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Primary Care Trust

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13th September 2007

Emailed to [redacted]
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Dear Mr Taylor

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

Thank you for your letter of the 24th April 2007.

We have taken your comments into account and are submitting our amended Appeal Document.

Yours sincerely

[redacted]

[redacted]
Chief Executive
Birmingham East and North PCT

Appeal by Birmingham East and North Primary Care Trust relating to the NICE Final Appraisal Determination: Pemetrexed for the treatment of malignant pleural mesothelioma (June 2007)

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1. This is an appeal to the National Institute for Health and Clinical Excellence Appeal Committee (the Institute) by Birmingham East and North Primary Care Trust [1] (the PCT). It 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).
    - Technology Appraisal Process: Guidance for Appellants (April 2004).
    - Guide to the Technology Appraisal Process (April 2004)
    - Guide to the Methods of Technology Appraisal (April 2004)
    - Social Value Judgements – Principles for the Development of NICE guidance (December 2005)
    - NICETAR 04/17: Pemetrexed disodium for the treatment of malignant pleural mesothelioma (Final Version).

2. The PCT is aware of its responsibility and duties including:

    - Improving the health and well-being of the population.
    - Commissioning cost-effective and affordable comprehensive health care services for the population.
    - Providing health care services.

[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.

3. It makes this appeal in order to bring to the attention of the Appeal Commitee the absence of a properly arguable case for the treatment of malignant pleural mesothelioma (MPM) with pemetrexed in the Final Appraisal Determination (FAD), and in the knowledge that if NICE publish this Guidance it will lead to a demand for this treatment which will reduce the ability of the PCT to meet other medical and health needs.

4. These grounds have been amended after reflection on the matters raised in the letter from Mr. Mark Taylor, the Chair of the NICE Appeals committee, dated 24th August 2007. In the light of that letter and the NICE guidance the PCT wishes to appeal on the following grounds:

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

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

    c. Ground 3: The Institute exceeded its powers.

5. The Grounds have been sub-divided into Grounds 1A, 1B and so on in order to make the position clear.

Ground 1A: That 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.*

6. The Institute has stated in its document *Guide to the Methods of Technology Appraisal* that in recommending treatments with a high ICER, the Committee must set out its reasoning as stated in section 6.2.6.10 -11 (page 33-34) as follows:

    "6.2.6.10: Below a most plausible ICER of £20,000/QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate. Above a most plausible ICER of

£20,000/QALY, judgements about the acceptability of the technology as an effective us of NHS resources are more likely to make more explicit reference to factors including:

i. The degree of uncertainty surrounding the calculation of ICERs
ii. The innovative nature of the technology
iii. The particular features of the condition and population receiving the technology
iv. Where appropriate, the wider societal costs and benefits.

6.2.6.11 Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong. The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the 'Considerations' section of the guidance."

7. In making the assessment the Committee ought to have looked at comparators in accordance with paragraph 5.3.1.2 (page 21) of the Guide to Methods namely:

"Comparator: Alternative therapies routinely used in the NHS"

8. The Committee in considering the relevant comparator noted the following in 4.3.3 (page 12) of the FAD:

"clinical specialists advised that cisplatin monotherapy would not normally be used to treat MPM in clinical practice in England and Wales because of a lack of evidence of its effectiveness and its relatively unfavourable adverse-effect profile."

and

"The Committee noted that the results of meta-analysis investigating prognostic factors for MPM suggest that survival with ASC without chemotherapy may be no worse than with chemotherapy"

9. The first point that the PCT raises under this part of the appeal is that, given the above evidence and assuming the Guide to Methods has been followed the Committee was incorrect to have used a comparison between cisplatin monotherapy and combined therapy of cisplatin with pemetrexed in conducting its

cost effectiveness assessment. The comparison should have been between the combined therapy of cisplatin with pemetrexed and active symptom control. The analysis given in 4.3.8 of the FAD (page 14) was thus flawed:

> *"4.3.8 The Committee discussed the subgroup of patients with both advanced disease and good performance status, in view of the relatively favourable ICERs of pemetrexed plus cisplatin versus cisplatin alone (£37,000 per QALY gained, or £34,000 per QALY gained assuming a 100-mg pemetrexed vial becomes available) that were calculated for this subgroup."*

10. In addition under 6.2.6.10 - 11 in its *Guide to Methods* the Institute is required to explain the full reasoning behind its decision. The key paragraph of the June *2007 Final Appraisal Document* (page 15-16) states:

> *"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."*

11. The PCT makes the following points in relation to this finding:

    a. The Committee has based its evidence on one RCT. The evidence base is therefore small and the uncertainties associated with the proposed treatment are thus high. This uncertainty does not appear to have been reflected in the findings;

    b. There was insufficient objective evidence from RCT that the treatment was clinically better than Active Symptom Control to justify the recommendation in line with the principles under which NICE operates;

c. All of the patients who received the drug in the trial suffered the possibility of side effects whereas only half received benefits. It is unclear how the Committee treated (if at all) these adverse symptoms (extending beyond the population who could potentially benefit from the treatment);

d. The final ICER used by the Committee to justify the conclusion is not stated. It is therefore not possible to determine if it said to be above or below the £20,000 guideline figure as set out above, or between £20,000 and £30,000 or above £30,000. It is therefore impossible to determine from the paragraph which evidential standard required under 6.2.6.10 – 11 was required to be satisfied and thus the PCT cannot determine whether it was so satisfied, though it appears not to have been so satisfied;

e. It is not clear from this paragraph whether the ICER is calculated on the basis of 4, 5 or 6 cycles per patient. Although the evidence was that patients who are later shown to be within the 42% who respond to this treatment do so after 4 cycles, there was no evidence that clinical practice was to stop treatment after 4 cycles in non-responding patients and no such proposed direction in the FAD. Thus:

    i. any assumption that the NHS will fund an average of 5 cycles is unsupported by evidence and/or;

    ii. this assumption is highly unlikely to be the case in practice; and

    iii. thus any ICER calculations which may have been based on an average of 4 or 5 cycles would be misconceived (and have not been demonstrated). The number of cycles which will be used in a proportion of patients may be higher.

f. There is no 100-mg vial of pemetrexed presently available (as to which see below) and/or the price of such a treatment was unknown;

g. It was wrong, in principle, for the Committee to take account of the fact that MPM is a rare condition. The Institute's *Social Value Judgements* does not allow it to assess economic benefit giving differential value to health gain in the treatment of rare conditions;

h. It was wrong, in principle, for the Committee to be influenced by the fact that the condition was an "aggressive malignancy". This is taken account of within the QALY;

i. It was wrong, in principle, for the Committee to be influenced by the fact that the condition was generally (but not exclusively) caused by occupational exposure (as to which see below). The Institute's *Social Value Judgements* does not allow it to assess economic benefit giving differential value to health gain in the treatment of occupationally acquired conditions.

Ground 1B: 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*.

12. Social Value Judgments, published on the 8th December 2005 states (paragraph 1.2 page 7):

> *"These guidelines describe the social value judgements that should, generally, be incorporated into the processes used to develop NICE guidance and be applied when preparing individual items of NICE guidance. The Institute recognises, however, that there will be circumstance when – for valid reasons – departures from these general principles are appropriate. When departure from these principles are made, the reason should be explained (section 1.2)"*

13. The Institute's Social Value Judgements document was accepted and approved by the Board on 21st September 2005. On the 8th December 2005 a Press Release was issued by the Institute which stated that this report *'sets out clearly if, and how, social value judgements should be considered in producing NICE healthcare guidance for the NHS'.* The document's place in the Institute's

decision making was again reiterated in NICE's submission to the Health Select Committee (NICE 71 page Ev 5 House of Common HC503-11). The PCT concludes that NICE considers the Social Value Judgements document integral to its decision making.

14. Further the relevance of the document to the NICE decision making was advanced by NICE in the High Court in the recent case of *Eisai Ltd. v The National Institute for Health and Clinical Excellence (Nice) [2007] EWHC 1941 (Admin)* where the Judge held that:

> *"The key principle underlying NICE's approach to appraisals is that the NHS's limited resources should be targeted on those treatments which provide best value for money. The principle is to be found at paragraph 4.1 of NICE's "Social Value Judgments – principles for the development of NICE Guidelines" (8th December 2005) and is summarised by Professor Andrew Stevens, the chair of the Appraisal Committee which appraised the AChEIs in the present case, (Stevens [12A/3/251, para.7]):*
>
> > *"If money is spent on donepezil for patients with mild Alzheimer's disease, then that money is not available to spend elsewhere on the treatment of other patients. The role of NICE's appraisal committees is therefore to judge whether the clinical and cost effectiveness of a technology being appraised is such as to justify spending the NHS's money on that technology, rather than on one of the many other technologies competing for the finite resources available."*

15. It is therefore not open to NICE to now deny the relevance of the said document in this appeal and the Appeal Chairman is invited to reconsider and accept this point.

16. The *Social Value Judgements* document goes on to clearly confirm that the notion of "deservedness" should <u>not</u> be taken into consideration when developing NICE Guidance (paragraph 5.5). In agreeing principle 10 NICE took into account its own Citizen Council's recommendations that:

> *"The Citizen's Council considered that in developing its guidance NICEshould not take into consideration whether or not a particular condition was self-induced (2)*

There were two reasons for reaching this conclusion: firstly, the Council believe it was impossible – at least in circumstances such as ischaemic heart disease – to decide whether an individual's condition was 'self-inflicted' or due to some others factor(s); secondly, the Council rejected the notion of deservedness in priority setting within the NHS (2)"

17. The principle of deservedness has broad application. In rejecting the concept the Citizen's Council has also rejected, as irrelevant to decision making, whether or not an individual deserved to contract their illness. (Indeed most individuals contracting a condition do not 'deserve' to have that condition.) As such no differentiation can be made as to the cause of the condition, and in particular rejects the notion of a 'hierarchy of deservedness'.

18. It follows from the above that, in reaching decisions about treatment, NICE should assess treatments for patients as they present and irrespective of the circumstances which led to them contracting the condition. The document does not suggest or state anywhere that positive discrimination, on grounds of a lack of fault should lead to the patient deserving additional public investment in their condition. The only logical conclusion from the approach advocated by NICE is that the fact that a patient may have contracted a condition through his or her occupation, and thus was not at fault in contracting the condition, gives rise to no greater justification for public investment in treatment for that patient than patients who had other conditions where they were not at fault or indeed, to follow the logic of the Council, where they were at fault.

19. There must be a level playing field here or the following points arise:

    a. There is unjustifiable discrimination between different patient groups, each of which contracted their condition through no fault of their own; and

    b. If the precedent which views "occupationally related conditions" as grounds for more investment per health outcome is accepted then there is indirect and unlawful sexual discrimination. Men are more likely to take advantage of the more generous qualification criteria for investment in occupation related conditions than women whose conditions may be equally serious and blameless but are not occupation related.

20. Further it is wrong in law to favour this particular occupational health injury for additional health investment over all the other occupational health injuries. The Health and Safety Executive reported in 2004/5:

> ***"Each year over 2 million people suffer from ill health which they think is work-related ...***
>
> *Overall, in 2003/04 an estimated 2.2 million people were suffering from an illness which they believed was caused or made worse by their current or past work; around 600 thousand of these first became aware of the illness in the past 12 months"*

21. There is no logical or defensible reason why sufferers of this occupational health condition should be favoured over others with occupational illnesses (whether fatal or otherwise).

22. The "Rule of Rescue" should play no part in the allocation of treatment in the NHS. If there is effective treatment then the effectiveness will be captured in the QALY and does not need an additional rule. On the contrary, if the prognosis for a condition is poor then additional investment cannot be justified to seek to rescue the patient from the condition. Pemetrexed cannot be said to alter prognosis.

Ground 2A: That the Institute has prepared guidance which is perverse in light of the evidence submitted.

23. In as much as any of the matters above tend to perversity they are repeated under this ground.

24. The Guide to the Methods of Technology Appraisal clearly specifies the comparator to be used in the reference case under section 5.3.1.2, Box 5 that the comparison should be alternative therapies used in the NHS as set out above.

25. Currently best supportive care is considered best practice within the UK rather than cisplatin monotherapy. This is confirmed in the FAD under section 4.3.6 (page 13) which states:

> *"The Committee heard from clinical specialists that cisplatin could be considered a valid chemotherapeutic agent even though it is not favoured in the UK"*

26. *The FAD also states (pg 12, 4.3.3),*

> *"clinical specialists advised that cisplatin monotherapy would not normally be used to treat MPM in clinical practice in England and Wales because of a lack of evidence of its effectiveness and its relatively unfavourable adverse-effect profile."*

27. The PCT's case is that it is perverse that the Committee assessed the opportunity cost of pemetrexed to the NHS using an ICER for a comparator treatment not routinely used in the NHS. The appropriate ICER for the committee's consideration should have used best supportive care as the comparator. The estimated cost-effectiveness of treatment with pemetrexed is incorrect unless cisplastin can be offered at zero cost to the NHS.

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

28. The assessment in the above paragraph was partly based upon *"the potential availability of a 100mg pemetrexed vial".* The electronic Medicines Compendium which lists all the licensed drugs in the UK only list the following product as available in the UK:

> *"Alimta ® 500mg powder for concentrate for solution for infusion (**http://emc.medicines.org.uk**) viewed on 05/09/07)"*

29. The PCT cannot find any confirmation that a 100mg vial will be available in the UK and none was available at the date of the FAD. It is wrong in principle and/or perverse to conduct a QALY assessment and/or recommend a treatment, based

on cost effectiveness analysis on a product formulation that is not available to the NHS and for which the price is unknown.

30. The PCT also considers it to be perverse for the Institute to publish technology appraisal guidance which mandates PCTs to make funding available for pemetrexed when the NHS cannot currently procure the vial size that the Institute considered likely to be cost effective and/or fails to include this as a condition in the FAD. Further unless and until the manufacturer undertakes to manufacture a 100mg vial for the UK market, the Committee could not have known the price and therefore could not undertake the cost-effectiveness analysis.

31. Further if the Guidance is published in its present form the manufacturer will have no incentive to make such a vial as it will be able to sell the product through the existing vial.

Ground 3: The Institute has exceeded its powers by making a recommendation which was in relation to a product which does not presently exist (the 100mg vial) and by introducing a more advantageous test for occupationally related conditions.

32. The PCT repeats the submissions made above relating to the reference to a 100mg vial and the inclusion of the occupational origin of this condition.

33. It is beyond the powers of the Committee to make a recommendation that the NHS should provide a treatment in a form which presently does not exist.

34. It is also beyond the powers of the Committee to seek to use the NHS as a form of quasi-statutory compensation for occupationally contracted diseases. In particular the PCT notes that:

    a. If a patient has a cause of action in negligence related to the disease the patient has the absolute right to claim the costs of private medical treatment without recourse to the NHS. See section 2(4) of the Law Reform (Personal Injuries) Act 1948;

b. The government has set up the Department for Work and Pensions' Industrial Injuries Scheme;

c. Providing a statutory compensation system outside the above is no part of the functions of NHS and NICE has no lawful remit to make decisions on such a basis.

[Ends]