



Worldwide Pharmaceutical Operations

16th April 2008

Dear Dr Longson,

Appeal by Pfizer Limited against the Final Appraisal Determination of pegaptanib sodium for age-related macular degeneration by the National Institute for Health and Clinical Excellence

Pfizer have reviewed the Final Appraisal Determination and all of the supporting information which has resulted in a negative decision for pegaptanib sodium. Pfizer would like to formally notify the Institute that we are appealing against this decision.

Pfizer have provided robust evidence throughout this appraisal which has demonstrated that pegaptanib is a cost-effective treatment option for the sub-group of patients with wet age-related macular degeneration who have visual acuity between 6/12 and 6/24.

We are appealing on two grounds of appeal, as laid out in the 'Technology Appraisal Process: Guidance for Appellants':

Ground 1:

The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process

Ground 2:

The Institute has prepared guidance which is perverse in the light of the evidence submitted

The attachment accompanying this letter presents the aspects and basis for our appeal which relate to these grounds.

Yours sincerely

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Appeal by Pfizer Limited against the Final Appraisal Determination of pegaptanib sodium for age-related macular degeneration by the National Institute for Health and Clinical Excellence

Pfizer Limited disagrees with the Institute's appraisal of pegaptanib sodium as presented in the Final Appraisal Determination (FAD), 26th March 2008. We therefore provide formal notification of our appeal for pegaptanib to be made available for the sub-group of patients who have visual acuity between 6/12 and 6/24. The Institute has acknowledged it is plausible that this sub-group is likely to benefit more from treatment with pegaptanib than people with lower pre-treatment visual acuity. A full evaluation of our appeal for pegaptanib for this sub-group of patients is therefore warranted. Pfizer wish to make it clear that they do not wish to delay implementation for treatment with ranibizumab which has been recommended in the FAD.

The three areas which we are appealing on relate to:-

- The unfair and perverse way in which an arbitrary 50% increase has been applied for treatment of the first eye,
- Failure to take into account consultee feedback on the appropriate current and most likely future location for the anti-VEGF injection procedure,
- Denied patient and physician choice for access to pegaptanib due to the failure to fully take into account uncertainty and equity issues.

We are appealing on the following grounds:-

Ground 1

The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process

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).

Aspect 1.2 The impact on the cost-effectiveness of treating a patient's first eye has been over-emphasised, since only 30% of patients present with disease in their first eye.

Aspect 1.3 There is inconsistent decision making by the Institute regarding the impact of treating the first eye in this Technology Appraisal compared to the previous Technology Appraisal in 2003 for photodynamic therapy.

Aspect 1.4 The Institute has acted unfairly in reaching its decision by not taking into account consultee feedback on the way the NHS infrastructure will evolve following implementation of the guidance.

Aspect 1.5 No sensitivity analysis has been conducted for the final estimates of cost-effectiveness. It is therefore not possible to determine whether estimates for pegaptanib overlap those for ranibizumab.

Ground 2

The Institute has prepared guidance which is perverse in the light of the evidence submitted

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

Aspect 2.2 The Institute has failed to take into account consultee feedback that significantly more than 25% of anti-VEGF treatments are currently administered in Outpatients facilities and this will rise in the future.

GROUNDS OF APPEAL

Pfizer appeal against the guidance in the FAD on the following grounds:-

GROUND 1: PROCEDURAL UNFAIRNESS

“The institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute’s Guide to the Technology Appraisal Process”

Pfizer have five aspects to appeal which relate to this particular Ground for Appeal.

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).

Basis for Appeal

- The negative decision for pegaptanib in the FAD has resulted from a decision by the Institute to apply a 50% uplift to the cost/QALY calculation for pegaptanib, to take into account a patient’s first eye being treated. The wording in the FAD, section 4.3.21 states that:

‘...the Committee agreed that an expected cost per QALY for a first eye strategy would be about 50% higher than for treating the better seeing affected eye’

- When applying this 50% uplift, the cost/QALY for pegaptanib increases from £23,124 to £34,700. Pfizer therefore conclude that this 50% uplift is a critical factor that determines whether or not pegaptanib is considered cost effective.
- In Pfizer’s response to the second ACD in December 2007, we challenged this assumption of a 50% uplift stating that:

‘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’

- In publishing the FAD in March 2008, the Institute has not addressed the uncertainty associated with this figure. An estimate of 25% instead of 50% would bring the cost/QALY for pegaptanib down to £28,905.
- No evidence or justification supporting this fundamental assumption was provided by the Institute in the FAD. The only response was in relation to the appropriateness of treating the first eye. Whilst Pfizer wish to make it clear that we support treating patients with disease in their first eye, the Institute has not satisfactorily explained where this value of 50% originated.
- The lack of transparency regarding the calculation of cost-effectiveness when a patient’s first eye is treated is not in line with one of the Institutes Guiding principles, as stated in the Guide to the Methods, section 5.2

‘All relevant evidence needs to be assembled systematically and synthesised in a transparent and reproducible manner.’

It is of vital importance to this Appraisal that the Institute provides the evidence for applying such an arbitrary and random figure which has resulted in pegaptanib no longer being cost-effective.

ASPECT 1.2. The impact on the cost-effectiveness of treating a patient's first eye has been over-emphasised, since only 30% of patients present with disease in their first eye.

Basis for Appeal

- In the Additional analysis commissioned by the NHS R&D HTA Programme on behalf of NICE, September 2007 the Institute concluded (from consultee feedback) that only a minority (30%) of the wet AMD population will present with disease in their first eye only; the vast majority (70%) present with disease in their second eye also.
- The cost/QALY estimate for pegaptanib of £23,124 is therefore applicable to the vast majority of patients who present with disease in their second eye. Application of the 50% uplift on this figure to account for the minority of patients presenting with disease in their first eye is not evidence-based and over-emphasises the weighting that should be applied to the evidence for the cost-effectiveness of treating the first eye.
- In addition, the Appeal Committee should be mindful that the Additional analysis commissioned by the NHS R&D HTA Programme on behalf of NICE in September 2007, identified major uncertainties in modelling the cost and outcomes of treating one or both eyes. In their overview they 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.'

- Pfizer conclude that the Institute has acted unfairly, according to their own Guidance by giving a higher weighting to a theoretical, non evidence based figure of 50% and applying it to the economic modelling for pegaptanib.
- The Institute acknowledges in its Guide to Methods, Section 6.2.6.5 that evidence derived from a theoretical evidence base should be given less weighting:

'...the Appraisal Committee is likely to give greater weighting to evidence on cost effectiveness that is underpinned by the best quality clinical data than to evidence that is dependant to a large extent on theoretical grounds alone'.

The Appeal Committee should carefully consider whether the inflation of the cost/QALY by an arbitrary 50% is fair given the fundamental impact on this appraisal. NICE prides itself on sourcing the most robust evidence when undertaking Technology Appraisals; in this Appraisal that has taken two years, all of the evidence-based analysis has been invalidated with the application of a single estimate that overrides the final decision.

ASPECT 1.3. There is inconsistent decision making by the Institute regarding the impact of treating the first eye in this Technology Appraisal compared to the previous Technology Appraisal in 2003 for photodynamic therapy.

Basis for Appeal



- The proposed guidance outlined in the FAD is inconsistent with the decision making process which was applied to the previous Appraisal in 2003 for photodynamic therapy (PDT).
- The cost-effectiveness calculation in 2003 was not inflated to take into account treatment of the first eye, but instead a recommendation for treatment of the first eye was issued by NICE based on economic results from models treating the second (better seeing) eye.
- This inconsistency of approach is in conflict with the Institutes own guidance; ‘consistency between submissions is needed to allow comparison between appraisals of different technologies and over time’ (Guide to the Methods Section 5.2.1.1)

‘It is crucial that the Appraisal Committee’s decisions are seen to be consistent across appraisals and that the views of the consultees in the appraisal are taken into account’ (section 6.1.3)

Pfizer conclude that the Institute has acted unfairly due to the inconsistency existing between these two Technology Appraisals. It is not possible for the NHS to determine appropriate positioning between ranibizumab and PDT or whether pegaptanib would be a cost-effective alternative to PDT for any particular sub-group of patients.

ASPECT 1.4. The Institute has acted unfairly in reaching its decision by not taking into account consultee feedback on the way the NHS infrastructure will evolve following implementation of the guidance.

Basis for Appeal

- The proposed guidance outlined in the FAD is partly based on assumptions by the Institute as to where the intravitreal procedure for these treatments will take place; either as a more costly Day Case procedure in theatre (where the injection procedure costs £395) or as a less costly Outpatient procedure (where the injection procedure costs £90.20).
- The conclusion in the FAD gave the final estimate, for current practice to be 75% of procedures to be undertaken as a Day Case and 25% to be undertaken as an Outpatient. Pfizer uphold their challenge to this assumption which has not been adequately addressed by the Institute throughout this appraisal.
- Pfizer conclude that the Institute has acted unfairly by not taking into account consultee feedback on where the most likely setting will be for this procedure **in the foreseeable future**. The Institute itself acknowledges in their own Guide to the Methods Section 5.10.2 that the **expected appropriate** implementation and uptake rates of the appraised technologies should be supplied:-

‘Evidence-based estimates of the current baseline treatment rates and expected appropriate implementation/uptake/treatment rates of the appraised and comparator technologies in the NHS should be supplied.’

- Pfizer conclude that the Institute are not acting fairly as they are not following their Procedural Guidance; by assuming that 75% (the vast majority) of procedures will occur in the more costly Day Case setting for the foreseeable future. This decision does not take into account the impact of the necessary implementation and funding to deliver the final NICE guidance to make ranibizumab available in the NHS.
- The evidence provided to the Institute indicated that the ‘expected appropriate uptake’ of these treatments would result in far more cases taking place in the Outpatient setting:

In their response to the first ACD in July 2007, the Royal College of Ophthalmologists (RCO) provided the Institute with an assessment from their members as to what the future real-life setting would be:

'...once funding has become available 90% of treatments will be offered as an out-patient procedure.'

NHS Quality Improvement Scotland (NHSQIS) commented in their response to the second ACD in December 2007 that:

'The non-drug costs (i.e. the costs of administration and monitoring) are still overestimated in my opinion. There should be encouragement to establish the procedure as an Outpatient procedure (75% day case is far too high).'

- The Institute has acted unfairly in its failure to take into account consultee feedback which supports where the anti-VEGF procedure will be administered. This is in conflict with their own guidance, as stated in the Guide to the Methods Section 5.2.1.1

'It is crucial that... the views of the consultees in the appraisal are taken into account' (section 6.1.3)

Pfizer concludes that the weight of feedback will leave the Appeal Committee in no doubt as to the most likely location for where the majority of injection procedures will take place in future following implementation of the final guidance, and that this will be in an Outpatient setting.

ASPECT 1.5. No sensitivity analysis has been conducted for the final estimates of cost-effectiveness. It is therefore not possible to determine whether estimates for pegaptanib overlap those for ranibizumab.

Basis for Appeal

- The proposed guidance as outlined in the FAD has been based on decisions concerning some questionable assumptions as outlined in the previous sections (the 50% uplift and the 75% Day Case). Pfizer have therefore concluded that the Institute has acted unfairly in making their decision without assessing the uncertainty in these assumptions.
- In addition, no sensitivity analysis has been undertaken on the final cost/QALY estimates to address the uncertainty in the final point estimates.
- Pfizer requests that the Appeal Panel considers whether the Institute has acted fairly when considering only the final cost/QALY point estimates.
- The cost/QALY outcomes for ranibizumab (minimally classic or occult no classic lesions) and pegaptanib ('early treatment' subgroup) were quoted as £29,900 and £34,700 respectively. The difference between the two treatments is only 14% (£4800).
- This small difference between point estimates has resulted in ranibizumab being recommended and pegaptanib not being recommended.
- The uncertainty associated with the point estimates has not been explored by the Institute and this is in direct conflict with their own guidance. One of the Institutes Guiding principles in their Guide to the Methods Section 5.2., sub section 5.2.1.1, states:

'The uncertainty surrounding the estimates of cost effectiveness needs to be explored'

Furthermore in section 5.2.4.1 it is stated that:

'It is important for the Appraisal Committee to know about the uncertainty associated with clinical and cost effectiveness information. This requires the appropriate use of rigorous methods to quantify the implications of parameter and methodological uncertainty for the results of an analysis.'

Further detail is given in section 5.8.4 for exploring the uncertainty associated with modelling methods:

'It is important for models to quantify the decision uncertainty associated with a technology- that is, the probability that a different decision would be reached if we were able to ascertain the true cost-effectiveness of each technology before making a decision.'

- Without undertaking sensitivity analysis, the Institute cannot conclude what proportion of estimates within the uncertainty around the quoted £34,700, could overlap with estimates for ranibizumab.

Pfizer conclude that there are estimates for a sub-group of patients with pegaptanib that could lie in the same area of cost-effectiveness as ranibizumab. Based on the level of uncertainty inherent in these estimates, it is unfair to deny patients and the physicians the choice of pegaptanib. Section 4.3.24 of the FAD states:

'It concluded that there was no impact on any particular group of patients which required particular action in order to comply with the Institute's obligations under the equalities legislation, noting that ranibizumab would be recommended as a treatment option for the whole patient group.'

We argue that the exclusion of pegaptanib for the sub-group of patients with visual acuity between 6/12 and 6/24 does not comply with the Institute's obligations under the equalities legislation as, despite ranibizumab being available, there will be patients that would benefit from pegaptanib should they be unsuitable for treatment with ranibizumab. The need for pegaptanib in addition to ranibizumab was a consistent request from the majority of consultees to the second ACD.

GROUND 2: THE INSTITUTE HAS PREPARED GUIDANCE WHICH IS PERVERSE IN THE LIGHT OF THE EVIDENCE SUBMITTED

Pfizer have two concerns which relate to this particular Ground for Appeal.

ASPECT 2.1. The Institute has made an error in its calculation for the cost effectiveness of pegaptanib when the first eye is treated.

Basis for Appeal

- A significant factor which has influenced the proposed guidance in the FAD was the decision by the Institute to apply a 50% uplift to the cost-effectiveness calculation to account for treatment in the first eye.
- In the Additional analysis commissioned by the NHS R&D HTA Programme on behalf of NICE, Sept 2007 the Institute concluded (from consultee feedback) that only a minority (30%) of the wet AMD population will present with disease in their first eye only; the vast majority (70%) present with disease in their second eye also.
- For the 70% of patients who present with disease in their second eye, the original cost/QALY calculation for pegaptanib for second eye treatment for the “early treatment” group should remain at £23,124.
- For the 30% of patients who present with disease in their first eye, if we assume a 50% uplift, the cost/QALY calculation becomes £34,700.
- Pfizer therefore conclude that a more accurate figure, taking into account treatment of first and second eye, would be £26,597 (i.e. a weighted average of the above two figures) for the “early treatment” group. This is the cost/QALY output for pegaptanib which should have informed the Institutes decision.

Pfizer therefore conclude that a simple uplift of the overall cost/QALY by 50% when the first eye is treated is perverse as the 50% uplift should only be applied to the minority (30%) of patients who present with disease in their first eye. This is a critical oversight that denies a sub-group of patients the choice and equity to have treatment with pegaptanib.

ASPECT 2.2. The Institute has failed to take into account consultee feedback that significantly more than 25% of anti-VEGF treatments are currently administered in Outpatients facilities and this will rise in the future

Basis for Appeal

- Pfizer conclude that the assumption that 75% of procedures will occur as a Day Case procedure has resulted in guidance being perverse in the light of evidence submitted by consultees throughout the process.
- Evidence provided by Pfizer, the Royal College of Ophthalmologists and the NHSQIS during the Appraisal process challenged the assumption by the Institute that the majority (their estimate being 75%) of procedures would be undertaken as a more costly Day Case:

In their response to the first ACD in July 2007, the Royal College of Ophthalmologists (RCO) commented:

‘50% of respondents currently treat their patients as out-patients but once funding has become available 90% of treatments will be offered as an out-patient procedure.’

NHS Quality Improvement Scotland (NHSQIS) commented in their response to the second ACD in December 2007 that:

'The non-drug costs (i.e. the costs of administration and monitoring) are still overestimated in my opinion. There should be encouragement to establish the procedure as an Outpatient procedure (75% day case is far too high).'

In light of this evidence from consultees, Pfizer contends that the Institute's insistence that the vast majority of procedures are delivered as a Day Case procedure currently and for the foreseeable future is perverse.

CONCLUSION

Pfizer requests an oral hearing before NICE's Appeal panel for the determination of this Appeal. Pfizer wish to make it clear that they do not wish to delay implementation for treatment with ranibizumab which has been recommended in the FAD. Our appeal relates to pegaptanib only for the sub-group of patients with visual acuity between 6/12 to 6/24. We would therefore urge the Appeal Committee to consider this appeal for pegaptanib only.