www.lilly.co.uk

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL

Tel: +44 (0) 1256 315000

HTA and Health Outcomes

Medical and Product Information: +44 (0) 1256 315999

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Dr Carole Longson
Director, Centre for Health Technology Evaluation
National Institute of Health and Clinical Excellence
MidCity Place
71, High Holborn
London
WC1V 6NA

Dear Dr Longson

Re: Appraisal consultation document on gefitinib in the first-line treatment of locally advanced or metastatic non-small cell lung cancer

We welcome the opportunity to review and comment on the appraisal consultation document (ACD) for gefitinib in first-line NSCLC.

Lilly believe that the summaries of clinical and cost effectiveness in the ACD appear to be reasonable in the light of the available clinical evidence. However, we have some concerns relating mainly to the methodology of the mixed treatment comparison (MTC) and the economic analysis, which are described below.

MTC incorporates hazard ratios from different patient sub-groups for different comparators

We acknowledge the difficulties of providing suitable evidence versus comparators commonly used in UK clinical practice with an indirect comparison methodology. This methodology requires that the studies selected for such comparison address similar patient populations to ensure robustness of results. To that end, we are concerned that the manufacturer's submission uses efficacy data for the non-squamous subgroup of patients for pemetrexed/cisplatin, when the efficacy data for all the other comparators in the network are for patients with all NSCLC histologies. Lilly believe that a separate indirect comparison between pemetrexed/cisplatin and gefitinib would allow a more robust evaluation of their comparative efficacy in more specific histology subgroups.

Use of progression-free survival and immature overall survival data in the economic model

Data from IPASS has shown that gefitinib improves progression-free-survival (PFS) compared to paclitaxel/carboplatin. The data on PFS are the basis of the economic model in the manufacturer's submission. Whilst we think PFS is important because it allows to assess the direct effect of the drug without the confounding effect of subsequent therapy, from an economic point of view it has some disadvantages since PFS in itself does not provide the evidence on extensions of length of life that is required for the estimation of QALYs gained from treatment.

The economic analysis should ideally incorporate more mature OS data from the IPASS trial. While it is reasonable to use immature OS data in the absence of final OS data, we would like to ensure that additional assumptions are explored in the projection of OS data to characterise the uncertainty this may have on the ICER estimates. In the absence of additional clinical trial data establishing the OS benefit for gefitinib in any other NSCLC setting, it is essential that other methods to model OS are fully explored in order to increase the level of confidence in the ICERs.

Additional concerns regarding the economic model

- The results of the MTC for pemetrexed in terms of safety appear to be inconsistent with its known tolerability profile, i.e., the risk of anaemia, fatigue and nausea/vomiting appear to be unduly high for pemetrexed/cisplatin compared to paclitaxel/carboplatin.
- The same rate of G-CSF use (22%) has been applied across all regimens. We believe that it would be more appropriate to apply a differential rate based on the probability of neutropaenic events with each regimen. For example, in the phase III trial comparing pemetrexed/cisplatin with gemcitabine/cisplatin in first-line NSCLC (Scagliotti et al, J Clin Oncol 2008) G-CSF was used in only 3.1% of patients in the pemetrexed/cisplatin arm and 6.1% of patients in the gemcitabine/cisplatin arm. Furthermore, the cost of G-CSF assumes that all patients would receive the maximum duration of 14 days. The model should therefore reflect current UK practice in terms of treatment duration for G-CSF, which would then be explored in the sensitivity analyses.
- Due to limitations in reported data, alopecia was not included in the MTC. However, the assumption of an equivalent rate across all non-gefitinb regimens is unlikely to be valid. Though alopecia does not carry cost implications in the economic model, it has a relevant impact on utility values.

Choice of comparators to gefitinib

Omission of pemetrexed/cisplatin as comparator in the original submission

Subsequent to the publication of NICE guidance (TA181) recommending pemetrexed/cisplatin in first-line NSCLC, this regimen is increasingly accepted as one of the main treatment options for patients with adenocarcinoma and large cell carcinoma in England and Wales.

According to the marketing authorisation for gefitinib and the manufacturer's submission to NICE, the target population for gefitinib appears to be the subgroup of patients with adenocarcinoma and EGFR-TKI positive mutations. Since most adenocarcinoma patients in the NHS currently are eligible to receive pemetrexed/cisplatin, it is the most suitable comparator to gefitinib in this subgroup of patients. We are therefore pleased that the appraisal committee have requested additional analyses comparing gefitinib with pemetrexed/cisplatin.

Efficacy of gemcitabine/ cisplatin in advanced NSCLC compared to other platinum doublets

Prior to the introduction of pemetrexed, gemcitabine in combination with cisplatin or carboplatin has been widely accepted in UK clinical practice as the gold standard for first-line NSCLC patients, irrespective of tumour histology. Results of a meta-analysis by Le Chevalier et al. (2005), suggested that the gemcitabine/cisplatin doublet had a significant benefit over other platinum doublets. Therefore, we question the appropriateness of paclitaxel/carboplatin as the comparator of choice in the IPASS clinical trial as there is evidence suggesting that clinical benefits of paclitaxel/carboplatin are surpassed by another platinum doublet in use at the time.

In view of the fact that gemcitabine/platinum is still the most widely used chemotherapy doublet in patients not eligible for pemetrexed/cisplatin, Lilly agree with the ERG's comments that the First-SIGNAL trial comparing gefitinib to gemcitabine/cisplatin should have been included in the meta-analysis of gefitinib trials.

Transferability of IPASS efficacy outcomes to UK clinical practice

The main evidence used in the manufacturer's submission was based on IPASS, a trial that recruited patients exclusively from Asia. As stated in the European Assessment Report (EPAR) for gefitinib, data from a pooled analysis from clinical trials and the literature show that in EGFR M+ tumours there is a higher response rate in Asians than in non-Asian. In addition, EGFR mutations occur more frequently in Asians than non Asians (40% vs 10%) and therefore these higher rates translate into better efficacy with gefitinib. The manufacturer has committed to providing new evidence to the EMA on the efficacy of gefinitinib in a Caucasian population. Until that evidence is available, due consideration should be given to the uncertainty around efficacy outcomes and the corresponding transferability of such outcomes to the UK clinical practice.

Yours sincerely

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Lilly UK

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