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Pfizer Global Pharmaceuticals

Dear Dr Longson,

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

After consideration of the stakeholder responses to the additional economic re-analysis, Pfizer would like to acknowledge and thank the Appraisal Committee for issuing a second ACD.

Despite the additional re-analysis and considerable uncertainty concerning, in particular, where anti-VEGF treatments should be administered and the cost of treating the first eye, Pfizer are disappointed to learn that the Appraisal Committee have concluded that pegapatanib is not a cost-effective option to treat wet AMD. Pfizer are surprised and disappointed by this recommendation and are concerned that the Committee have made significant errors when arriving at this decision. Hence, Pfizer would like the Committee to address the following concerns:-

1. The ACD reports inadequate and insufficient estimates for the cost-effectiveness of pegaptanib in the subgroup of patients with wet AMD and a baseline visual acuity of 6/12 to 6/24
2. There is a lack of transparency as to the estimates on which the Committee have based their decision making. Several modelled scenarios for pegaptanib in the subgroup 6/12 to 6/24 present cost/QALY estimates below £30,000; including:
    a. Treatment for two year assuming a greater uptake in outpatients
    b. Treatment for two years for the better seeing eye
    c. Treatment for one year

    There is no clear justification in the ACD for why the Committee has rejected these scenarios.
3. For patients with high cardiovascular risk, it is important to maintain physician and patient choice with regards the potential safety advantage that pegaptanib, a selective anti-VEGF treatment, may offer when compared to a non-selective VEGF treatment for patients.

These points are explored in more detail in the attachment accompanying this letter.

In conclusion, we would recommend that the Committee reconsiders the weight of evidence for cost-effectiveness of pegaptanib versus the potential safety issues associated with a non-selective VEGF-A antagonist. 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.

Yours sincerely

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AWARDED TO PFIZER LIMITED

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ATTACHMENT

1. The ACD reports inadequate and insufficient estimates for the cost-effectiveness of pegaptanib in the subgroup of patients with wet AMD and a baseline visual acuity of 6/12 to 6/24

Pfizer are concerned that the Committee has given its negative decision for pegaptanib based on an inadequate and insufficient assessment of the modelling estimates for the subgroup 6/12 to 6/24.

Throughout the appraisal process, Pfizer has demonstrated that pegaptanib is a cost-effective treatment option over both one and two years for patients with wet AMD for the 6/12 to 6/24 sub-group. The Committee have also acknowledged that this is the most cost-effective subgroup.

The Committee have acknowledged that the Assessment Group model may inaccurately model the treatment effect of pegaptanib for this sub-group and Pfizer therefore support the additional modelling which was undertaken by the Decision Support Unit (DSU). This modelling approach resulted in a cost per QALY of £25,583 or £26,329 (year 3 disease modifying effect or Brazier utilities respectively). This assumes that 100% of procedures are conducted as a Day Case.

In the second ACD, Pfizer note with concern that it is unclear what the particular assumptions adopted by the Committee are as these are not explicitly stated in the document for this sub-group. The resulting cost/QALY estimates are not presented either. It is therefore hard to understand how a decision was made by the Committee in the absence of the relevant information being made available. Pfizer therefore request that all of the Committees assumptions and the cost/QALY outcomes are explicitly presented for the sub-group 6/12 to 6/24. Pfizer also requests that the Committee provides a copy of the DSU economic model which has been produced in support of the second ACD, as a fully accessible and working version.

Hence, as the second ACD has omitted to present some important scenarios for the sub-group 6/12 to 6/24, Pfizer has therefore conducted some additional analysis based on the best interpretation of the assumptions described in the second ACD. The outputs from this analysis are presented in Table 1, below and should assist the Committee to re-consider their initial decision for pegaptanib.

Table 1: ICER outputs for additional scenarios for the 6/12 to 6/24 subgroup using the DSU model.

Assumption	Incremental change to ICER	Resulting ICER
"Base Case" , i.e. DSU model Brown utilities Disease modifying effect 100% Day Case procedure		£23,104*
"Base Case" with disease modifying effect in Year 3 only	£2,479 increase	£25,583*
"Base Case" with Brazier utilities	£3,225 increase	£26,329*
"Base Case" with Proportion of patients going blind who receive 25% community care	£3,496 decrease	£19,608**
"Base Case" when 25%	£2,567 decrease	£20,537***

procedures undertaken in Outpatient, 75% Day Case		
"Base Case" with treatment of first and second eye	50% increase to "Base Case"	£34,656

*Table 2, page 12 DSU report Sept 2007
** Table 3, page 13 DSU Report Sept 2007
*** calculated by Pfizer as the cost QALY using the DSU model for the 6/12 to 6/24 subgroup has not been provided by the Committee

Pfizer would like to challenge the Committee on three of the assumptions which it has adopted in its modelling which may have led to the negative recommendation:

- The split of patients treated as an Outpatient is 25% and those treated as a Day Case is 75%

The Committee have failed to present the cost/QALY output when the above split is assumed. Pfizer request that this is provided.

Pfizer are confident that as more procedures are performed in the less costly Outpatients setting, pegaptanib can be delivered cost-effectively. Pfizer have demonstrated that the cost/QALY is highly sensitive to the proportion of patients treated in Outpatient or Day Case settings. For example, sensitivity analyses, presented to the Committee by Pfizer, when all procedures are undertaken as an outpatient resulted in the cost/QALY being £12,826 compared to a cost/QALY of £23,104 when all procedures are undertaken as a Day Case (Table 1).
The Committee has concluded in its second ACD that ranibizumab should be recommended to treat all patients with AMD. Over the last year or more, many Primary Care Trusts have been waiting for the NICE guidance on anti-VEGF treatments before developing an effective and efficient AMD service to deliver anti-VEGF treatments. The current service provision in England and Wales is therefore under-developed and in its infancy and probably led the Committee to conclude that only 25% of administrations would occur in Outpatient setting compared to 75% of administrations occurring in the Day Case setting. Service provision will need to change over the coming months and years to cope with the increase in patient numbers. This will lead to economies of scale whereby delivery of pegaptanib will also be a cost-effective option. Implementation of the NICE guidance will require the service to expand; it is therefore logical to assume that new and existing patients will be treated in the less costly Outpatient setting. As a point of reference, the Committee may want to take note of the situation in Scotland where the service provision for anti-VEGF's has been established longer and it is now more usual for the administrations to occur in the Outpatient setting. For these reasons the negative decision for pegaptanib is therefore partly dependent on the evolution of services; an important fact which the Committee has failed to take into consideration when making their decision and thereby have stifled the introduction of an innovative medicine that has the potential to be delivered cost-effectively in the NHS.

- Assumption that the cost of treating the first eye will increase the cost/QALY by 50%

The Committee has estimated that the cost per QALY for pegaptanib (and ranibizumab) would increase by 50% if the first eye was to be treated as opposed to the better-seeing eye only. There is no evidence or justification supporting this estimate and importantly no testing of the impact of the uncertainty associated with the 50% estimate on the cost/QALY. Pfizer consider the figure of 50% is an inappropriate one to apply to the sub-group 6/12 to 6/24 since these patients typically

present at a later stage of disease. It is therefore unlikely that VA will lie between 6/12 and 6/24 in the first eye. The more likely scenario for this sub-group will be patients presenting with disease in their second eye and requiring treatment. As demonstrated in Table 1, pegaptanib is cost-effective when the second eye is treated and therefore pegaptanib should be recommended as a treatment option for the second eye.
Pfizer therefore conclude that the availability of these medicines should not be dependent on this estimate. This decision should be consistent with the previous NICE guidance for photodynamic therapy, where no adjustment was made for treating the first eye.

- Use of Brazier utilities.

Table 1 above demonstrates that if Brazier utilities are adopted the cost/QALY increases by £3,225. The second ACD states that the use of Brazier utilities for pegaptanib will increase the cost/QALY by £8,000 (Second ACD section 4.2.4.5). Pfizer request that the Committee clarifies this and corrects the error if appropriate.

2. There is a lack of transparency as to the estimates on which the Committee have based their decision making.

Throughout this Appraisal, the Committee have chosen to undertake at least four modelling approaches (from the manufacturer Pfizer, the Assessment Group, the Decision Support Unit and further modelling outputs from the Assessment Group) which have resulted in numerous scenarios being modelled and numerous cost/QALY outputs being available. Pfizer conclude that the wealth of outputs has generated a confused view of the appropriate cost-effectiveness estimates for pegaptanib. Key modelling scenarios and resulting outcomes appear to have been omitted from the ACD and therefore may not have been made available to the Committee to inform and guide them in their decision making.
Pfizer have confidence that many scenarios modelled have demonstrated that pegaptanib is cost-effective for both two years treatment and one year treatment (whereby it is even more cost effective). Pfizer would like to draw the Committees attention to these scenarios, and the cost/QALY outputs are presented in Table 2 below.
Pfizer conclude that pegaptanib is a cost effective treatment option for patients with wet AMD and a baseline VA of 6/12 to 6/24. These outputs are for the treatment of the second eye; however some remain below £30,000 per QALY even applying the 50% estimate for treating the first eye.

Table 2: ICER outputs for some relevant scenarios for pegaptanib, 6/12 to 6/24 sub group

Scenario	Utility	Location	Disease Modifying Effect	Treatment Duration	ICER
DSU model	Brown	100% Day Case	100%	2 years	£23,104
DSU model	Brown	100% Outpatient	100%	2 years	£12,826*
DSU model	Brown	100% Day Case	Year 3	2 years	£25,583
DSU model	Brown	25% outpatient 75% Day Case	100%	2 years	£20,537*
DSU model	Brazier	100% Day Case	100%	2 years	£26,329
Pfizer model	Brown	100% Outpatient	100%	2 years	£15,068
Pfizer model	Brown	100% Outpatient	100%	1 years	£7,580

*calculated by Pfizer as the cost QALY using the DSU model for the 6/12 to 6/24 subgroup has not been provided by the Committee

3. **For patients with high cardiovascular risk, it is important to maintain physician and patient choice with regards the potential safety advantage that pegaptanib, a selective anti-VEGF treatment, may offer when compared to a non-selective VEGF treatment for patients.**

Despite the Committee acknowledging that ranibizumab's Summary of Product Characteristics shows that the overall incidence of arterial thromboembolic events from the MARINA, ANCHOR and PIER trials was higher for patients treated with ranibizumab 0.5 mg (2.5%) compared with the control arm (1.1%), patient and physician choice has been restricted. The wet AMD patient population is generally older and present with co-morbidities. An interim analysis of data from the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) study showed a "higher incidence of stroke in the 0.5-mg dose group compared with the 0.3-mg dose group (1.2% vs. 0.3%, respectively $P = 0.02$). " Additionally, it was noted that "patients with a history of stroke appeared to be at higher risk for a subsequent stroke"[1]. Pfizer would like to point out to the Committee that these cardiovascular safety signals described for ranibizumab are based on one year data from the PIER and ANCHOR trials and less than one year of treatment (230 days) for the SAILOR interim analysis. Only the MARINA trial reported two year safety data. The outstanding second year safety data from PIER and ANCHOR are now becoming available and may provide additional evidence of this potential cardiovascular safety risk.

Based on the above information, Pfizer therefore conclude that ophthalmologists should have access to pegaptanib to facilitate an informed decision between treatment options for each individual patient.

In addition it is important that treatment choice is available where Lucentis may be contraindicated for clinical reasons other than cardiovascular risk. Again, referring to ranibizumab's Summary of Product Characteristics section 4.3 states that patients with active severe intraocular inflammation are contraindicated. In section 4.4 "Special warnings and precautions for use", it is stated that *"As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. Patients should be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation."*

In consideration of all the reasons presented above, both anti-VEGF treatments need to be available to support and facilitate physician and patient choice.

REFERENCES

1. Food and Drug Administration (FDA). FDA drug alert; Genentech, January 2007a. Available at: http://www.fda.gov/medwatch/safety/2007/Lucentis_DHCP_01-24-2007.pdf. Accessed Oct 26, 2007.