Scottish Medicines Consortium

gefitinib 250mg film-coated tablets (Iressa®) No. (615/10)
AstraZeneca UK Ltd

09 April 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

gefitinib (Iressa®) is not recommended for use within NHS Scotland.

Licensed indication under review: the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of epidermal growth factor receptor tyrosine kinase (EGFR-TK).

In a comparative study in previously untreated patients, gefitinib was superior to a platinum-based doublet chemotherapy regimen in terms of progression-free survival; subgroup analysis supported this finding in patients with activating mutations of EGFR-TK.

However, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and in addition, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of epidermal growth factor receptor tyrosine kinase (EGFR-TK).

Dosing information

One 250mg tablet orally once daily.

Treatment with gefitinib should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Product availability date

14 September 2009

Summary of evidence on comparative efficacy

Gefitinib is an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor which blocks EGFR downstream signalling processes that activate cell proliferation, cell migration, angiogenesis and cell survival.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in those patients with previously untreated locally advanced or metastatic NSCLC with activating EGFR-TK mutations i.e. only as a first line therapy.

The key evidence to support the indication under review comes from the results of one phase III open-label study in 1,217 Asian patients with advanced or metastatic NSCLC. Eligible patients were aged ≥18 years with adenocarcinoma histology, were ex-light or never smokers and had received no previous chemotherapy, biologic or immunologic therapy. Patients were randomised in a ratio of 1:1 to receive gefitinib (250mg orally daily, n=609) or paclitaxel (200mg/m^2 intravenously) followed by carboplatin (area under the curve 5 or 6mg/ml/min) every three weeks for up to 6 cycles (n=608). Treatment was continued until disease progression, unacceptable toxic effects, patient withdrawal or until six chemotherapy cycles were reached. Randomisation was balanced for World Health Organisation (WHO) performance status, smoking status, sex and study centre. Following disease progression, patients in the gefitinib group could cross-over to treatment with paclitaxel/carboplatin, or other treatment at the physician's discretion; paclitaxel/carboplatin patients could receive further therapy at the physician's discretion on progression.

The primary endpoint was progression-free survival (assessed from the date of randomisation to the earliest sign of disease progression according to the Response Evaluation Criteria in Solid Tumours [RECIST]) or death from any cause. Non-inferiority of gefitinib was assessed versus paclitaxel/carboplatin using a pre-defined non-inferiority limit. If the 95% confidence interval (CI) for the hazard ratio was below 1.2 then non-inferiority was assumed and if below 1 then superiority was assumed. Secondary endpoints included overall survival, objective response rates according to RECIST and disease related symptom and quality of life scores.

After a median follow-up of 5.6 months, median progression-free survival was 5.7 months in the gefitinib group and 5.8 months in the paclitaxel/carboplatin group. However, using Kaplan-Meier estimates, the progression-free survival rates were 25% and 6.7% respectively

at 12 months; hazard ratio of 0.74 (95% CI: 0.65 to 0.85) demonstrating non-inferiority and superiority of gefitinib.

In a pre-specified subgroup analysis of 261 patients (21%) who had positive EGFR mutations, progression-free survival was significantly longer in the gefitinib group compared with the paclitaxel/carboplatin group (9.5 months versus 6.3 months respectively; hazard ratio 0.48 [95% CI: 0.36 to 0.64]). Conversely in a subgroup of 176 patients with negative EGFR mutations, progression-free survival was significantly shorter in the gefitinib group (1.5 months versus 5.5 months; hazard ratio 2.85 [95% CI: 2.05 to 3.98]).

The secondary endpoint of overall survival was performed after 450 deaths (37% of population) and was not significantly different between the groups: median of 18.6 months in the gefitinib group and 17.3 months in the paclitaxel/carboplatin group; hazard ratio 0.91 (95% CI: 0.76 to 1.10). In the subgroup with EGFR mutation positive, the difference in median overall survival was not significant between groups (not reached in the gefitinib group and 19.5 months in the paclitaxel/carboplatin group; hazard ratio 0.78 [95% CI: 0.50 to 1.20]). Mature overall survival results are awaited.

In the overall study population, objective response rates, including complete and partial responses, were significantly higher in the gefitinib (43%) than the paclitaxel/carboplatin group (32%). The difference was also significant in the EGFR mutation positive subgroup (71% versus 47% respectively). In this subgroup, the quality of life scores and symptom improvement rates were significantly higher in the gefitinib than the paclitaxel/carboplatin patients.

Summary of evidence on comparative safety

During the key study, patients treated with gefitinib compared with paclitaxel/carboplatin reported significantly higher incidences of rash or acne (66% versus 22% respectively), diarrhoea (47% versus 22% respectively) and elevated liver aminotransferase levels. The incidence of neurotoxic effects (11% versus 70% respectively), nausea (17% versus 44% respectively), vomiting (13% versus 33% respectively) and haematological toxic effects were significantly lower in the gefitinib than the paclitaxel/carboplatin group. Interstitial lung disease is a potentially fatal co-morbidity of NSCLC which has been associated with gefitinib and other cancer treatments. In the key study, interstitial lung disease occurred in 2.6% of gefitinib patients (three of whom died) and in 1.4% of paclitaxel/carboplatin patients (one of whom died).

Summary of clinical effectiveness issues

The results of the key study indicate that gefitinib is more effective than paclitaxel/carboplatin in terms of progression-free survival as first-line treatment of advanced or metastatic NSCLC. However the study was open-label and the primary outcome was assessed without blinding. A sub-group analysis of this study provided efficacy data for the population covered by the indication under review, namely patients with EGFR-TK mutation positive status (261/1217 [21%]). However the study was not powered for this subgroup analysis and, since randomisation was not stratified by EGFR-TK mutation status, the treatment groups in the subgroup analysis may not be well balanced. In the overall population, the progession-free survival curve favoured paclitaxel/carboplatin up to about 6 months and this was attributed to the benefit of chemotherapy but not gefitinib in the EGFR mutation negative subgroup. The subsequent benefit favouring gefitinib was due to prolonged progression-free survival in the EGFR mutation positive subgroup.

Overall survival was a secondary endpoint and available data are not yet mature. On the basis of 450 events, there was no significant difference between gefitinib and paclitaxel/carboplatin. The results of follow-up survival analysis are likely to be confounded by patients crossing over from gefitinib to paclitaxel/carboplatin on disease progression and subsequent lines of treatment; 39% of gefitinib patients subsequently received paclitaxel/carboplatin and 10% other anticancer therapy; 40% of paclitaxel/carboplatin patients subsequently received an EGFR-TK inhibitor and 14% other anticancer treatment.

The key study enrolled Asian patients with adenocarcinoma who were non- or ex-light smokers and mainly female making the generalisability of the results to the Scottish population questionable. Treatment with EGFR-TK inhibitors is most effective in patients with these clinical characteristics. Asian patients have a higher incidence of EGFR mutation-positive tumours. The European Medicines Agency noted that there was a need to confirm the efficacy of gefitinib in the selected population with EGFR mutation positive tumours prospectively in a Caucasian population. The manufacturer has committed to submit such data.

The Scottish Intercollegiate Guidelines Network recommends a maximum of four treatment cycles with a platinum-based combination doublet regimen in the advanced NSCLC population. The key study permitted up to six cycles of paclitaxel/carboplatin and the median number administered was six.

There is no direct clinical evidence comparing gefitinib with gemcitabine/carboplatin or vinorelbine/cisplatin, the more commonly used treatments in Scotland for advanced NSCLC.

EGFR-TK mutation testing will be necessary to identify patients eligible for treatment with gefitinib under its licensed indication. This is currently not routine clinical practice within Scotland. It is not clear if the test used in the study would be the same as that likely to be used in practice.

Gefitinib's oral formulation offers an advantage in terms of ease of administration.

Summary of comparative health economic evidence

The manufacturer presented a five year Markov model with a 21-day cycle that compared gefitinib with gemcitabine/carboplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK. The additional comparators of:

- gemcitabine/cisplatin
- paclitaxel/carboplatin
- vinorelbine/cisplatin
- pemetrexed/cisplatin

were also considered, but without the range of sensitivity analyses that were presented for the principal comparison of gefitinib with gemcitabine/carboplatin. The primary comparator reflected Scottish practice. The model included the four main health states of response, stable, progressive and dead, with the impacts of adverse events being additional to these.

When patients progressed, half were assumed to receive an active second-line therapy and the remainder best supportive care. Active second-line therapy was assumed to be: paclitaxel/carboplatin for the gefitinib arm; and, erlotinib for the chemotherapy doublet arms. Second-line treatments served to increase the post-progression treatment cost by around 10% per cycle in the chemotherapy doublet arms as compared to the gefitinib arm due to the

higher cost of erlotinib. Active third-line treatment was also not considered, though this may become an option in clinical practice.

The effectiveness of gefitinib and paclitaxel/carboplatin was drawn from the pivotal gefitinib trial results among the EGFR mutation positive patient sub-group. The effectiveness of the other chemotherapy doublets was drawn from a mixed treatment comparison, within which paclitaxel/carboplatin provided the link to the results of the pivotal gefitinib trial. It was assumed that the relative results derived from the mixed treatment comparison would also apply to the EGFR mutation positive patient sub-group.

A Weibull curve was fitted to the Kaplan-Meier progression free and overall survival curves of the pivotal trial, the hazard ratios from the mixed treatment comparison being used to extrapolate these results to the other chemotherapy doublets.

Utility data were mainly drawn from a paper in the literature relating to second-line chemotherapy for NSCLC patients. The costs of adverse events were mainly drawn from industry submissions to NICE single technology assessments.

For the primary comparison of gefitinib against gemcitabine/carboplatin the modelling resulted in an estimated incremental 0.186 QALYs from gefitinib use. The incremental cost was estimated as £13,692, yielding a cost effectiveness estimate of £73,827 per QALY.

For the other comparators the cost effectiveness of gefitinib was estimated as:

	Incremental cost per QALY
• gemcitabine/cisplatin	£95,163/QALY
• paclitaxel/carboplatin	£85,969/QALY
• vinorelbine/cisplatin	£79,001/QALY
• pemetrexed/cisplatin	£154,022/QALY

Results for the comparison with gemcitabine/carboplatin were particularly sensitive to the hazard ratio for overall survival for gefitinib, there being considerable uncertainty around this. Results were also sensitive to the hazard ratio for overall survival for gemcitabine/ carboplatin; the hazard ratio for progression free survival for gemcitabine/carboplatin; the costs of second-line erlotinib for gemcitabine/carboplatin, the maximum number of cycles for gemcitabine/carboplatin; IV administration costs; and the prevalence of EGFR mutation positive.

While the manufacturer demonstrated that among a family of smooth survival curves fitted to the survival data the Weibull performed the best, it was not entirely clear that a smooth survival function best reflected the data of the pivotal trial.

Additional significant weaknesses included:

- a maximum of six cycles of chemotherapy being assumed compared to the four recommended by SIGN;
- possible bias arising from the handling of active second-line treatments in the model;
- no obvious adjustment for differences in use of 2nd-line therapies in the platinum doublet mixed treatment comparison; and
- uncertainty as to the EGFR mutation positive prevalence in the presenting Scottish population.

Additional sensitivity analysis was received from the manufacturer to show the impact of addressing a number of these concerns i.e. the number of cycles of chemotherapy and the cost of second line treatments. The combined effect of making these adjustments was to raise the ICERs above still further.

As a consequence, and in addition to the high cost per QALY, the manufacturer did not present a sufficiently robust economic case to gain acceptance by the SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 80, a national clinical guideline: Management of patients with lung cancer, in February 2005. It states that chemotherapy with a platinum based combination doublet regimen should be considered in all Stage IIIB and IV patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive it. Chemotherapy is not generally recommended for NSCLC patients who are Performance Status 3 or 4. For patients with advanced NSCLC the number of chemotherapy cycles should not exceed four. There is a note on the SIGN website that a need for an update is currently being considered.

The National Institute for Health and Clinical Excellence published Clinical Guideline 24: The diagnosis and treatment of lung cancer, in February 2005. It states that chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.

Additional information: comparators

The current standard first-line treatment in patients with advanced disease consists of platinum-based doublet regimens (combination of gemcitabine, vinorelbine, docetaxel, or paclitaxel with cisplatin or carboplatin). Experts consulted by SMC have advised that combinations of gemcitabine/carboplatin and vinorelbine/cisplatin are more commonly used in Scotland.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (£)
Gefitinib*	**250mg orally daily**	**2,023**	**8,093**
Pemetrexed Cisplatin	500mg/m^2 iv infusion day 1 75mg/m^2 iv infusion day 1	1,651	6,604
Gemcitabine plus platinum			
Gemcitabine Carboplatin	1,200mg/m^2 iv infusion day 1 and 8 575mg/m^2 iv infusion day 1	1,141	4,563
Gemcitabine Cisplatin	1,000mg/m^2 iv infusion day 1, 8 and 15 100mg/m^2 iv infusion day 1 (4-week cycle)	938	3,752
Gemcitabine Cisplatin	1,250mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion day 1 (3-week cycle)	827	3,308
Paclitaxel plus platinum			
Paclitaxel Carboplatin	200mg/m^2 iv infusion day 1 690mg iv infusion day 1	1,039	4,155
Paclitaxel Cisplatin	175mg/m^2 iv infusion day 1 80 mg/m^2 iv infusion day 2	719	2,876
Docetaxel plus platinum			
Docetaxel Cisplatin	75mg/m^2 iv infusion on day 1 75mg/m^2 iv infusion on day 1	1,074	4,296
Vinorelbine plus platinum			
Vinorelbine cap Cisplatin	60 to 80mg/m^2 orally day 1 and 8 75mg/m^2 iv infusion on day 1	535 to 667	2,139 to 2,667
Vinorelbine iv Cisplatin	25 to 30mg/m^2 iv infusion day 1 and 8 75mg/m^2 iv infusion on day 1	331 to 390	1,324 to 1,562

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 February 2010, BNF edition 58 (September 2009) or MIMs (February 2010). A body surface area of 1.8m^2 was used for dose calculations and one course comprises four cycles. *Costs for gefitinib were calculated on a 28 day cycle to allow comparison but gefitinib treatment will be continuous. Costs for additional vitamin supplements for pemetrexed and corticosteroids for pemetrexed, paclitaxel and docetaxel have not been included. iv= intravenous.

Additional information: budget impact

The manufacturer estimated that 2000 NSCLC patients would be staged and found to have locally advanced or metastatic disease. Around 30% or 612 of these were estimated to be eligible for chemotherapy. In the pivotal trial despite 85% of patients agreeing to provide samples, 45% were either not available or unsuitable for assessing EGFR mutation status. Applying the residual 40% to the 612 patients eligible resulted in an estimated 245 patients being tested for EGFR mutation status, with an assumed EGFR mutation positive prevalence of 17%.

The manufacturer's estimates showed a gross drug cost in year one of £916k rising to £1.09m by year five. The net drug costs were £727k and £869k in years one and five respectively.

SMC clinical experts have indicated that the manufacturer's projection of patient numbers may be an underestimate. Increasing the proportion of patients with lung tumour samples of sufficient quality and quantity for EGFR-TK mutation testing to 64% in year one rising to 94% in year five, resulted in net costs of £1.1m and £1.6m in years one and five respectively.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including **30 March 2010.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

The undernoted reference was supplied with the submission. The reference shaded grey is additional to the reference supplied with the submission.

Mok TS, Wu Y, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.

European Medicines Agency (EMEA) European Public Assessment Report (EPAR) for gefitinib (Iressa®), EMEA/H/C/001016 www.emea.europa.eu