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Pfizer Global Pharmaceuticals

RE: Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.

Pfizer would like to acknowledge and thank the Appraisal Committee for reconsidering the modeling approach originally undertaken by Pfizer. The resulting re-analysis which the Appraisal Committee requested the Decision Support Unit (DSU) to undertake for pegaptanib more accurately models the cost effectiveness of pegaptanib as it uses individual patient level data and more accurately predicts the probability that a patient may lose or gain vision as this is dependant on their pre-treatment visual acuity (VA).

Whilst Pfizer acknowledge that the revised analysis from the DSU is structurally accurate and demonstrates that pegaptanib could be cost effective in a particular sub-group (i.e. Subgroup 1, when VA is between 6/12 and >6/24), we have three concerns regarding data assumptions used in the model which we would like the Appraisal Committee to take into consideration. All of these issues are summarised below with further detail provided in the attachment.

1. **Cost of Blindness**

Pfizer disagree with the cost of blindness which has been assumed for the base case. As highlighted by the RNIB and other consultees, there is considerable underestimation of the appropriate costs of blindness. The base case costs used by the DSU resulted in an ICER of £23,104 for Subgroup 1 (VA 6/12 to >6/24). The new estimates from the RNIB have been incorporated into the model individually by the DSU resulting in improved cost effectiveness outputs for pegaptanib (ICERs range from £19,608 to £22,737). This should still be challenged. All of the revised values provided by the RNIB to the Appraisal Committee should be applied to the model simultaneously. When this is done, the ICER for pegaptanib is as low as £14,416.

The ICER presented by the DSU of £23,104 could be considered to be at the upper limit of cost-effectiveness for pegaptanib and the lower limit of cost effectiveness could be considered to be £14,416. Both these estimates should be made available at the Committee Meeting.

2. **Cost of Administration**

a) Real-Life Setting for Intravitreal Injections

Pfizer challenge the assumption in the base case that the administration of pegaptanib will always be undertaken as a Day Case (in theatre), and not as an outpatient procedure. The DSU calculated the ICER to be £23,104 when administration is delivered for everybody as a Day Case.

However, there is considerable uncertainty concerning where the administration of pegaptanib will take place. The choice of location has a considerable influence on the cost effectiveness output particularly if it is assumed that the procedure is undertaken as a more costly Day Case procedure. Three other stakeholders (the RNIB, the RCO and Novartis) have already provided evidence to NICE that the procedure does not need to be undertaken as a Day Case and instead can be routinely administered as an out-patient procedure which is less costly and less resource intensive.
When cost effectiveness modeling is based on real-life practice, i.e. when the injection is often undertaken as an outpatient procedure, the ICER for pegaptanib improves. If it is assumed that only

25% of procedures are undertaken as an out-patient the ICER is £20,537 (Subgroup 1). The ICER improves significantly if all procedures are undertaken as an outpatient; the ICER becomes £12,826.
The cost effectiveness range therefore for pegaptanib, for Subgroup 1, may lie between £12,826 and £23,104. Both these estimates should be made available at the Committee Meeting.

b) Relative Costs of Intravitreal Injections versus other Ophthalmic Procedures
There is another important point to consider in relation to the assumed costs for a Day Case. When these costs are put into context with other more invasive ophthalmic and surgical procedures, the cost for Day Case procedure of £781 could be considered out of line and unrealistically high. This procedure is less invasive yet more costly than the cost for Phakoemulsification Cataract Extraction and Insertion of lens (HRG code B13) which has an NHS reference tariff of £764 assigned to it.

3. Disease Modifying Effect

There is inconsistency in the evidence-based approach between pegaptanib and ranibizumab. The disease modifying effect is derived directly from a randomised controlled trial and it is supported by leading methodologists that have published their findings in a peer reviewed journal[1]. To question the validity of this is in direct contrast to the Appraisals Committee's approach to undertake additional modeling for ranibizumab, which is clearly not evidence based. The Assessment Group's report provides additional cost effective analysis when reduced injection frequency schedules are modeled for ranibizumab. The assumption has been made that the same efficacy results from a reduced injection schedule as is demonstrated when ranibizumab injections are given every 4 weeks for two years. This assumption by the Appraisal Committee is based on unpublished, limited observational data. Data recently published in May 2007[2] does not support this assumption; a decrease in dosing frequency from monthly to an "as needed" basis, has demonstrated a decreasing trend in visual acuity.

The disease modifying effect for pegaptanib should be accepted in the cost effectiveness modeling.

In summary, age related macular degeneration (AMD) may ultimately lead to blindness, and prior to the introduction of these two treatments there was significant unmet need. In consideration of all of the clinical evidence, the safety profiles (in particular the potential safety risk associated with long term treatment with a non-selective VEGF inhibition which becomes a serious consideration in a population of AMD patients who are likely to be elderly and have cardiovascular co-morbidities) and the cost effectiveness, access to both VEGF treatments should be made available to facilitate physician choice to deliver the most appropriate treatment to their patients.

Pfizer therefore conclude the following:-

- The DSU model is valid and should be used based on RCT evidence of a disease modifying effect
- Significant uncertainty exists around costs of blindness and administration. The assumptions currently used by the Assessment Group provide high estimates of cost/QALY
- Use of alternative estimates from stakeholders provide lower estimates for pegaptanib
- Lower estimates of cost/QALY for pegaptanib from the DSU model with all the RNIB costs of blindness or with an outpatient administration should be made available to the Appraisal Committee

ATTACHMENT

1. Cost of blindness

The RNIB have provided alternative robust cost of blindness values (Table 9, page 9 of the Assessment Group report). Pfizer note that the Assessment Group (AG) have taken each of the revised values in turn and incorporated them into the modeling via a univariate approach (page 13, DSU report). For each value, and in particular the uptake of Community Care, the cost effectiveness improves for pegaptanib, in particular for Sub Group 1 (VA between 6/12 to >6/24). These improved ICERs range from £19,608 to £22,737. Since all of these revised RNIB values could be considered to more accurately reflect the costs of blindness, Pfizer have performed some additional cost effectiveness analysis when all revised values are applied simultaneously as the base case assumption. The ICER outputs are presented in the table below for the various sub-groups as defined by their visual acuity range:-

Table 1: ICER outputs when alternative cost of blindness values are inputted

	Inc Cost £	Inc QALY	ICER £
Assessment Group Base Case Results (Table 4.22 of TAR)	8,062	0.26	30,986
All AG sensitivity analysis values adopted (AG Incr QALY estimates applied*)	7,172	0.26	27,656
All AG sensitivity analysis values adopted (Pfizer Incr QALY estimates applied**)			
6/12 to 6/95	7,172	0.297	24,148
6/12 to < 6/24	6,167	0.428	14,416
6/24 to > 6/60	7,736	0.244	31,679
6/60 to > 3/60	8,025	0.090	88,969

*Taken from TAR, Table 4.22
**Taken from DSU report, p15
The A.G sensitivity analysis examined Community Care uptake at 17% and 25%; values in the table represent 25% uptake.

In such a scenario, for Sub-group 1, the cost-effectiveness of pegaptanib lies below the £20,000 threshold; the incremental cost per QALY is £14,416. This ICER could represent the lowest valid cost effectiveness outputs, and the DSU value of £23,104 could represent the upper limit of cost effectiveness.
We would therefore urge the Committee to reconsider their assumptions and recommend that all of the revised RNIB costs of blindness are assumed for the base case.

Pfizer also considered the impact of just one of the items, the uptake of Community Care. In the AG report, the sensitivity univariate analysis for this item assumes a base case of 6% uptake and 25% for the upper limit. An alternative piece of research by Meads et al[3] reports that the upper limit could be a 40% uptake by patients. The cost effectiveness for the 6/12 to > 6/24 group improves when the value of 40% is applied; the ICER is £15,537. This compares with an ICER of £23,104 when it is assumed that the uptake is 6%, and an ICER of £19,608 when it is assumed the uptake is 25%.

2. Cost of Administration

a) Real-Life Setting for Intravitreal Injections

There is considerable uncertainty concerning where the intravitreal injection should take place, either as a Day Case in a theatre (much more costly) or in the out-patient setting (less costly). In the Assessment Group Report page 29, an acknowledgement is made by the Committee regarding the responses they have received from stakeholders who were concerned that "costing the injection procedure as a Day Case was adopting a unit cost at the extreme high end of possible values". Pfizer do not consider that administration of pegaptanib will need to occur in theatre. Both the RNIB and the RCO do not support the assumption that a theatre procedure is required. Pfizer therefore consider that the cost effectiveness outputs provided for pegaptanib in the additional analyses represent the highest limit of what would occur in real life practice.
A research study completed by Novartis, estimated that 25% of procedures are carried out in the out-patient department and 75% are carried out in the theatre. This split has been applied in the sensitivity analysis which has been undertaken by the Assessment Group for ranibizumab but has not been presented for pegaptanib using the DSU model
.
Pfizer are concerned that the Assessment Group are continuing to adopt the assumption that the procedure is conducted as a Day Case despite considerable evidence to the contrary. The Day Case procedure significantly, and negatively, influences the cost effectiveness for pegaptanib.

Pfizer would urge the Committee to reconsider the base case administration costs which they have assumed in the additional DSU modeling. The re-analysis provided by the DSU, using costs sourced from the Assessment Group, assumes a theatre procedure, and hence the higher costs (£395) have been applied. If it is assumed that it is undertaken as an Outpatient, the cost is much lower (£90.20).

Pfizer have conducted some additional analysis when it is assumed the procedure is done as an out-patient.

Table 2: ICER outputs when Administration costs are varied

	Base Case 6/12-6/95	Subgroup 1 (6/12 to >6/24)	Subgroup 2 (6/24 to >6/60)	Subgroup 3 (6/60 to >3/60)
Administration costs				
Assessment Group Base Case Costs: 100% costed as out-patient	£20,755	£12,826	£28,512	£62,557
Assessment Group: Injection costed as 75% day case, 25% outpatient	£31,864	£20,537	£42,073	£98,357
Assessment Group: Injection costed as 100% day case	£35,614	£23,104	£46,588	£110,223

This additional modeling clearly demonstrates that the cost effectiveness significantly improves when the procedure is undertaken as an outpatient. If 100% of the procedures are assumed to be an outpatient, the ICER for the sub-group with VA between 6/12 to >6/24 is £12,826. If the values from the Novartis survey (25% are out patient procedures) are assumed, the ICER is £20,537.

b) Relative Costs of Intravitreal Injections versus other Ophthalmic Procedures

Pfizer would also like to highlight to the Committee how their assumed cost for a Day Case compares with other more invasive ophthalmic and surgical procedures. These values are presented in Appendix 1 whereby it can be shown that the Day Case, (total = £781) is more costly than three HRG's (particularly HRG B13: phakoemulisfication cataract extraction and insertion of lens) which may be considered to be more invasive and resource intensive than the administration of an intravitreal injection.

3. Disease Modifying Effect

Pfizer recommend that the Assessment Group accept the disease modifying effect for pegaptanib in their cost effectiveness modeling. This analysis originates from robust evidence directly from pivotal randomised controlled trial data. The methodology underpinning this effect has been analysed by leading methodologists and has been published in a peer-reviewed journal[1].

Since an evidence-based approach has always been the bedrock of appraisals conducted by NICE, it is with interest and concern that Pfizer reviewed the Assessment Group re-analysis for ranibizumab. In this re-analysis, the Assessment Group has assumed the same efficacy for a reduced injection frequency schedule for ranibizumab and cost effectiveness outputs are provided when this has been modeled. Pfizer would like to challenge the assumption that reduced injections would lead to the same efficacy benefit as a 4 weekly schedule for two years, as reported from the pivotal ANCHOR and MARINA trials which support the ranibizumab license. The assumption that a reduced injection frequency will produce identical efficacy as the 4 weekly schedule is not evidence based. Another study, the PIER study, also supported the license, however this study used a reduced injection frequency (every four weeks for three months, and then one injection every 3 months thereafter) which demonstrated reduced efficacy; patients returned to their baseline VA after one year. This tendency for vision loss has also been reported more recently in an open label extension study (FVF2508g) of the MARINA and ANCHOR trials, which was presented as a poster at the Association of Research in Vision and Ophthalmology annual meeting in May 2007.[2] Study results reported in the poster suggest that following a decrease in dosing frequency from monthly to an "as needed" basis, at the start of the extension phase, there is a subsequent decreasing trend in visual acuity. This trend is observed despite an additional increase in the dose from 0.3 to 0.5mg ranibizumab. Furthermore, this potential for loss of VA gains acquired through monthly dosing is acknowledged by the authors of the poster.

The disease modifying effect for pegaptanib should be accepted in the cost effectiveness modeling. Pfizer would like to seek clarification as to why the Assessment Group has assumed the same efficacy when a reduced injection schedule is initiated for ranibizumab. Randomised controlled trial data does not support this. An inconsistency is apparent as to whether NICE are adhering to their principal of evidence based medicine to support key decisions for pegaptanib versus ranibizumab.

REFERENCES

1. Mills E, Heels-Ansdell D, Kelly S and Guyatt G.A randomized trial of Pegaptanib sodium for age-related macular degeneration used an innovative design to explore disease-modifying effects Journal of Clinical Epidemiology, Volume 60, Issue 5, May 2007, 456-460

2. Antoszyk A, Shapiro H, Shams N. Long-term (3 year) experience with Lucentis® (ranibizumab) in patients with neovascular age-related macular degeneration. Poster presented at: Annual meeting of ARVO; May 6-10 2007.

3. Meads C, Hyde C. What is the cost of blindness? British Journal of Ophthalmology, 2003 Volume 87, 1201-1204

APPENDIX 1

The table below provides a ranking of some ophthalmology procedures and their associated NHS tariffs. The table also includes the Assessment Group costs and the RCO costs for administration of an anti-VEGF treatment, which have been used in the cost effectiveness modelling.

HRG Code	National Schedule of Reference Costs - NHS Trusts **Day Cases HRG Data** Common (> 100,000 FCEs) and ophthalmic (> 1,000 FCEs)	**£**
A.G	VEGF Treatment only: assuming injection in out-patient dept	255
F98	Chemotherapy with a Digestive System Primary Diagnosis	277
F06	Diagnostic Procedures, Oesophagus and Stomach	418
S27	Malignant Disorder of the Lymphatic/ Haematological los <2 days	426
B32	Non Surgical Ophthalmology with los <2 days	433
L21	Bladder Minor Endoscopic Procedure w/o cc	442
A.G	VEGF Full Assessment: assuming injection in out-patient dept	477
F35	Large Intestine - Endoscopic or Intermediate Procedures	490
B26	Glaucoma / Uvea Low Complexity	506
B15	Other Lens Surgery Low Complexity	513
A.G	VEGF Treatment only: assuming operating theatre	560
B29	Surgical Retina Low Complexity	561
RCO	VEGF Tx Only: Royal College of Ophthalmologists	565
A07	Intermediate Pain Procedures	576
J37	Minor Skin Procedures - Category 1 w/o cc	605
B19	Orbit / Lacrimal Low Complexity	620
B16	Oculoplastic Low Complexity	636
B22	Cornea / Sclera Low Complexity	658
C58	Intermediate Mouth or Throat Procedures	663
RCO	VEGF Full Assessment: Royal College of Ophthalmologists	677
B28	Glaucoma / Uvea High Complexity	742
B13	Phakoemulsification Cataract Extraction and Insertion of Lens	764
B17	Oculoplastic Intermediate Complexity	770
A.G	VEGF Full Assessment: assuming operating theatre	781
B27	Glaucoma / Uvea Intermediate Complexity	797