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20th July 2007

Emailed to [redacted] at 4.30pm
Faxed to [redacted] at 4.30pm

Dear Dr Longson

Re: Our appeal in respect of the Final Appraisal Determination: Pemetrexed for the treatment of malignant pleural mesothelioma (June 2007)

I understand that as the successor organisation to North Birmingham PCT, Birmingham East and North is one of the two PCTs in England with a right to appeal against the above determination, this letter lodges an appeal against the above determination in respect of Pemetrexed. Please find details of our appeal attached.

Yours sincerely

[redacted]

[redacted]
Chief Executive
Birmingham East and North PCT

Appeal in respect of the Final Appraisal Determination: Pemetrexed for the treatment of malignant pleural mesothelioma (June 2007)

This appeal to the National Institute for Health and Clinical Excellence (the Institute) from Birmingham East and North Primary Care Trust [1] (the PCT) is submitted following careful consideration of the Institute's published documents including:

- Final Appraisal Determination – Pemetrexed for the treatment of malignant pleural mesothelioma (June 2007).
- Consultee and commentator comments on the Appraisal Consultation Document
- Technology Appraisal Process: Guidance for Appellents (April 2004).
- Guide to the Technology Appraisal Process (April 2004)
- Social Value Judgements – Principles for the Development of NICE guidance (December 2005)
- NICE Citizen's Council: Ultra Orphan Drugs (November 2004)
- Appraisal Consultation Document – Pemetrexed for the treatment of malignant pleural mesothelioma (March 2007).
- The Institute's Appeal Panel Decision (October 2006).
- Final Appraisal Determination – Pemetrexed for the treatment of malignant pleural mesothelioma (June 2006).
- NICETAR 04/17: Pemetrexed disodium for the treatment of malignant pleural mesothelioma (Final Version).

The PCT is aware of its responsibility and duties including:
1. Improving the health and well-being of the population.
2. Commissioning cost-effective and affordable comprehensive health care services for the population.
3. Providing health care services.

In accordance with the detailed guidance for appellants, the PCT wishes to appeal on the following grounds:

1. Ground 1: That the Institute has failed to act fairly and in accordance with its published procedures.

   Specifically:
   A: Lack of transparency
   B: Failure to apply the Institute's values to the decision

2. Ground 2: That the Institute has prepared a FAD that is perverse in light of the evidence submitted.

   Specifically:

   C: Adoption of an inappropriate ICER as part of its final considerations
   D: Concluding that the ICER was below the £30,000 threshold for NICE guidance
   E: Providing guidance which is divorced from the Committee's cost-effectiveness argument with respect to the use of fewer cycles

[1] North Birmingham PCT merged with Eastern Birmingham PCT to form Birmingham East and North PCT. This successor body came into being on the 1st October 2006.

F: Providing mandatory guidance which requires the use of a product that is not currently available within the UK.
G: Providing guidance which is divorced from the Committee's cost-effectiveness argument with respect to the use of 100mg vials

3. Ground 3: That the Institute has exceeded its powers.

   Specifically:

   H: Introducing a new principle into resource allocation decisions within England which is currently at odds with NHS values and practice; a move which demands full public debate.

Ground 1: The Institute has failed to act fairly and in accordance with its published procedures

A. Lack of transparency

The PCT has reviewed a number of earlier documents related to this technology appraisal. In particular the 2006 FAD, the 2007 ACD, and the report of the 2006 Appeals Panel.

There is consistency of approach across these three documents in that:

- the ICER for pemetrexed was consistently found to be above £30,000 *and*
- the case for considering pemetrexed an as exceptional circumstance for supporting its use above the usual threshold was rejected.

The most recent FAD presents largely the same information with unchanged ICER figures.

No new significant evidence or analysis has been introduced to the report nor reviewed by the Committee. As such it is not at all clear why the Institute came to such a different conclusion. If the Institute came to a different conclusion as the result of either new evidence or a new analysis or a re-analysis of existing data this has not been made clear. As such the PCT considers the Institute to have been less than transparent in its process.

The PCT is also unclear about the expected treatment cycles and the level of reduction anticipated because this is not specified. The cost of the treatment quoted in the FAD, and all other earlier documents, is based on an average of 5 cycles – not 6. This appears to already take into account expected clinical practice based on 47% of non-responders receiving 4 cycles and the remaining responders receiving 6 cycles. If however, paragraph 4.3.11 means that the actual usage will be below even this level then the Committee appears to be taking the position that for the ICER to be below the £30,000 threshold all patients, both non-responders and responders, should only receive 4 treatments. The PCT seeks clarification and explanation on this point. From the documentation it appears that if the previously evaluated regime of 6 cycles pertains the ICER would remain significantly above the £30,000 ceiling.

B. Failure to apply the Institute's values to the decision

In paragraph 4.3.11 the FAD states:

> *The Committee also noted that MPM is a rare and aggressive malignancy caused by occupation exposure to asbestos and was mindful that this disease has a very poor prognosis.*

Occupational exposure

The above statement indicates that occupational exposure has been taken into account.

The implication of this statement is that this patient group should have special consideration by virtue of the fact that their disease was contracted through occupational exposure.

The Institute's Social Value Judgements: Guidance to the Institute's Advisory Committees, explicitly states that responsibility is not a legitimate ground for differentiating value of health gain. Specifically reference has been made to the Citizen's Council rejection of the notion of 'deservedness' in priority setting within the NHS (section 5.5 page 26).

Principle 10 refers to discriminating against individuals who have self inflicted conditions. By ruling out deservedness however the Institute has also ruled out positive discrimination by virtue of an environmental cause for an individual condition or positive harm by any type of organisation. Namely the document does not sanction discrimination on the basis of how an individual's condition came about – namely personal responsibility versus 'natural' disease (such as a genetic cause) versus environmental exposure regardless of source.

Paying a premium for a disease's orphan status or for the 'rule of rescue'

The 'rule of rescue' principle has been removed in the current version of Social Value Judgements. As such the document makes no statement on the legitimacy of paying a premium for either orphan disease status or for the 'rule of rescue'. Currently there is no policy framework or guiding principles available to the NHS for agreeing to treatments above the £30,000 threshold. In Social Value Judgements the Institute is required to explain the basis for such a decision.

The only internal guidance available to the Institute is from the Institute's Citizen's Council report on ultra-orphan drugs. Their view was that a premium might be considered in the following circumstances (given in descending order of importance) (Section One - page 4):

- The degree of severity of the disease
- If the treatment will provide health gain, rather than just stabilise the condition
- If the disease or condition is life threatening

Mesothelioma is, sadly, a fatal disease. Paragraph 4.3.11 references "that this disease has a very poor prognosis" as though that were an additional argument for the treatment. Unfortunately, Pemetrexed does not alter prognosis in any way and at best stabilises the condition for a maximum of 3 months. The treatment does not therefore meet the recommendations of the Citizen's Council.

The Council also indicated that 'rule of rescue' should only be a legitimate basis for paying a premium when *inter alia* 'the intervention is required to avoid immediate loss of life; it results in significant improvements in quality of life and a significant improvement in life expectancy.' (Ref)

Patients recommended for treatment with pemetrexed are not facing immediate loss of life without treatment. Therefore the utilisation of the rule off rescue is not consistent with the considered recommendations of the Citizens Council.

Ground 2: The Institute has prepared a FAD that is perverse in light of the evidence submitted

The PCT has reviewed a number of earlier documents related to this technology appraisal, in particular: the 2006 FAD, Appraisal Consultation Document and the report of the Appeals Panel.

There is consistency of approach in these three documents in that:

- the ICER for pemetrexed was consistently found to be above £30,000 *and:*
- the case for considering pemetrexed an as exceptional circumstance for supporting its use above the usual threshold was rejected.

The most recent FAD presents largely the same information with unchanged ICER figures. No new significant evidence or analysis has been introduced to the report nor referred to by the Committee. As such it is not at all clear why the Institute came to such a different conclusion.

The PCT can only make a judgment on the information put before it. On this basis it would appear that the change in policy rests totally on the assumptions and statements made in paragraph 4.3.11.

> *Having considered the likelihood of lower numbers of treatment cycles in clinical practice, the potential availability of a 100mg pemetrexed vial and the likelihood of greater quality of life benefits than assumed by the cost-effectiveness analysis, the Committee agreed that the ICER for pemetrexed plus cisplatin in the fully supplement subgroup with advanced disease and good performance status was likely to fall within acceptable levels. The Committee also noted that MPM is a rare and aggressive malignancy caused by occupation exposure to asbestos and was mindful that this disease has a very poor prognosis. The Committee concluded that pemetrexed in combination with cisplatin should be recommended as an option for the treatment of MPM only in people who are considered to have advanced disease and who have a WHO performance status of 0 or 1, in whom surgical intervention is not considered appropriate.*

This paragraph is the only material change to the document. The PCT argues that it is perverse for the Institute to change its decision on the basis of this paragraph.

The PCT will deal with each element of paragraph 4.3.11 separately.

C: Adoption of an inappropriate ICER as part of its final considerations

The FAD repeatedly states that normal NHS practice is active supportive care. We would agree that this is current best practice. As such the relevant baseline ICER should be one which compares pemetrexed with ASC and not cisplatin. This means the baseline ICER is £47,567 and not £37,700.

The Institute is therefore is not using the most relevant comparator as defined by its own document.

D: Concluding that the ICER was below the £30,000 threshold.

Based on the evidence presented, the PCT is of the view that the Institute has failed to demonstrate that the ICER is under £30,000.

Paragraph 4.3.11 makes a number of claims that have not been supported by new evidence or analysis. The FAD view that it is 'likely' that the ICER for pemetrexed would be below £30,000 is based on three factors:

- The use of 100mg vials.
- The fact that fewer cycles are likely to be used.
- Improvements in quality of life have been underestimated.

The Institute's own estimate of the impact of 100mg vials when using cisplatin as a comparator is to reduce the ICER from £37,700 to £34,000. Use of the valid comparator (ASC) would not further reduce the ICER. On the basis of the FAD evidence, the use of 100mg vials alone would not therefore put the threshold below £30,000, and within the ceiling for approval.

The actual price of the 100mg, if and when they are made available within England is not known, and there is therefore at least 50% likelihood that it will be more expensive than assumed (the assumptions are not available) and thus that the ICER would be even greater than £34,000.

The cost effectiveness analysis undertaken by the TAR team includes a probabilistic sensitivity analysis including the uncertainty around the utility gain associated with treatment, (Table 7c, TAR report). The 'likelihood that the quality of life benefits are greater than those assumed in the analysis is appropriately captured in this uncertainty analysis. It is this aspect of the analysis that produces the 20% probability that pemetrexed has an ICER below £30,000 per QALY, reported in the Appraisal Consultation Document but omitted from the FAD.

This point also applies to the number of cycles per patient.

The conclusion that the ICER is likely to fall within acceptable levels is inconsistent with the evidence on the uncertainty both around the number of cycles each person receives and the quality of life impact of the treatment as properly considered in the probabilistic sensitivity analysis by the Technology Assessment Team Report. The additional consideration of this issue by the committee described in paragraph 4.3.11 represents a double counting of uncertainty on this parameter, it appears to the PCT that an incorrect conclusion has been drawn.

The statement in paragraph 4.3.11 that *'the ICER for pemetrexed plus cisplatin in the fully supplement subgroup with advanced disease and good performance status was likely to fall within acceptable levels'* is therefore contested.

E: Providing guidance which is divorced from the Committee's cost-effectiveness argument with respect to the use of fewer cycles'

The opinion that the ICER for pemetrexed falls below the threshold is predicated, in part, on the basis that average number of cycles will be less than expected.

The guidance as stated in 1.1 makes no mention of the number of cycles that non-responders and responders should receive to ensure that the usage that will provide cost-effective practice to the NHS. There is therefore no current assurance in the system to achieve effective cost effective implementation.

F: Providing mandatory guidance which requires use of a product that is not available within the UK.

The opinion that the ICER for pemetrexed falls below the threshold is predicated, in part, on the introduction of the use of 100mg vials. The 100mg vial will not be available in the UK at the time the guidance will be issued. Only the 500mg vial will be available to the NHS and these are licensed for single use only, thus increasing significantly the ICER above £34,000.

The PCT would contest that it is irrational to base a mandatory requirement on the NHS to provide a product that is not available.

G: Providing guidance which is divorced from the Committee's cost-effectiveness argument with respect to the use of 100mg vials.

The opinion that the ICER for pemetrexed falls below the threshold is predicated, in part, on the basis that 100mg vials are used. However, the guidance, as stated in 1.1 makes no mention of a requirement to use 100mg vials, or of how access to 100mg vials will be achieved. In their absence, providers would have to use 500mg vials thus significantly exceeding the £34,000 ICER.

Ground 3: The Institute has exceeded its powers.

H: Introducing a new value into resource allocation within England which is currently at odds with NHS values and practice; a move which demands full public debate.

By introducing occupational exposure as a differentiating factor, the PCT would also argue that the Institute has acted outside its powers.

On the face of it, a natural justice argument would suggest that victims of external circumstance should be given the care they need and therefore be given preferential treatment in terms of access to services. It also appears to be a common view that individuals with self inflicted conditions should have either a lower priority or not be treated for those conditions on the NHS.

However, to date, when tested, the NHS has rejected the notion of distribution of resources based on "merit". The implication of applying a "merit" principle is that the NHS will provide differential access and allocate different priorities to groups who have developed disease as a result of different causes. On this basis, the NHS might give preferential treatment to lung cancer patients who have contracted their disease as a result of occupation exposure (such as working in a public house) to those who have smoked.

By introducing this factor into this FAD the Institute is breaking with the current value system being applied in the NHS which responds to all patients on the basis of current health need rather than Aetiology of disease. It is merely introducing a principle that has significant implications for resource allocation and treatment prioritisation across the National Health System. As such, the introduction of such a principle requires wider public debate before being adopted. The PCT considers the Institute to have exceeded its remit and introduced in this context inappropriate considerations in to what should be an evidence based assessment of cost effectiveness.