NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Pemetrexed for the first line treatment of advanced 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

Nominating organisation	Comment	Response
Lilly UK	The original submitted Markov model has been modified to a) more accurately represent the outcomes of the JMDB trial using Weibull distributions and b) take into account the concerns raised by the committee in 3.17 and 3.18 of the ACD to re-estimate the incremental cost-effectiveness of pemetrexed/cisplatin when compared to gemcitabine/cisplatin.	Comment noted. Please see FAD sections 3.20, 3.21 and 4.11
Lilly UK	An additional trial-based economic analysis has been conducted using the individual patient survival outcomes (censored) and resource use events from the JMDB clinical trial database	Comment noted.
Lilly UK	Findings from the economic model used for the PBAC HTA submission in Australia, which was based upon the patient level data from the clinical trial and used Weibull distributions to extrapolate survival, have also been provided to further validate our submitted estimates of cost-effectiveness for pemetrexed/cisplatin compared to gemcitabine/cisplatin.	Comment noted
Lilly UK	Thorough validation processes have been followed according to the NICE request such as double build for the trial-based model, and internal and independent external reviews, for both the modified and clinical trial-based models.	Comment noted

Nominating organisation	Comment	Response
Lilly UK	The modified, the trial-based and the PBAC models all demonstrated consistent results to the original submitted model, with incremental cost-effectiveness ratios in the range of £22,202 to £25,967 for the adeno and large cell carcinoma patient population when pemetrexed was used for up to four cycles, in accordance with UK practice	Comment noted. Please see FAD section 3.20
Lilly UK	*Model structure:* The submitted Markov model was a valid structure used in previous oncology models in accordance with the NICE reference case. The estimates produced by the submitted model fairly reflected the incremental cost-effectiveness of pemetrexed when compared to gemcitabine. When the model was modified to include Weibull (time dependent) distributions, the results were consistent with the submitted model.	The Committee noted that that there were serious issues with the modeling relating to consistency with the trial data and errors in the calculations (see FAD sections 4.9 to 4.11).
Lilly UK	*Overall survival*: No modelled survival distribution or 'fit', whether exponential or Weibull, is perfect. The exponential distribution is used as standard within analyses of oncology clinical trials and is commonly utilised for modelling the cost-effectiveness of oncology therapies. The use of exponential distribution led to estimates within the submitted model that were consistent with our regulatory submission and also increased the simplicity of the model. The modified model confirms that use of Weibull distribution compared to exponential has increased the complexity of the model with little impact upon the cost-effectiveness estimates	The Committee noted that the Weibull distribution does not fit the trial data (see FAD sections 4.9 to 4.11).

Nominating organisation	Comment	Response
Lilly UK	*Progression-free survival and response rates:* It is agreed that PFS and tumour response are not key drivers of survival in lung cancer. However, they are health states that are of clinical importance in terms of physician decision-making and patient experience. The discrepancy in total response between the trial and model was very small and in favour of gemcitabine leading to an underestimate of the benefit of pemetrexed within the model and therefore a conservative estimate of cost-effectiveness within the original submission.	Comment noted.
Lilly UK	*Half-cycle correction*: The half-cycle correction was disabled for costs because the majority of costs in cancer are incurred at the beginning of the cycle at drug administration. When the half-cycle correction was adjusted as requested in the modified model, this had minimal impact on the results. Therefore, the half-cycle correction used in the original submission did not interfere with the ability of the model to produce credible results.	Comment noted.

Nominating organisation	Comment	Response
Lilly UK	*Adverse event rates*: As the majority of patients within the trial (80%) experienced zero or only one adverse event and there was a very limited rate of grade 3/4 adverse events, although of great importance to patients, adverse events were not a major driver within the cost-effectiveness model. Therefore, the assumption made within the original model did not limit the model's ability to determine the cost-effectiveness of the pemetrexed compared to gemcitabine. *Mortality risk used for febrile neutropenia:* As stated in the ERG report (pg57), the advantage conferred by the febrile neutropenia mortality rate to pemetrexed is of such small value (difference of 0.6% from baseline value) that it had no effect upon the model's ability to produce credible results.	Comment noted

Comments received from clinical specialists and patient experts

Consultee	Comment	Response
British Thoracic Oncology Group	We think the appraisal committee have identified the areas that there is further evidence that could be used in the assessment e.g. other comparator drugs. Our concern is that there is a growing body of evidence that histological subgroup and other pathological markers are important in the selection of specific drugs in the management of NSCLC. Being aware that a number of groups are actively studying this we would expect that the publication / presentation of further data is imminent. If this data confirms pemetrexed to be superior for some subgroups and the committee remains minded to recommend against then a number of patients will be disadvantaged before the proposed review date.	The Committee accepted the clinical evidence that pemetrexed is effective for people with adenocarcinoma and large cell carcinoma (see FAD sections 4.2 to 4.8). The new analyses based on amendments of the Markov model, a trial based analysis of the JMDB trial and the ERGs exploratory analysis were considered to prove the cost effectiveness of pemetrexed for people with adenocarcinoma and large cell carcinoma. See FAD sections 4.12 to 4.14.
British Thoracic Oncology Group	We think the clinical summary is reasonable. The cost effectiveness analysis seems to indicate that pemetrexed is cost effective for some histological subgroups and am surprised that the committee is minded to recommend against	Comment noted. After consideration of the manufacturer's additional analysis and ERG critique and exploratory analysis the Committee concluded that pemetrexed should be recommended for those with adenocarcinoma or large cell carcinoma. See FAD section 1.1

Consultee	Comment	Response
British Thoracic Oncology Group	We think the clinical trials provide strong evidence for that pemetrexed / cisplatin is equivalent to the currently available first line chemotherapy treatments for NSCLC. Experience of the regime in the treatment of mesothelioma is that it has an acceptable side profile which compares well with cisplatin /gemcitabine and cisplatin / vinorelbine. The trial data indicates the superiority of the pemetrexed combination in some histological subtypes also appears robust and if confirmed would change UK practice. The cost analysis data submitted indicated in these subgroups treatment may be very cost effective and issues identified by the committee need to be addressed to justify the committees' 'mind to recommend against' this technology.	The Committee accepted that pemetrexed was clinically effective (see FAD sections 4.2 to 4.8). However, the Committee requested additional analysis to demonstrate that pemetrexed was cost effective since the originally submitted model results were not consistent with the trial data. Please see FAD section 4.9.
British Thoracic Oncology Group	Lung cancer patients generally come from the more socially and economically deprived sections of the population.	Comment noted.
British Thoracic Society	The British Thoracic Society feels that the appraisal so far is balanced and fair.	Comment noted.

Consultee	Comment	Response
Royal College of Pathologists	The evidence now suggests that pemetrexed is effective on only those 'non-small cell carcinomas' (NSCCs) of the lung that show no element of squamous differentiation; that is on 'pure' adenocarcinomas, there would be implications for histo- and cytopathologists reporting bronchial or transthoracic needle biopsies, or cytological specimens, from patients with carcinoma of the lung, if the drug came into use for the treatment of bronchial carcinoma. This is because a simple morphological diagnosis of 'NSCC' would be no longer acceptable for targeting the use of the drug. In a morphologically poorly differentiated NSCC in which neither squamous nor glandular differentiation were evident morphologically, it would need to be sought by immunochemistry. It is likely that this can be achieved with a very high level of certainty by immunolabelling tumours for p63 protein and for TTF-1. This is not difficult with an adequate histological specimen, but might be much more difficult with a cytological preparation. It certainly would have significant implications in terms of resources and turnaround time and interpretation might be by no means always straightforward, especially in the hands of 'non-experts'.	The Committee noted the effect of histological subtype on the clinical effectiveness of pemetrexed. Therefore, the recommendations are targeted to those with adenocarcinoma and large cell carcinoma. Please see FAD sections 4.4 and 4.5.

Consultee	Comment	Response
Roy Castle Lung Cancer Foundation	We are extremely disappointed that, despite the expert testimony of our representative and of other key lung cancer professionals during the Appraisal Committee Meeting, the recently issued ACD on the use of Pemetrexed for the first line treatment of non-small cell lung cancer, reveals that the Committee is minded not to recommend this therapy. We are, however, pleased to note in paragraph 4, the Committee's conclusion that Pemetrexed is clinically effective in UK clinical practice, with increased survival and lower toxicity as compared with established therapy. We remind the Committee of the overall low survival rates for this patient group. We do note the Appraisal Committee's request to the manufacturer for further clarification and cost-effectiveness analyses. After consideration of this, we strongly urge the Committee to issue a positive FAD for this therapy indication.	Comment noted
Royal College of Nursing	Nurses working in this area of health have reviewed the Appraisal Consultation Document. We are disappointed that, despite the testimony of experts at the Appraisal Committee Meeting, the ACD on the use of Pemetrexed for the first line treatment of non-small cell lung cancer indicates that the Committee is minded not to recommend this therapy. This will be a blow to the patients for whom this drug provides a life line.	Comment noted
Royal College of Nursing	We are pleased to note the Committee concluded that Pemetrexed is clinically effective in UK clinical practice, with increased survival and lower toxicity as compared with established therapy. It is worth noting that the overall survival rate for this patient group is low.	Comment noted

Consultee	Comment	Response
Royal College of Nursing	We note that the Appraisal Committee has requested the manufacturer to submit further clarification and cost-effectiveness analyses for this technology. Following the Appraisal Committee's further deliberation, we strongly urge the Committee to issue a positive FAD for the use of this therapy for the first line treatment of non small cell lung cancer.	Comment noted. After consideration of the manufacturer's additional analysis, ERG critique and exploratory analysis the Committee concluded that pemetrexed was clinically and cost effective and therefore should be recommended for the treatment of non-small- cell lung cancer for people with adenocarcinoma or large cell carcinoma. Please see FAD section 1.1
Department of Health	The Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.
Sanofi-Aventis	No comments at this time regarding this appraisal.	Comment noted.

Comments received from commentators

Commentator	Comment	Response

Commentator	Comment	Response

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	**Section 3** (The technology) 3.1	It is stated that Carboplatin is still commonly used because patients "do not need the same hydration that is necessary with Cisplatin". This is not correct many clinicians will prescribe Carboplatin in preference to Cisplatin because of its better tolerance, and very similar efficacy. (Hotta et al Jou Clin Oncology Vol 22, No 19 2004 p3853-3859) Â I would have thought the committee should compare the technology with all approved regimes that is Carbo or Cisplatin in combination with Docetaxel or Paclitaxel as well as with Gemcitabine and Vinorelbine. I believe it is important for the committee to note that Paclitaxel is now off patent and the cytotoxic drug cost per cycle in combination with Carboplatin is less than a Â£100 per cycle of treatment in my unit. Gemcitabine is also shortly to come off patent and therefore both of these factors if taken into consideration would have a significant impact on the cost effectiveness of the technology.	FAD amended see FAD section 4.3. The Committee considered that gemcitabine was the main comparator of interest in the appraisal due to its market share and clinical expert statements. The Committee considered the issue of the price of gemcitabine, and recommended an early review of guidance when the price has been established see FAD section 4.14

* 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
NHS Professional 1	**Section 4** (Evidence and interpretation) 4.2 See comment on 3.1	Carboplatin is used in preference primarily because of toxicity issues as opposed to logistical reasons. 4.6 I presume the committee are referring to non squamous carcinoma here, there is no evidence overall that Pemetrexed is more clinically effective than Gemcitabine in combination with cisplatin. 4.8 The infusion time of Pemetrexed/Cisplatin is not significantly different from Gemcitabine/Cisplatin though number of hospital would be far fewer with a Pemetrexed combination.	FAD amended please see FAD section 4.2. The licence for pemetrexed is restricted to those with non-squamous histology.
NHS Professional 1	**Section 7** (related NICE guidance)	There are significant new developments in the treatment of lung cancer (some of which are referenced above in section 6) for instance Gefitinib is likely to be licensed in the near future for selected patients with NSCLC, Gemcitabine is coming off patent soon and there two are studies on maintenance treatment which are reaching maturity, and likely to made public this summer. Therefore the whole algorithm for treating advanced lung cancer is rapidly changing and the present time lag from publication of results of trials, to NICE guidance being produced is still unacceptable. For instance the definitive study on erlotinib was published in July 2005 and yet NICE guidance was only produced in late 2008. The timelines outlined above are an improvement but still unreasonable. A rolling annual programme of assessment of new technologies ought to be considered.	NICEs topic selection ensures that appropriate topics are selected for the NICE work programmes such that NICE guidance is relevant, timely and addresses priority issues which will help improve the health of the population.

Role*	Section	Comment	Response
Member of the public 1	Section 1	It is regrettable that the Committee is minded not to recommend Pemetrexed within its licensed indication given the clear survival benefit and reduction in burden to lung cancer patients with this innovative development.	The Committee accepted that pemetrexed was clinically effective (see FAD sections 4.2 to 4.8). However, the Committee requested additional analysis to demonstrate that pemetrexed was cost effective since the originally submitted model results were not consistent with the trial data. Please see FAD 4.9.
	Section 3.14	The Gemcitabine/Cisplatin comparator is entirely valid which is a well known regimen used throughout the UK. Following the Ardizzonni meta analysis, there is an increasing use of Cisplatin coupled with a hydration regimen which allows for day case administration.	The Committee recognised that gemcitabine/cisplatin is a valid comparator but noted that other treatments in current clinical practice by the NHS had been excluded in the modelling such as vinorelbine and docetaxel.
	Section 3.18	I am not sure that the additional concerns of the ERG are particularly important in changing the major aspects of the cost effectiveness analysis, but of course I am not an expert in such analysis.	Comment noted.
	Section 4.2	It should be noted that if an appropriate hydration policy is employed then Cisplatin can be given on an outpatient basis.	Comment noted

Role*	Section	Comment	Response
	Section 4.3	Gemcitabine/Cisplatin is not only commonly used in the UK, it is an extremely strong comparator given meta analyses reporting survival advantages of gemcitabine over non gemcitabine platinum regimens,and cisplatin over carboplatin when partnered with 3rd generation drugs such as gemcitabine. Therefore Gemcitabine/Cisplatin to be considered as an extremely strong comparator regimen over other comparators using taxanes vinorelbine etc.	The Committee considered that gemcitabine was the main comparator of interest in the appraisal due to its market share and clinical expert statements. see FAD section 4.4
	Section 4.5	Although there may be some Lung Cancer Units where distinction between adenocarcinoma and large cell is not common place, it is generally agreed that there would not be problems with implementation in any good UK Pathology Service supporting an Oncological Unit/Centre.	Comment noted.
	Section 4.8	It should also emphasised that both red and platelet cells transfusions were also reduced, compared with the gemcitabine /cisplatin. Again freeing up patients` ,carers` and Health Service time.	Comment noted.
	Section 4.10	Although further analysis has been recommended, hopefully this will not detract from the major patient and carer benefit of Pemetrexed for first line use in in a NSCLC target population of adenocarcinoma, large cell.	Comment noted.

Summary of comments received from members of the public

Theme	Response

Theme	Response