Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Pfizer Global Pharmaceuticals

Dear Dr Longson,

Pfizer comments on the Appraisal Consultation Document (ACD) for ranibizumab and pegaptanib for age-related macular degeneration (AMD)

Pfizer disagrees with the NICE preliminary decision to not recommend pegaptanib for any patients with wet AMD.

Our response focuses on three key concerns. There are summarised below and more detail is provided in the attachment:

1) An inequitable approach to decision making has been adopted, leading to a recommendation for ranibizumab in patients with predominantly classic lesions and no recommended use of pegaptanib

We note that an inconsistent approach to generate the cost-effectiveness estimates has been employed. Ranibizumab is recommended for the treatment of patients with predominantly classic lesions based on a treatment period of **one year** (12 injections). The cost-effectiveness estimates for pegaptanib, and the remaining lesion sub-types treated with ranibizumab, were, however, based on a treatment period of **two years**. It is clear that this differential treatment period is driving the cost-effectiveness results and decision making. We demonstrate in the attached response that under the same decision criteria of one-year treatment (9 injections), pegaptanib is highly cost-effective (£7,500 per QALY) for patients with all lesion sub-types of AMD.

2) We maintain that pegaptanib is cost-effective for 2 years of treatment versus usual care. We challenge two key elements of the NICE analysis:

a) NICE has not adequately recognised the value of pegaptanib for the treatment of early stage disease

As stated in the Pfizer response to the Technology Assessment Report, Pfizer strongly recommends that pegaptanib should be available as a treatment option for patients with wet AMD at an early stage of disease, i.e. when their visual acuity lies between 6/12 and 6/24. This is consistent with pegaptanib's Summary of Product Characteristics, which confirms that the data over a two-year period indicate treatment should be initiated as early as possible. The NICE economic model is unsuitable to estimate cost-effectiveness for this patient sub-group. Pfizer has demonstrated that pegaptanib is cost-effective for this sub-group of patients when appropriate modelling of baseline vision and time dependence is applied.

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

b) NICE has generated overly conservative estimates of cost-effectiveness by (i) costing administration as a Day Case Procedure and (ii) under-estimating the costs of blindness

(i) Pfizer has consulted with ophthalmologists and understands that intravitreal injections for pegaptanib are being administered as an outpatient procedure in many UK centres. Additionally, a recent document published by the Royal College of Ophthalmologists: "Commissioning Contemporary AMD Services: A guide for commissioners and clinicians" outlines the resource requirements for establishing and running an AMD service. This document is based on clinician experience and research and it does not recommend that intravitreal injections should be administered as a Day Case Procedure. As there are no regulatory or clinical requirements for treatment to be administered as a Day Case Procedure, the lower cost-effectiveness estimates using costs of an outpatient procedure should be used by the Committee to inform decisions.

(ii) Significant uncertainty surrounds the patient uptake and costs of services for people who progress to blindness. The actual cost of blindness to the NHS is fundamental to this appraisal because, by reducing progression to blindness, it is possible that pegaptanib provides more benefit for less cost than usual care. We ask the Committee to consider a higher cost of blindness based on up-to-date information and expert opinion; this will result in an improved cost-effectiveness for pegaptanib.

3) Treatment choice has been restricted without full consideration of the potential safety concerns of treating with ranibizumab, a non-selective VEGF-A agonist

Pfizer are concerned that the preliminary guidance recommends ranibizumab as the only anti-VEGF treatment to treat wet AMD. This would restrict physician and patient choice. Physicians should be able to prescribe the most appropriate treatment to each individual patient based on an informed assessment of risk as well as benefit. This is an important consideration in light of the evidence suggesting an increased risk of stroke associated with ranibizumab.

For the above reasons, Pfizer maintains that pegaptanib should be recognised as a cost-effective treatment for patients with all lesion sub-types of wet AMD and we urge the Committee to revise their draft recommendation.

Yours sincerely

[redacted]

ATTACHMENT

Pfizer would like to provide additional detail supporting our three concerns for the Committee's attention:-

1) **An inequitable approach to decision making has been adopted, leading to a recommendation for ranibizumab in patients with predominantly classic lesions and no recommended use of pegaptanib**

In our original submission, and in our response to the Technology Assessment Report (TAR), Pfizer provided cost-effectiveness estimates modelled using two year clinical trial data from the VISION trial. Two year data was also used by Novartis to model out the cost-effectiveness estimates for ranibizumab in minimally classic and occult sub-types using MARINA trial data. The Assessment Group model, built by the Southampton Health Technology Assessment Centre (SHTAC), also modelled out the cost-effectiveness using the two-year data from VISION and MARINA; neither pegaptanib or ranibizumab were considered to be cost-effective by NICE.

However, the ACD recommendation of ranibizumab for patients with predominantly classic lesion sub-type has been based on a maximum of 1 year of treatment (Sections 4.2.3.13 and 4.3.14 in the ACD). The treatment duration for these patients was assumed to be 1 year presumably because follow-up of the ANCHOR trial was restricted to 1 year at the time of the analysis. Hence, recommendation for ranibizumab in predominantly classic lesions has been based on one year data despite recognition that treatment will persist beyond this timeframe. This is inequitable as pegaptanib would be cost-effective for all lesion sub-types of AMD if modelling was based on one year of treatment.

Pfizer have addressed this inequity by modelling outcomes data for pegaptanib based on the same approach undertaken by the Assessment Group using 1 year data (9 injections for pegaptanib) from the VISION trial using the Pfizer model.

It can be demonstrated that pegaptanib is cost-effective when patients with early stage disease were treated with 9 injections in 1 year. The base case ICER is £7,580. The deterministic sensitivity analyses performed by the Assessment Group (reported in Table 4.24, page 138 of the TAR) were repeated for this analysis and all scenarios were cost-effective. All cost-effectiveness estimates are presented in Appendix 1, Table 1.

Having already demonstrated that pegaptanib was cost-effective in the "treat early" population using 2 year data (TAR response); we have now shown that pegaptanib represents even better value for money to the NHS when 9 injections are modelled in this sub-group of patients with visual acuity (VA) between 6/12 and 6/24 with all lesion sub-types of AMD.

We request the Committee address the question "How many injections can be considered cost-effective for these treatments?"

2) We maintain that pegaptanib can be shown to be cost-effective for 2 years of treatment.

a) ***NICE has not adequately recognised the value of pegaptanib for the treatment of early stage disease***

In our response to the TAR, we provided a cost-effectiveness estimate of £15k per QALY which:

- was modelled using two year clinical trial data from the VISION trial,
- adopted all monitoring and administration costs from the SHTAC model, and
- was specific to the SHTAC base case population of patients at an early stage of disease categorised by VA between 6/12 and 6/24.

When the data for the "treat early group" was modelled by the Assessment Group to generate the "base case" cost-effectiveness estimate using 2 year data, the incremental cost-effectiveness ratio (ICER) was £31,000, which we acknowledge is at the upper limit of what would be acceptable to the NHS as representing good value for money.

However, as we have already demonstrated in the Pfizer response to the TAR, comparison of the Assessment Group model prediction for outcomes in the first two years with those observed in the VISION trial demonstrates that the Assessment Group model substantially underestimates the benefit of pegaptanib during the period of trial follow-up for the "treat early group".

The inaccuracy of the Assessment Group model may be explained by the simplistic approach to modelling outcomes. Most notably, no attempt was made to account for the time-dependency of VA changes. Although it has been recognised by others[1] that VA change is dependent on pre-treatment VA levels (time to transition to lower VA level was found to be highly dependant on baseline Snellen; p=0.0065) probabilities derived from the VISION trial population with a VA range of 6/12 to 6/95 were used to model VA change for patients with a pre-treatment VA of between 6/12 and 6/24. The clinical data from the VISION trial did not support this assumption.

The Pfizer model more accurately models the benefit in this "treat early" group. The figure using the Pfizer model was £15,000 per QALY, which is often considered cost-effective and good value for money. The Pfizer model has now been accepted for peer-reviewed publication in Pharmacoeconomics (Wolowacz SE, Roskell N, Kelly S, Maciver FM, Brand CS. Cost-effectiveness of pegaptanib for the treatment of age-related macular degeneration in the UK. Pharmacoeconomics: Accepted; In Press).

Emphasis on treating early is clinically responsible as patients will have the greatest capacity to benefit from treatment. In addition, as disease awareness, diagnosis, and services improve, patient accessibility to receive earlier treatment will increase.

Furthermore, treating patients at an early stage of disease is supported by the wording in the Summary of Product Characteristics for pegaptanib which states that "Data over a two-year period indicate that Macugen treatment should be initiated as early as possible. In advanced disease the initiation and continuation of Macugen therapy should consider the potential for useful vision in the eye."

b) NICE has generated overly conservative estimates of cost-effectiveness by (i) costing administration as a Day Case Procedure and (ii) underestimating the costs of blindness

(i) Cost of administration as a Day Case Procedure

Pfizer note that in the ACD (section 4.3.11) the Committee have been advised by clinical specialists that administration of the intravitreal injections will be given as a Day Case Procedure and the (higher) associated costs for a Day Case should be adopted in the economic model. Pfizer have consulted with ophthalmologists who have advised that intravitreal injections for pegaptanib are being administered as an outpatient procedure in the UK centres.

Pfizer would also like to draw the Committees attention to a recent document published by the Royal College of Ophthalmologists:-
http://www.rcophth.ac.uk/docs/scientific/publications/FinalPDFV2CommissioningContemporaryAMDServices

This outlines the resource requirements for establishing and running an AMD service. This document is based on clinician experience and research and it does not recommend that intravitreal injections should be administered as a Day Case Procedure.

(ii) Costs of blindness and uptake of these services

The wide variation in the outcomes presented in Table 4.24 of the TAR demonstrates that there is considerable uncertainty associated with the costs and uptake of services for the blind. For example, if the costs are high and the uptake is high, pegaptanib was shown to be a dominant therapy (providing more benefit at less cost than usual care).

Pfizer have consulted with our key customer groups who have advised that the uptake of services for the blind is actually higher than currently estimated; therefore pegaptanib will demonstrate cost-effectiveness.

3) Treatment choice has been restricted without full consideration of the potential safety concerns of treating with ranibizumab, a non-selective VEGF-A agonist

Pfizer are concerned that the preliminary guidance states that ranibizumab should be the only anti-VEGF treatment which is recommended to treat wet AMD. This would restrict physician and patient choice. Physicians should be able to prescribe the most appropriate treatment to each individual patient based on an informed assessment of risk as well as benefit.

Ranibizumab is a non-selective VEGF-A agonist and pegaptanib is a selective VEGF treatment. The VISION study has shown that pegaptanib is well tolerated; the majority of ocular adverse events were attributed to the injection procedure. Systemic events attributable to pegaptanib occurred at a rate similar to the control group after two years. Three year safety data has produced no serious systemic safety signals and the ocular safety profile was sustained.[2,3]

Safety data from ranibizumab studies ANCHOR (n=423) and MARINA (n=716) indicate a trend in the occurrence of serious adverse events potentially related to systemic non-selective VEGF inhibition (such as arterial thromboembolic events and non-ocular haemorrhage).[4,5] In particular, in the one-year ANCHOR study there was an apparent increase in arterial thromboembolic events from 2.1% in the verteporfin group to 4.3% in the 0.5mg dose ranibizumab group. Additionally in ranibizumab Summary of Product Characteristics under the section 4.8 Undesirable Effects; hypertension/elevated blood pressure is reported as very common.[6]

A recent correspondence in the New England Journal of Medicine[7,8] between principal investigators of ranibizumab trials and other clinical experts in the field reflects the current uncertainty of the significance of these safety signals. They concluded that better estimates of the rates of the above adverse events would come from continued follow-up of patients. Pfizer support post-marketing surveillance studies to better establish the risk:benefit of anti-VEGF treatment options.

Section 4.3.5 in the ACD discusses the adverse events associated with both treatments and states that "*they have a broadly similar profile, there is a suggestion that ranibizumab may be associated with an increased risk of stroke (although it is currently inappropriate to draw conclusions)*". Treatment should be tailored to the individual patient and therefore the physician may feel it is necessary to recommend treatment with pegaptanib for patients who may have an increased cardiovascular risk; particularly patients who have already experienced a stroke.

The wet AMD patient population is generally older and present with co-morbidities. This is supported by a recent study comparing co-morbid conditions of patients with wet AMD and those without wet AMD.[9] Results showed an 11.6% higher risk of stroke, a 31.5% higher risk of hypertension and a 36.4% higher risk of lipid disorders in the wet AMD population. Therefore, cardiovascular safety becomes an important treatment consideration in this patient population when treating with anti-VEGF therapy.

We would therefore recommend that the Committee reconsiders the potential safety issues associated with a non-selective VEGF-A agonist. Access to both anti-VEGF treatments would ensure that eligible patients have access to the most appropriate treatment to manage their disease, with consideration of potential benefit and risk for the individual.

References

1. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. Br J Ophthalmol 2004 Sep;88(9):1107-12.

2. Suner, I. The Relative Systemic Safety of Differing AMD Therapies. Poster presented at American Academy of Ophthalmology Annual Meeting November 2006.

3.Singerman LG. Efficacy and Safety of pegaptanib (Macugen): 3 year results. Retina Subspecialty Day November 10, 2006. American Academy of Ophthalmology Annual Meeting November 2006.

4. Brown et al for the ANCHOR Study Group. Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration. NEJM 2006;355:1432-44.

5. Rosenfeld et al for the MARINA Study group. Ranibizumab for Neovascular Age-Related Macular Degeneration. NEJM 2006;355:1419-31.

6. Lucentis Summary of Product Characteristics.

7. Gillies MC and Wong TY. Ranibizumab for neovascular Age-related macular degeneration. NEJM 2007; 356(7): 748.

8. Liew G and Mitchell P. Ranibizumab for neovascular Age-related macular degeneration. NEJM 2007; 356(7): 747-8.

9. Shah S, Zlateva G, Zhou S, Javitt, JCl. Comparison of co-morbid conditions between wet AMD patients and a control cohort in the Medicare population. Poster presented at: Annual Meeting of AVRO; April 30-May 4 2006

APPENDIX 1

The results of the cost-effectiveness analyses when 9 injections are administered, i.e. 1 year of treatment with pegaptanib is presented in Table 1. The results have been generated using the Pfizer model, for a population of patients whose visual acuity at the start of treatment lies between 6/12 and 6/24. We have chosen to adopt the administration and monitoring costs provided by SHTAC (Assessment Group Model).

The ICER was estimated as £7,580/QALY (£5,249 to £12,571) over 10 years. The probability of cost-effectiveness was 100% at a threshold of £20,000/QALY. Hence using the Pfizer model with the above input parameters, pegaptanib is cost-effective when effectiveness for 9 injections of treatment is modelled for patients with early disease.

The deterministic sensitivity analyses performed by the Assessment Group (reported in Table 4.24, page 138 of the TAR) were repeated for this analysis and are also presented in Table 1. If all injection procedures were assumed to be performed as day case procedures in the operation theatre (at a cost of £395), the ICER estimate rose to £14,010 per QALY. The ICER estimate remained below £20,000 per QALY in all analyses with the exception of time-frames of 5 years or less.

Table 1. Deterministic Sensitivity Analysis: 1 Year Treatment (Pre-treatment VA of 6/12 to 6/24) adopting Assessment Group Treatment Costs

		Incremental cost	Incremental QALYs	ICER
Reference case (10 year time-frame)		£3,106	0.41	£7,580
Structural assumptions				
Time horizon (10 years)	3 years	£5,386	0.12	£43,955
	5 years	£4,422	0.22	£20,303
	8 years	£3,451	0.35	£9,978
Disease modifying effect	Year 3 only	Not Applicable, no assumption regarding disease-modifying effect is made in the reference case		
	Year 3 onwards			
Stop treatment on entering 6/60 state		Not applicable (this is reference case assumption)		
Don't stop treatment on entering 6/60 state		£3,198	0.42	£7,677
Methodological uncertainty				
Discount rates (3.5% for costs and outcomes)	0% for cost & outcome	£2,590	0.48	£5,425
	6% for cost & outcome	£3,411	0.37	£9,211
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	<75 years	£1,896	0.48	£3,942
	≥75 years	£3,658	0.37	£9,922
Proportion of cohort that is male (50%)	All male	£3,072	0.42	£7,340
	All Female	£3,110	0.40	£7,681
Visual acuity at aseline (6/12 to 6/24)	As VISION trial (6/12 to 6/95)	£3,751	0.31	£12,140
	6/24 to 6/60	£3,755	0.31	£12,166
Parameter uncertainty				
Number of injections (mean)	9 in Year 1 (8.6)*	£4,334	0.31	£14,042
	8 in Year 2 (6.9)	Not Applicable (1 year treatment being analysed)		
	9 in Year 1 (8.4) and 8 in Year 2 (6.9)			
Cost of injection procedure	Costed as day case procedure**	£5,740	0.41	£14,010
Health state utilities	Standard gamble values	£3,106	0.36	£8,526
	TTO values (Lower CI)	£3,106	0.42	£7,404
	TTO values (Upper CI)	£3,106	0.41	£7,580
Costs of blindness	High uptake/ high costs	-£6,614	0.41	Cost Saving
	Low uptake/ low costs	£5,959	0.41	£14,545
	High costs/ medium uptake	£680	0.41	£1,659
	Low costs/ medium uptake	£5,101	0.41	£12,451
	High uptake/ medium costs	-£2,096	0.41	Cost Saving
	Low uptake/ medium costs	£4,900	0.41	£11,960

*This analysis assumes all patients receive 9 injections regardless of predicted deaths and patients discontinuing because VA fell below 6/60. **Cost of day case procedure calculated as £395.27 based on data presented in Tables 4.23 and 4.24 of the Technology Assessment Report. Costs of blindness were taken from the Technology Assessment Report (Table 4.25). Treatment was continued for a maximum of 1 year and discontinued at any time if VA fell below 6/96 or the patient died. All other patients received 9 injections over 1 year. Mean number of treatments over 1 year = 8.6. Treatment Costs based on Assessment group assumptions (pages 129-133 and Table 1.10 of Evaluation Report).