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## Worldwide Pharmaceutical Operations

20<sup>th</sup> May 2008

Dear Mr Taylor,

### **Pfizer's Response to Appeal Chair Comments**

Pfizer acknowledge and thank the Appeal Chair for his review and consideration of the Appeal points presented by Pfizer in April 2008. Whilst we are pleased to learn that two points are arguable and will be heard at an oral hearing, we believe that further points are arguable and contest comments made by the Chair.

In summary, Pfizer maintain:

- The impact of treating the first eye on the QALY gain and cost savings due to blindness has not been modelled
- An arbitrary 50% uplift has been assumed to increase the cost-effectiveness to include treatment of the first eye
- The Institute have failed to perform sensitivity analysis to test the inherent uncertainty around the 50% uplift assumption
- Pegaptanib is an important treatment option, as an alternative to ranibizumab, to enable choice and equity for patients with pre-treatment vision between 6/12 to 6/24 "early treatment".

Pfizer are requesting access to a fully executable copy of the economic models in order to conduct sensitivity analyses to explore the impact of these assumptions.

The following clarifications to the Chair's comments support Pfizer's argument:

**1. We contest the Chair's comment that it is not legitimate to specifically focus on the cost-effectiveness of pegaptanib in the "early treatment" subgroup.**

We request that pegaptanib is given full consideration for this subgroup and decisions are made irrespective of the availability of ranibizumab.

**2. Response to Aspect 1.1:** There is a lack of transparency with regard to the calculation of cost effectiveness when the first eye is treated. An apparently arbitrary and non-evidence based figure of 50% increase has been applied to the cost/QALY for pegaptanib resulting in it not being cost-effective (£23,124 has become £34,700).

**a) The additional analysis referred to by the Appeal Chair does not provide the evidence supporting the 50% uplift.**

**b) No evidence or justification for the origin and application of the 50% uplift has been disclosed during Consultation.**

We request that Aspect 1.1 is re-considered as arguable.

**3. Response to Aspect 1.5:** No sensitivity analysis has been conducted for the final estimates of cost-effectiveness.

- a) Failure to perform sensitivity analysis on a pivotal assumption to the decision making should be considered procedurally unfair.**
- b) The equalities legislation needs to be taken into account for patients ineligible or unresponsive to treatment with ranibizumab.**

We request Aspect 1.5 is re-considered arguable with respect to the failure to perform sensitivity analysis. In addition, we request Aspect 1.5 is re-considered arguable with respect to whether the Institute has positively taken into account the inherent uncertainty in the £34,700 per QALY estimate for pegaptanib when considering its obligation to the equalities legislation.

- 4. Response to Aspect 2.1.** The Institute has made an error in its calculation for the cost effectiveness of pegaptanib when the first eye is treated.

**Application of the population average 50% uplift to an “early treatment” subgroup is inappropriate.**

We request that Aspect 2.1 is re-considered as arguable in light of the Chair’s interpretation for the 50% uplift.

All of these points are discussed in more detail in the following attachment.

Yours sincerely



## **ATTACHMENT: Pfizer's Response to Appeal Chair's Comments**

### **1. We contest the Chair's comment that it is not legitimate to specifically focus on the cost-effectiveness of pegaptanib in the "early treatment" subgroup.**

We note with concern the comments made by the Chair under Aspect 1.5.

*'I am also unpersuaded that it would be legitimate to focus on costs per QALY for the "early treatment" subgroup, as the committee appears to have decided, in light of its conclusions on the overall cost effectiveness of ranibizumab, that it was not appropriate to make recommendations based on subgroups at all.'*

As specified in the scope of the technology appraisal, a head to head comparison of pegaptanib and ranibizumab is not under consideration; therefore, the clinical and cost-effectiveness evidence for pegaptanib should be reviewed independently. Any conclusion made for ranibizumab should not have any influence on conclusions being made for pegaptanib. Full consideration of the cost-effectiveness should be given for all plausible subgroups of patients who may benefit from treatment with pegaptanib.

Pfizer re-iterate to the Appeal Committee that it has been shown that pegaptanib has the greatest capacity to benefit patients with pre-treatment vision between 6/12 and 6/24 and cost-effectiveness outputs have been provided to the Institute for this subgroup. The additional economic modelling, conducted by the Decision Support Unit, also concluded that this subgroup of patients will benefit most from treatment. The Appraisal Committee has concluded that it is plausible that people with better pre-treatment visual acuity are likely to benefit more from treatment than those with lower pre-treatment visual acuity (FAD 4.3.7). The conclusion drawn by the Chair is incorrect as it would be appropriate to recommend pegaptanib for a subgroup if the cost-effectiveness was demonstrated.

We request that pegaptanib is given full consideration for this subgroup and decisions are made irrespective of the availability of ranibizumab.

### **2. Response to Aspect 1.1:**

We do not agree with the Chairs comments and again strongly challenge the origin and application of the 50% uplift to the cost/QALY for the following reasons:-

#### **a) The additional analysis referred to by the Appeal Chair does not provide the evidence supporting the 50% uplift.**

The Chair's response to Aspect 1.1, directs us to pages 9-17 of the additional analysis commissioned from SHTAC dated September 21 2007, where he states that the 50% uplift and the 30% reduction in QALY gain are discussed in detail. Whilst the additional analysis explores the cost implication of treating the first eye, there is no analysis of the QALY gain or the saving on the costs of blindness. The reference to this evidence does not provide support for the 50% uplift figure, or the 30% QALY reduction. Furthermore, as stated in our Appeal, the authors state:

*‘We do not present any estimates of the expected outcomes for alternative scenarios of treating one or both eyes. Further work is required to determine the feasibility of modelling outcomes (in terms of visual acuity and quality adjusted life expectancy) and the costs associated with vision loss in patients who receive treatment in one or both eyes.’*

If the technical, independent experts at SHTAC have concluded that economic modelling for the first eye cannot be estimated, Pfizer challenge the Institute that no modelling has been performed for the first eye and there is a lack of transparency and considerable uncertainty for the 50% uplift. We request that Aspect 1.1 is re-considered as arguable.

**b) No evidence or justification for the origin and application of the 50% uplift has been disclosed during Consultation.**

Section 4.3.21 of the FAD states the 50% figure has been derived from an estimate that treatment of the first eye yields a 30% reduction in QALY gain, and a reduction in saving on the costs of blindness. These data are not referenced in any of the determinations or correspondence provided by the Institute throughout this Appraisal. Pfizer request that the Institute makes it explicit as to how they concluded that a figure of 30% QALY reduction would result when the first eye is treated. Requests for clarification on these assumptions have not been adequately addressed during the consultation and no evidence has been provided to Consultees.

We therefore conclude that it is not evidence based and the lack of justification and transparency in the derivation of this estimate is not in accordance with the technology appraisal process. We request that Aspect 1.1 is re-considered as arguable.

**3. Response to Aspect 1.5:**

**a) Failure to perform sensitivity analysis on a pivotal assumption to the decision making should be considered procedurally unfair.**

Pfizer would like to respond on the comment raised by the Chair:

*‘I am not persuaded that it is automatically procedurally unfair not to perform a sensitivity analysis’.*

Pfizer disagree with this statement in this instance and challenge the Appeal panel to reconsider this point.

Extensive sensitivity has been carried out throughout the appraisal process except for the pivotal assumption of the 50% uplift figure. It is best practice that any assumption that is uncertain and that has a significant impact should be subject to sensitivity analysis and we do not understand why this assumption should be treated differently to other assumptions in the process. All existing sensitivity analyses have been conducted on the cost-effectiveness of treating the second eye only. All of these analyses have been invalidated with the application of a single estimate of 50% uplift that drives the final decision. The Institute have not undertaken any sensitivity analysis around this figure of 50% despite previous requests by Pfizer (Pfizer response to second ACD dated December 2007). As we cannot assess the evidence for the 50% uplift we are also concerned as to the level of uncertainty, particularly considering the impact of the 50% uplift on the final cost-

effectiveness. Pfizer again requests that sensitivity analysis is undertaken by the Institute for the cost-effectiveness of treating the first eye.

**b) The equalities legislation needs to be taken into account for patients ineligible or unresponsive to treatment with ranibizumab.**

Pfizer would like to respond to the comment raised by the Chair seeking clarification why ‘*A failure to recommend pegaptanib for patients who are unsuitable for treatment with ranibizumab does not comply with equalities legislation*’

We have two comments to make on this point:-

Firstly, throughout the appraisal process consistent feedback has been submitted identifying a patient population that will be disadvantaged if pegaptanib is not available.

In the response to the second ACD, the Royal College of Ophthalmologists (RCO) stated: ‘*We wish that pegaptanib should be recommended for those patients who are unable to tolerate ranibizumab, through allergy or adverse reaction, or where such treatment with ranibizumab is clinically problematic*’

The RNIB also supported the above statement by the RCO. The Nominated Clinical Specialist 1 stated the following in response to the second ACD: ‘*I believe that clinicians and their patients should have the option to choose what treatment is in the patients best interest. Certainly at present ranibizumab will be the preferred treatment choice for most patients. However, some patients with wet AMD may not be able to tolerate ranibizumab, have an allergic reaction to this drug or may have a history of heart disease or stroke. One or more of these factors may make pegaptanib the preferred treatment option*’

The Nominated Clinical Specialist 2 provided the following support for the use of pegaptanib in their response to the second ACD:- ‘*Pegaptanib therapy  
This should in my opinion be available for selected cases where the use of ranibizumab is inappropriate. For example patients may develop hypersensitivity to ranibizumab, be unable to attend every 4 weeks or have no response to ranibizumab*’

In addition to this feedback, recent evidence is indicating the need for more than one anti-VEGF treatment. Tachyphylaxis in response to treatment with ranibizumab has been demonstrated and patients with a poor response to ranibizumab have been shown to yield a better response after switching to another anti-VEGF treatment.<sup>1,2</sup>

Secondly, the patient group identified above as ineligible or unresponsive to ranibizumab may already be partially blind which may amount to a disability. The lack of patient and physician choice may lead to additional disability and unnecessary blindness. We refer to the following paragraph from the NICE equality scheme:

**“the disability equality duty differs from other equality legislation in that it is not merely about treating disabled and non-disabled people in the same way. Rather, it**

**requires us to consider treating disabled people more favourably than other people, for example, by providing additional dedicated services or facilities, and does not restrict positive discrimination in favour of disabled people in any way.”**

Considering the inherent uncertainty around the cost-effectiveness estimate of £34,700 per QALY for pegaptanib for the “early treatment” subgroup, we argue that the Institute have not taken this into account to positively view the need for patient choice and equity for a treatment option that will benefit a disadvantaged patient group and avoid further disability.

We request Aspect 1.5 is re-considered arguable with respect to the failure to perform sensitivity analysis. In addition, we request Aspect 1.5 is re-considered arguable with respect to whether the Institute has positively taken into account the inherent uncertainty in the £34,700 per QALY estimate for pegaptanib when considering its obligation to the equalities legislation.

#### **4. Response to Aspect 2.1.**

**Application of the population average 50% uplift to an “early treatment” subgroup is inappropriate.**

Pfizer understands from the Chair’s comment that the 50% uplift figure is an average and originates from the whole population (i.e. patients with disease in their first eye only and patients with disease in their second eye). As we cannot ascertain from where the 50% estimate is derived, we maintain it is not clear whether the 50% uplift is to be applied to the whole population or only to the minority with disease in their first eye. We therefore maintain that it is possible that the 50% estimate could be applied to the minority of patients presenting with disease in their first eye. We agree with the chair that for the 50% to be an average and applied to the whole population, the estimate for the minority of patients being treated for the first eye would have to be very significantly higher.

Pfizer would like to present the following scenarios to the Chair in an attempt to explain the implications of applying a 50% uplift as an average for the whole population:

*Scenario 1: Patient A presents with disease in their second eye with vision 6/12 to 6/24.*

The majority of patients will present for treatment with disease in their second eye (as the ‘better-seeing’ eye, or second eye will have compensated for any loss of sight due to disease in the first eye). The Institute has provided a cost effectiveness estimate for pegaptanib of £23,124 per QALY for Patient A.

*Scenario 2: Patient B presents with disease in their first eye with vision 6/12 to 6/24.*

For the sub-group of patients who have early disease, a small percentage will present for treatment of the first eye. The Institute has not provided the cost-effectiveness estimate for Patient B. We argue that this is unacceptable. Table 1 therefore provides a calculated estimate for Patient B.

Table1

Subgroup	% Patient A Second eye	% Patient B First eye	CE of treating Patient A	% uplift to CE to treat Patient B*	CE of treating Patient B	CE for whole population
6/12 - 6/24	70	30	£23,124	267%	£61,664	£34,686

\* Calculated by taking average CE uplift of 50% for whole population

The current assumption by the Institute is that a 70/30 split exists between second eye/first eye presenters. Using this proportion, the population average of 50% uplift, and a cost/QALY for Patient A (second eye) of £23,124, we have been able to calculate the cost/QALY for Patient B (first eye) as £61,664 per QALY (Table 1).

Cost effectiveness calculations should be provided by the Institute for the population eligible for treatment. These calculations therefore very much depend on the proportion of Patient A's ('second eye presenters') and the proportion of Patient B's ('first eye presenters') who will present for treatment. Expert clinical opinion suggests that patients with disease in their first eye do not present with early stages of disease. It is therefore logical that only a fraction of the 30% of 'first eye presenters' will be eligible for pegaptanib within the subgroup of 6/12 to 6/24.

Since it is likely that fewer eligible patients will present with disease in their first eye in the 'early treatment' subgroup for pegaptanib, we present revised 'population average uplift' estimates in Table 2, below.

Table 2

Subgroup	% Patient A Second eye	% Patient B First eye	CE of treating Patient A	CE of treating Patient B	% uplift for whole population	CE for whole population
6/12 - 6/24	80	20	£23,124	£61,664	33%	£30,755
	85	15	£23,124	£61,664	25%	£28,905
	90	10	£23,124	£61,664	16%	£26,824

In conclusion there is no justification or modelling of data to support an elevation of the overall cost-effectiveness by 50%. A population average of 50% cannot be applied to the subgroup of 6/12 to 6/24 as the proportion of patients presenting with disease in their first eye is likely to be significantly less than 30% for the "early treatment" subgroup. As indicated in our Appeal letter, if the uplift applied was 25%, then the cost/QALY for pegaptanib would be £28,905.

We request that Aspect 2.1 is re-considered as arguable in light of the Chair's interpretation for the 50% uplift.

## **References**

1. Keane PA, Liakopolous S, Ongchin SC et al. Quantitative subanalysis of optical coherence tomography features after treatment with ranibizumab for neovascular age-related macular degeneration. IOVS In Press April 2008
2. Gasperinin JL, Fawzi A, Lam L et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularization. Association for Research in Vision and Ophthalmology Apr 2008.