NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Pemetrexed for the maintenance treatment of non-small cell lung cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Eli Lilly and Company	Pemetrexed as maintenance therapy is a well-tolerated medicine that provides a significant step-change in the treatment of patients with advanced non-squamous NSCLC who have not progressed with first-line therapy by extending median survival by more than five months, compared to best supportive care only, the current standard of care. An increase in survival of over five months and median overall survival of approximately 18 months from start of chemotherapy are unprecedented benefits for patients with advanced NSCLC. Lilly are pleased that the Committee concluded that the evidence submitted by the manufacturer was robust enough to show that maintenance treatment with pemetrexed fulfilled the supplementary advice from NICE for appraisal of treatments which extend lives of patients with otherwise short life expectancy and which are licensed for indications that affect a small number of patients. However, we are concerned that the Appraisal Committee did not recommend pemetrexed for maintenance therapy in their preliminary decision even when the end of life criteria, intended to improve access to medicines for patients with terminal conditions, are taken into consideration Our key comments are on the following topics:	Comment noted Comment noted. Pemetrexed has now been recommended for maintenance therapy following a revised cost-effectiveness analysis submitted by the manufacturer and reviewed by the ERG. Please see FAD sections 1.1 and 4.19

Consultee	Comment	Response
Eli Lilly and Company	**Impact of treatment duration on the uncertainty around the cost-effectiveness estimate.** Duration of therapy for the maintenance treatment of NSCLC is not established as it is a new option of clinical care in NSCLC. At this stage it is difficult to anticipate the most appropriate duration for therapy to accomplish the maximum benefit from pemetrexed. In the pivotal clinical trial (JMEN), the majority of patients received a maximum of up to 15-20 cycles of treatment and the median number of cycles in the non-squamous patient population was 6. Furthermore, around 10% of patients received more than 17 cycles (i.e. 1 year of treatment) and less than 5% received more than 35 cycles (i.e., 2 years of treatment). Only one patient received 55 cycles. The approach followed by Lilly in the submitted economic model was an attempt to reflect the most likely scenario of expected clinical practice based on the distribution observed in the JMEN trial. In response to the discussion around treatment duration for pemetrexed in maintenance, Lilly have performed additional scenarios in the economic model adjusting costs and benefits at different treatment durations: 1 year, 2 years and duration as seen in the JMEN trial. The results obtained show that the ICERs are most likely to vary between £46,000 and £49,000.	Comment noted. The committee considered the number of cycles in the trial to be the most appropriate data on which to base an analyses for clinical and cost-effectiveness of pemetrexed. The committee considered scenario 5 which based the costs of treatment on the number of cycles used in trial, and lower utility for pemetrexed compared with standard care, to represent the most plausible assumptions for the modelling of pemetrexed for maintenance therapy. Please see section 4.16 of the FAD

Consultee	Comment	Response
Eli Lilly and Company	**Application of end of life supplementary advice** • <u>Principles of end of life criteria</u> The end of life criteria together with other recent developments in pharmaceutical and industrial policy such as the Kennedy Report, advocate for NICE to have a broader perspective and more pragmatic approach when assessing new medicines. In line with the NICE Citizens Council and the NICE social value judgements, other factors such as: severity of disease, terminal illness, and medicines where cost of treatment may far outweigh best supportive care, should be taken into consideration in the decision making process. This is particularly the case in the assessment of end of life treatments where medicines that extend life are penalised for keeping patients alive and that are unlikely to ever be cost-effective under the traditional ICER thresholds. The use of a standard higher cost per QALY threshold as the key decision making factor for end of life treatments will miss out on the overall value of these products.	Comment noted Comment noted

Consultee	Comment	Response
Eli Lilly and Company	• <u>The size of QALY weight to be considered for acceptable current threshold range</u>. Despite the recognition of the significant clinical value of pemetrexed and the application of the supplementary advice, the Committee concluded that the size of the additional weight that would need to be assigned to the QALY benefits for the ICER to fall within the current threshold range would be too great to be cost-effective even considering the supplementary advice. Although NICE has not provided an explicit upper threshold for end of life treatments, a Committee has already approved treatments with a de facto QALY weight of 1.7 (i.e. upper limit of £50,000/QALY). In the case of sunitinib for the treatment of renal cell carcinoma (RCC), the Committee concluded that '*although it might be at the upper end of any plausible valuation of such benefits, in this case there was a significant step-change in treating a disease for which there is only one current standard first-line option*". We believe pemetrexed as a maintenance treatment offers a similar step-change for patients with advanced non-squamous NSCLC. The new cost-effectiveness estimates provided for various scenarios (see Appendix 2), consistently fall within the ICER range that NICE appears to have considered acceptable in prior appraisals subject to the end of life supplementary advice, of values of about £50,000/QALY. At present the cost-effectiveness of pemetrexed without a patient access scheme is in the same range as sunitinib with a patient access scheme. Therefore, pemetrexed should be considered even more cost-effective since it does not have the burden of managing a patient access scheme within the NHS. More detailed feedback on the application of the end of life supplementary advice is provided in Appendix 1.	The committee has now recommended pemetrexed as an option for the maintenance treatment of NSCLC. Please see section 1.1 and 4.19 of the FAD Comment noted. The committee considers each appraisal on its own individual merit based on the evidence presented on its clinical and cost effectiveness. The committee considered scenario 5, which based the costs of treatment on the number of cycles used in trial, and lower utility for pemetrexed compared to standard care, to represent the most plausible assumptions for the modelling of pemetrexed for maintenance therapy. Please see section 4.16 of the FAD

Consultee	Comment	Response
Eli Lilly and Comapny	**Small patient population leading to limited budget impact for the NHS.** The eligible population for maintenance treatment is very small as only a subgroup of those receiving first-line therapies will be suitable for maintenance treatment (n=949 across England and Wales, MS submission Section 6.4, Table 9). The eligible population will decrease in size as pemetrexed first-line becomes standard of care in non-squamous NSCLC patients (NICE TA181) as pemetrexed maintenance therapy is not licensed for use following first-line pemetrexed treatment. According to the cycle distribution in the clinical trial, the proportion of patients likely to receive more than 17 cycles (about 10%) would translate to less than 100 patients in England and Wales. The number of patients being treated beyond two years would translate to less than 5%, fewer than 50 patients. Therefore, only 7 patients per PCT (considering 147 PCTs in England) would be eligible for maintenance treatment with less than one patient per PCT going beyond one year of treatment. Taking the small number patient population into consideration and the average treatment cost per patient of approximately £12,076 the overall impact of introducing pemetrexed into the NHS is relatively small.	Comment noted Comment noted

Consultee	Comment	Response
Eli Lilly and company	**Issues with Patient Access Schemes** Although manufacturers of other oncology drugs appraised under the end of life criteria have proposed patient access schemes to allow patients to have access to new treatments, the approval, implementation and monitoring of patients under such schemes is very burdensome to the NHS and the manufacturer. NHS customers and the Department of Health (DH) believe '*the proliferation of schemes is creating an unnecessary burden to the NHS*' and consider '*they should be the exception not the norm*'. As patient access schemes have the potential to be administratively burdensome with a danger that the extra workload will fall on clinical staff, it is not considered appropriate or helpful to introduce a patient access scheme within the context of increasing NHS productivity, when the eligible population for pemetrexed as maintenance treatment is so very small.	Comment noted Comment noted

Consultee	Comment	Response
Eli Lilly and Company	**Conclusions** • Pemetrexed as maintenance therapy represents a step-change in the therapeutic approach to advanced non-squamous NSCLC. • Pemetrexed is a well tolerated medicine that increases survival by more than five months, an unprecedented benefit for patients with advanced NSCLC. • The new cost-effectiveness results are consistently below or around £50,000 per QALY irrespective of treatment duration. • The ICER values (without a patient access scheme) are in line with other products already approved under the end of life criteria. The additional burden and cost of implementing patient access schemes in the NHS should be taken into consideration in the decision making process. • This is even more so, if we consider that the estimated number of patients that will be eligible for treatment following first-line treatment is likely to be small, given that pemetrexed is fast becoming the new standard for first-line treatment, and pemetrexed maintenance is not indicated for use after first-line pemetrexed.	Comment noted Comment noted Comment noted Comment noted Comment noted

Consultee	Comment	Response
Eli Lilly and Company	We also enclose in Appendix 2 our response to points raised by the Appraisal Committee and the ERG in relation to the economic model. In Appendix 3 we include a table with observed factual inaccuracies in the ACD. Pemetrexed represents a new well tolerated option of treatment for patients with advanced non-squamous NSCLC that significantly increases survival in a challenging terminal disease. We hope that the above information will enable NICE to recommend, as an option of care, pemetrexed in the maintenance treatment of patients with advanced non-squamous NSCLC	Comment noted Comment noted Comment noted

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP/JCC	Page 17 4.14 Decision to cap the number of cycles of maintenance pemetrexed at 17 (Mean plus one standard deviation). The distribution of the number of cycles is almost certainly not normal. In fact only 23% of patients received more than 10 cycles. The median number of cycles (5.0) should be used or at very most 10 but not 17 This will have to be recalculated	Comment noted The committee considered that the number of cycles in the trial represented the best data to be used in clinical and cost-effectiveness analysis

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP/JCC	The adjustment of the utility scores in 4.15 is unjustified as the toxicity of this drug is very low and indeed the utility scores may improve in some patients as an additional 5% had a further partial response which should alleviate their lung cancer related symptoms The original utility scores should be used This will have to be recalculated	The committee considered that pemetrexed should be assigned a lower utility compared with best supportive care to reflect the patient level data reported from the trial
British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group	Thanks for asking the British Thoracic Society to comment on this ACD. Whilst we are disappointed that a promising treatment for lung cancer patients has not passed the cost-effectiveness test, we feel that overall this is a fair judgement which does take all the relevant evidence into account and is therefore a suitable basis for guidance to the NHS.	Comment noted

Comments received from commentators

Commentator	Comment	Response
None		

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Given the 5.3 month survival increase and few side effects pemetrexed SHOULD be recommended	Comment noted. Pemetrexed has now been recommended for maintenance therapy following a revised cost-effectiveness analysis submitted by the manufacturer which was reviewed by the ERG. Please see FAD sections 1.1 and 4.19 The Committee considered the scenario analysis presented by the manufacturer during consultation which probabilistically modelled the cost effectiveness of pemetrexed for different treatment durations and with alternative utility assumptions. The Committee considered scenario 5 (which represented treatment until disease progression and a slightly lower utility in the pemetrexed compared the with placebo arm) to be most consistent with clinical practice in the UK. The Committee considered the revised analysis in light of the end of life considerations and concluded that pemetrexed represented a cost effective use of NHS resources and therefore recommended pemetrexed as an option for maintenance therapy in NSCLC. For further information see sections 4.16 to 4.19 of the FAD.
	Section 2 (The technology)	Batching drug doses eliminates waste of partially used vials and reduce the total vial number used and cost	Resource use based on vial sharing arrangements was not presented in the manufacturers submission.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	Section 3 (The manufacturers submission)	3.8 In routine practice continuing treatment beyound a year would be most unusual eg as for erlotinib use	Comment noted
		3.13 The ERG reveals a distubing lack of understanding.In routine practice chemotherapy is given generally to PS01 patients who tend to be 70 years ,so the trial design is apposite.In 2010 the same treatment is not given to everybody with the same condition!	Comment noted. The committee considered the performance status as used in the trial appropriate. Please see FAD section 4.11
		3.14 Given the NICE approval for the 3rd generation drugs which included comparisons against BSC it is reasonable to expect an improved(or at the very least no change) in QOL with less use of hospice admisisions, radiotherapy etc.	Comment noted
		3.15 Survival data for the licensed 2nd line drugs erlotinib pemetrexed docetaxel are extremely similar and differing uptakes in the 2 arms are not of concern in survival interpretation.Speculation on the efficay of unlicensed drugs is unreasonable	Comment noted
		3.16 This has been dealt with and accepted(also by NICE) in the 1st line trial which also used histology as a prespecified analysis factor	Comment noted
		3.19 FU as descibed is for patients with out progression, in reality it is more frequent especially in the first year when 2nd line and BSC are almost always needed.eg 3-6 w weekly	Comment noted