078-84.

3. Fine SL, Berger KW, Maguire MG, Ho AC. Age related macular degeneration. *New England Journal of Medicine* 2000;342(7):483-92.

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5. Olsen TW, Feng X, Kasper TJ, Rath PP, Steuer ER. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004;111:250-5.

6. Kourlas H, Schiller DS. Pegaptanib sodium for the teatment of neovascular age-related macular degeneration: a review. *Clinical Therapeutics* 2006;28(1):36-44.

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8. National Institute for Clinical Excellence. Guidance on the use of photodynamic therapy for age-related macular degeneration. *Technology Appraisal Guidance* 2003;68.

9. Pfizer Ltd. Summary of Product Characteristics. Macugen 0.3 mg solution for injection. 2006.

10. Genentech Inc. Preliminary Phase III Data from Head-to-Head Study of Lucentis Shows Lucentis Improved Vision Compared to Visudyne in Patients with Wet Age-Related Macular Degeneration. Press Release 14th January 2006. http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9307 (accessed 9 May 2006)

11. American Academy of Ophthalmology. Age-related macular degeneration. Preferred Practice Pattern. 2000. National Guidelines Clearinghouse.

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15. Drummond MF, O'Brien BJ, Torrance GW, Stoddart GL. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.

16. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment (Winchester, England)* 2004;8(36):1-158.

Appendix 1 Draft search strategy

Draft search strategy for Medline. This will be amended for use with other databases.

1 exp Macular Degeneration/ (7090)
2 (age related maculopath$ or maculopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1729)
3 age related macula$ degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3258)
4 macula$ degeneration.mp. (6910)
5 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30)
6 (geographic$ adj5 atrophy).mp. (228)
7 (AMD or ARMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2453)
8 age related eye disease$.mp. (122)
9 senile macula$ degenerat$.mp. (309)
10 (neovascular adj5 macular degeneration).mp. (284)
11 (disciform adj5 macular degeneration).mp. (84)
12 (choroidal neovascularization or CNV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2937)
13 Choroidal Neovascularization/ (1406)
14 (wet adj5 (macular degeneration or AMD or ARMD)).mp. (83)
15 (exudative adj5 (macular degeneration or AMD or ARMD)).mp. (440)
16 (dry adj5 (macular degeneration or AMD or ARMD)).mp. (69)
17 (non-neovascular adj5 macula$ degen$).mp. (3)
18 or/1-17 (12067)
19 pegaptanib.mp. (47)
20 macugen.mp. (9)
21 ranibizumab.mp. (14)
22 lucentis.mp. (5)
23 (19 or 20) and 18 (42)
24 (21 or 22) and 18 (11)
25 23 (42)
26 limit 25 to (humans and english language) (36)
27 24 (11)
28 limit 27 to (humans and english language) (6)

Appendix 2 Data extraction form

Data extraction form for primary studies

Reviewer:		**Date:**	**Version:**
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author et al., year [id] Country Study design Number of centres *Setting:* *Funding:*	(including, dose etc) 1. 2. *Duration of treatment:* *Other interventions used*:	*Target population:* (state if specific location or composition of lesion) *Number of Participants:* Total: 1. 2. *Sample attrition/dropout*: *Inclusion/exclusion criteria for study entry*:	*Primary outcomes:* *Secondary outcomes:* *Method of assessing outcomes:* *Length of follow-up:*

Characteristics of participants:

	Treatment X (*specify)* (n=)	**Treatment Y (*specify)* (n=)**	**P Value**
Age, years			
Sex			
Classification			

Results

Outcomes	**Treatment X (*specify)* (n=)**	**Treatment Y (*specify)* (n=)**	**P Value**
Visual acuity			
Comments			
Contrast sensitivity			
Comments			
Adherence to treatment			
Comments			
Other (specify)			
Comments			
QoL			
Comments			
Comments			
Adverse Effects			
Comments			
Resource Use			
Comments			

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

- Allocation to treatment groups:
- Blinding:
- Comparability of treatment groups:
- Method of data analysis:
- Sample size/power calculation:
- Attrition/drop-out:

General comments

- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	