NICE National Institute for Health and Care Excellence

NICE guidance

Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Necitumumab, in combination with gemcitabine and cisplatin, is not recommended within its marketing authorisation for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-expressing squamous non-small-cell lung cancer that has not been treated with chemotherapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with necitumumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 Information about necitumumab

Description of the technology

2.1 Necitumumab (Portrazza, Eli Lilly) is a fully human monoclonal antibody, which inhibits the epidermal growth factor receptor (EGFR).

Marketing authorisation

2.2 Necitumumab has a marketing authorisation in the UK, in combination with gemcitabine and cisplatin chemotherapy, for treating locally advanced or metastatic EGFR-expressing squamous non-small-cell lung cancer (NSCLC), in adults who have not had chemotherapy for this condition.

Adverse reactions

2.3 The most common adverse reactions associated with necitumumab include skin reactions, venous thromboembolic events and laboratory abnormalities (hypomagnesaemia and albumin-corrected hypocalcaemia). For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

2.4 Necitumumab is given by intravenous infusion, at a dose of 800 mg on days 1 and 8 of each 3-week cycle.

Price

2.5 Necitumumab is available at a list price of £1,450 per 800-mg vial (excluding VAT; company submission). This equates to £2,900 per cycle, and an average of £30,740 per course (excluding the cost of gemcitabine and cisplatin; based on an average of 4.6 cycles per course for induction therapy and 6 cycles per course for maintenance therapy).

2.6 The company had agreed a patient access scheme with the Department of Health. If necitumumab had been recommended, this scheme would provide a simple discount to the list price of necitumumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

Evidence

The appraisal committee considered evidence submitted by Eli Lilly and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of necitumumab, having considered evidence on the nature of squamous non-small-cell lung cancer (NSCLC) and the value placed on the benefits of necitumumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

3.1 The committee heard from the clinical and patient experts that squamous NSCLC causes many distressing and debilitating symptoms, and typically has a poor prognosis. It heard that it is important for people with this condition to be able to function as fully as possible, for as long as possible, and that even a small extension to life would be very significant. The clinical and patient experts stated that there have been very few advances in first-line treatment of squamous NSCLC in the last 20 years. The committee concluded that there is an important unmet need for people with advanced or metastatic squamous NSCLC who have not had previous chemotherapy.

3.2 The committee understood that previously untreated advanced or metastatic squamous NSCLC is usually treated with chemotherapy comprising a platinum drug in combination with gemcitabine, vinorelbine, docetaxel or paclitaxel (most commonly gemcitabine). The clinical experts stated that these platinum-based regimens were all similar in efficacy. Given that gemcitabine combinations are the most commonly used regimens and that necitumumab has a marketing authorisation in combination with gemcitabine plus cisplatin, the committee concluded that gemcitabine plus cisplatin was the most important comparator for

necitumumab in this appraisal.

3.3 The committee noted that necitumumab has a marketing authorisation for treating tumours that express the epidermal growth factor receptor (EGFR), and queried whether tests for EGFR expression are routinely carried out in clinical practice. The clinical experts stated that, although EGFR-mutation testing was common for lung cancer (particularly non-squamous NSCLC), EGFR-expression testing was not widely used and would need to be introduced for people with squamous NSCLC if necitumumab were recommended. The experts stated that this test is already used for other cancers and so would be straightforward to implement for lung cancer. The committee heard from the clinical experts that differentiating between EGFR-expressing and non-expressing tumours (that is, those with an H-score above 0 or equal to 0 respectively) was appropriate, although the relevance of testing for different levels of EGFR expression (for example, high or low expression based on an H-score above or below 200) was less certain. The committee concluded that it would be necessary to test tumours for EGFR expression in people with advanced or metastatic squamous NSCLC if necitumumab were to be introduced into clinical practice.

Clinical effectiveness

3.4 The committee noted that the key clinical-effectiveness evidence for necitumumab was taken from the SQUIRE trial: a randomised, phase 3 study comparing necitumumab (in combination with gemcitabine plus cisplatin for induction therapy, followed by maintenance therapy with necitumumab alone; referred to in this document as the necitumumab group) with gemcitabine plus cisplatin. The committee noted that this trial included people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; 9% of people in the trial had a performance status of 2. It heard from the clinical experts that this was an advantage of the SQUIRE trial compared with previous trials in lung cancer, because people with a performance status of 2 are often excluded from trials, yet they comprise up to a quarter of people with advanced or metastatic squamous NSCLC in clinical practice. It also noted that 83% of the trial population was male, and heard from the clinical experts that this reflects the gender balance seen in clinical practice in England. The committee noted that patients were followed up for an average of more than 2 years, and that more than three-

quarters of patients died during the study, and so considered that the data were relatively mature. The committee concluded that the SQUIRE trial was of good quality and that the results would be generalisable to clinical practice in England.

3.5 The committee noted that the company presented evidence from 4 populations within the SQUIRE trial: the intention-to-treat population (ITT, n=1,093); patients having treatment in western Europe (n=348); patients with EGFR-expressing tumours in the whole-trial population (n=935; referred to in this document as 'EGFR-expressing [whole trial]'); and patients with EGFR-expressing tumours in the western European population (n=300; referred to in this document as 'EGFR-expressing western European'). The committee discussed in detail the most appropriate population to inform decision making.

- It noted that necitumumab has a marketing authorisation for treating EGFR-expressing tumours. The European Medicines Agency granted this marketing authorisation because people with tumours that did not express EGFR did not appear to benefit from necitumumab. Most people in the SQUIRE trial had EGFR-expressing tumours (about 95% of people for whom tumour samples were available for analysis, and about 85% of the population overall), and the patient characteristics were well balanced between treatment groups in these populations. The committee noted that, in the SQUIRE trial, subgroups based on high or low EGFR expression (H-score above or below 200) were prespecified; but, the EGFR-expressing populations were based on an H-score above 0, and this was not prespecified in the trial. The committee concluded that, although the EGFR-expressing populations were not prespecified, it was appropriate to use the results from these groups to inform decision making because they are consistent with the marketing authorisation for necitumumab.

- The committee heard from the clinical experts that it is helpful to identify populations that closely match clinical practice in England. However, the committee also noted that, on balance, the clinical experts considered that the whole-trial populations were likely to be more appropriate for decision making than the western European groups. The committee agreed that there were important limitations in the analyses of the western European populations. It noted the concerns raised by the evidence review group (ERG), in particular that these populations were relatively small post-hoc subgroups with a high risk of bias and that there was no statistically

significant interaction between subgroups based on region; it considered that these were important limitations. It also heard from the ERG that there was limited clinical justification for why the effectiveness of necitumumab may differ between regions, although it understood from 1 of the clinical experts that there may be some reasons why differences in effectiveness between regions could theoretically arise (for example, if people are diagnosed at different stages of disease or if there is varying effectiveness of a drug in people with different family origins). However, the committee understood that the ERG's clinical adviser considered that evidence from all geographical regions would be representative of people in England. The committee was aware that the overall survival in people with squamous NSCLC treated with necitumumab was similar in the ITT and western European populations, and that the apparent differences between the populations in overall-survival benefit were caused by lower survival in the gemcitabine plus cisplatin group of the western European populations. The committee was also aware that, in the western European populations, there were differences between the necitumumab and gemcitabine plus cisplatin treatment groups in the number of people with an ECOG performance status of 2. It heard from the clinical experts that performance status can strongly influence survival outcomes, and so considered that this imbalance may have influenced the outcomes in these populations. Because of the important limitations in these populations (including the high risk of bias and the potential influence of performance status on the outcomes), and taking into account the clinical experts' view that the whole-trial populations were more appropriate, the committee concluded that the western European populations were not appropriate for decision making.

The committee concluded that the most appropriate population on which to base its considerations was the EGFR-expressing (whole trial) population.

3.6 The committee noted that in the EGFR-expressing (whole trial) population, necitumumab was associated with statistically significant improvements in overall survival and progression-free survival compared with gemcitabine plus cisplatin: the median overall-survival gain associated with necitumumab was 1.74 months (hazard ratio 0.79; 95% confidence interval 0.69 to 0.92; p=0.002). The clinical experts stated that the median overall-survival gain was small, but the hazard ratio showed that the results were highly clinically significant. The experts also

highlighted that this hazard ratio is consistent with views, published in a recent article from the American Society of Clinical Oncology, on what constitutes a clinically meaningful treatment effect in lung cancer, and is similar to the hazard ratios seen in past clinical trials that have led to changes in practice. The patient expert emphasised that even small improvements in survival are very important for people with squamous NSCLC. The committee was reassured that the overall-survival benefit associated with necitumumab was consistent across prespecified subgroups, including in people with an ECOG performance status of 2. However, the committee was aware that necitumumab did not seem to be associated with improvements in quality of life, and understood the importance of improving quality of life for people with squamous NSCLC. The clinical experts emphasised that adding necitumumab to an established chemotherapy regimen did not worsen quality of life. The committee also heard from a clinical expert that a recently published subgroup analysis suggested that pain, breathlessness and quality of life improved in people with highly symptomatic disease. However, the committee was aware that this was a post-hoc analysis and so was subject to uncertainty. The committee concluded that it was uncertain whether necitumumab improves quality of life, but it is still an effective treatment option and offers small but clinically important improvements in overall survival compared with gemcitabine plus cisplatin.

3.7 The committee considered the effectiveness of necitumumab compared with other platinum-based chemotherapies presented in the company's network meta-analysis. This analysis suggested that necitumumab was associated with improved overall survival and progression-free survival compared with all regimens included in the analysis, although the 95% credible intervals were wide and many of them crossed 1. The committee noted important limitations in the network meta-analysis raised by both the company and the ERG, including limitations in the quantity and quality of evidence informing the analysis, the large number of links in the network, differences between the trial populations, and concerns about the choice of an unadjusted fixed-effects model. The committee considered that the results of the network meta-analysis were uncertain and it was difficult to draw conclusions from this analysis. It recalled that the platinum-combination regimens commonly used for squamous NSCLC are similar in effectiveness (see section 3.2), and therefore concluded that it was sufficient to consider the clinical effectiveness of necitumumab compared with gemcitabine plus cisplatin using the direct evidence from the SQUIRE trial.

3.8 The committee noted that in the SQUIRE trial, necitumumab was associated with a risk of hypomagnesaemia. The committee was also aware that the marketing authorisation for necitumumab in the US includes a warning about a risk of cardiopulmonary arrest. The committee acknowledged that the link between these 2 effects was unproven, and that the trial population included people with several comorbidities (including hypertension), but considered that both hypomagnesaemia and cardiopulmonary arrest may be important adverse effects of necitumumab. The committee was reassured by the clinical experts that hypomagnesaemia is a well-known effect of antibodies that target EGFR, and also chemotherapies such as cisplatin, and that magnesium levels are routinely monitored in people having chemotherapy for lung cancer. The committee concluded that the adverse effects associated with necitumumab were likely to be manageable in clinical practice.

Cost effectiveness

3.9 The committee noted that the company's economic model used a state-transition structure with a lifetime time horizon, and costs and benefits were discounted at a rate of 3.5% per year. The committee noted that the ERG considered that the model was appropriately structured and well implemented, and the committee concluded that the company's economic model was suitable for decision making.

3.10 As in the clinical-effectiveness evidence, the committee noted that the company also presented results for 4 populations (ITT, western Europe, EGFR-expressing [whole trial], and EGFR-expressing western European). In each population, necitumumab was compared with gemcitabine plus cisplatin and other platinum-based regimens using direct and indirect evidence respectively. The committee noted that the company considered the EGFR-expressing western European population to be the most generalisable to people in England and therefore the relevant population for its base case. The committee was aware that the population had a substantial effect on the economic model results: in the company's base case (EGFR-expressing western European population), necitumumab was associated with an incremental cost-effectiveness ratio (ICER) compared with gemcitabine plus cisplatin of £57,725 per quality-adjusted life year (QALY) gained, whereas in the EGFR-expressing (whole trial) population the ICER was £110,248 per QALY gained primarily due to the smaller QALY gain with

necitumumab in the EGFR-expressing (whole trial) population. The committee recalled its considerations on the clinical-effectiveness evidence (see sections 4.5 and 4.7), and considered that it was appropriate to take the same approach for the cost-effectiveness evidence. That is, the committee concluded that the EGFR-expressing (whole trial) population was the most appropriate population on which to base its considerations, and that comparing necitumumab with gemcitabine plus cisplatin using direct evidence was appropriate for decision making.

3.11 The committee noted that the company extrapolated the overall-survival results from the SQUIRE trial to the lifetime time horizon of the model using a log-logistic function. The ERG commented that the clinical plausibility of the log-logistic extrapolation was uncertain, and proposed that a Weibull function may be more appropriate. The committee was aware that the extrapolation function had a significant effect on the model results. It noted that the log-logistic function predicted that 2 to 5% of people would survive for 5 years (company model, EGFR-expressing [whole trial] population), and some would survive for as long as 15 years. The Weibull function predicted lower long-term survival rates (the 5-year survival rates were about 0.5% in the ERG's analysis, EGFR-expressing [whole trial] population). The committee was aware that the model included people with advanced or metastatic squamous NSCLC, for whom the prognosis is usually poor, and that in the SQUIRE trial 90% of people had metastases at 2 or more sites; the committee queried whether it was clinically plausible that people would survive for as long as the log-logistic model predicted. It heard from the clinical experts that a small number of people in this population would be expected to survive for 5 years, but that it was very rare for people to survive for 15 years. The committee considered that the most appropriate function for extrapolating overall survival was uncertain, but concluded that the results based on the Weibull function were likely to be more clinically plausible than the log-logistic function, and so the Weibull function was the more appropriate function to use for decision making.

3.12 The committee noted that the company applied its extrapolation from the end of the trial data onwards. It heard from the ERG that this approach meant that the model had been strongly influenced by the later stages of the survival data, when very few patients remained in the analysis, so the data were uncertain. The ERG suggested applying the extrapolation from an earlier time point. The committee

agreed that applying the extrapolation from the end of the survival data (when the curves were highly uncertain) was not appropriate. However, the committee noted that the ERG chose an earlier time point to start the extrapolation, using the time at which at least 20 patients remained in the analysis. The committee noted that the choice of this earlier time point was arbitrary. The committee was also aware that in exploratory analyses (presented in the ERG's addendum), changing the starting point of the extrapolation had inconsistent effects on the model results: as the starting point of the extrapolation moved earlier, the cost effectiveness of necitumumab first decreased but then increased. The committee agreed that it was not appropriate to start the extrapolation from the end of the survival data (as in the company's model). It recognised that the most appropriate starting point for the extrapolation was uncertain, but concluded that it would have to be at an earlier time point when more patients remained in the analysis.

3.13 The committee noted that the company incorporated quality of life into the economic model by applying utility values to each health state. The utility values for the pre-progression states were based on EQ-5D data from the SQUIRE trial, pooled between the necitumumab and gemcitabine plus cisplatin treatment groups. The committee noted that the company also incorporated the effects of adverse events on quality of life, by applying utility decrements to each event. It noted that the ERG had some concerns about the values used, and understood that the company had not explored a possible alternative approach in which adverse events would have been captured by using different utility values for each treatment. The committee was aware that quality of life did not seem to differ between the 2 treatment groups in the SQUIRE trial (see section 3.6), and was also aware that the effects of adverse events on the model results were small. The committee concluded that the company's approach to capturing quality of life in the economic model was acceptable.

3.14 The committee noted that the costs of the EGFR-expression tests that would need to be introduced alongside necitumumab treatment (see section 3.3) were not included in the company's model. The company's response to the factual accuracy check of the ERG report stated that EGFR-expression testing costs £42 per test. The committee considered that these costs should be included, even though they would have a small effect on the model results. The committee concluded that the costs of EGFR-expression testing should have been included.

3.15 The committee considered the most plausible ICER for necitumumab compared with gemcitabine plus cisplatin. It had previously concluded that the EGFR-expressing (whole trial) population was the most appropriate for decision making (see section 3.10), and so considered results for this population only. It noted that in the company's analysis for this population – based on a log-logistic extrapolation function applied from the end of the survival data – necitumumab was associated with an ICER of £110,248 per QALY gained compared with gemcitabine plus cisplatin. The ERG's preferred analysis for this population used a Weibull extrapolation function applied from before the end of the survival data (when at least 20 patients remained in the analysis), and in this analysis the ICER was £169,612 per QALY gained. It was aware that the most appropriate function and starting point for the extrapolation were uncertain, although the Weibull function was likely to be more clinically plausible than the log-logistic function and applying the extrapolation from the end of the survival data was inappropriate (see sections 4.11 and 4.12). The committee considered that, although uncertain, the ERG's analysis more closely matched its preferred assumptions than the company's analysis. The committee concluded that the most plausible ICER for necitumumab compared with gemcitabine plus cisplatin was between £110,000 and £170,000 per QALY gained, and was likely to be towards the upper end of this range.

3.16 The committee considered the innovative nature of necitumumab. It heard from the patient and clinical experts that there have been few improvements in the treatment of squamous NSCLC in the last 20 years, and that there is an important unmet need for people with this condition. It understood that the survival benefit associated with necitumumab, although small, was clinically significant and important for people with squamous NSCLC. The committee concluded that necitumumab is innovative, but there were no additional benefits associated with this treatment that had not been captured in the economic analysis.

3.17 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

  In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are sufficiently robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

3.18 The committee noted the evidence presented by the company, which showed that people with advanced or metastatic squamous NSCLC have a life expectancy of less than 24 months: it noted that the median survival in people in the gemcitabine plus cisplatin group of the SQUIRE trial (EGFR-expressing [whole trial] population) was 9.99 months, although the mean survival predicted by the economic model was higher (the value is commercial in confidence). The committee concluded that people for whom necitumumab is indicated have a short life expectancy, so this criterion was met. The committee considered that the extension to life associated with necitumumab was uncertain. The median overall-survival gain in the SQUIRE trial (EGFR-expressing [whole trial] population) was 1.74 months. However, the mean overall-survival gain predicted by the economic model was strongly influenced by the function and starting point of the overall-survival extrapolation. The committee was aware that in the ERG's analysis, the overall-survival gain associated with necitumumab was 2.25 months. It noted that the gain would be larger if a log-logistic function were used or the extrapolation were started at a different time point; the overall-survival gain increased to 2.84 months when a log-logistic function was applied from the time when at least 20 patients remained in the analysis. Noting the important uncertainties in the survival gain, the committee was not convinced that there was sufficiently robust evidence (based on plausible and objective assumptions) to accept that necitumumab met the extension to life criterion, even when taking into account the life expectancy for this population. The committee concluded that necitumumab did not meet the criteria to be considered a life-extending, end-of-life treatment.

3.19 Taking into account the most plausible ICER for necitumumab (between £110,000 and £170,000 per QALY gained; see section 3.15), the innovative nature of necitumumab and the fact that necitumumab did not meet the criteria to be

considered a life-extending, end-of-life treatment, the committee concluded that necitumumab was not recommended as a cost-effective use of NHS resources.

3.20 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee heard from the company that necitumumab may be considered for funding through the Cancer Drugs Fund. However, because of the timing of this appraisal, the company had not had an opportunity to present a case for including necitumumab in the Cancer Drugs Fund. The committee considered that the most plausible ICER for necitumumab (see section 3.15), and all of the ICERs presented for the EGFR-expressing (whole trial) population, were substantially higher than the range normally considered a cost-effective use of NHS resources, and so necitumumab did not have the plausible potential for satisfying the criteria for routine use. The committee also considered that although there were uncertainties in the evidence for this appraisal, the clinical-effectiveness evidence from SQUIRE was relatively mature (see section 3.4) and there were no clinical uncertainties that could be addressed by collecting outcome data from people in the NHS, which could be used to inform a subsequent update of the guidance. The committee concluded that necitumumab did not meet the criteria to be considered for use in the Cancer Drugs Fund.

3.21 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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