Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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2nd Re-submission

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

AstraZeneca UK Limited

06 November 2015

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 Scotland. The advice is summarised as follows:

ADVICE: following a second re-submission

gefitinib (Iressa®) is accepted for restricted use within NHS Scotland.

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).

SMC restriction: in patients with previously untreated locally advanced or metastatic NSCLC with activating EGFR-TK mutations i.e. as a first-line therapy.

In patients with EGFR mutation-positive, advanced NSCLC, randomised controlled studies demonstrated an improvement in the progression-free survival and tumour response rates for those treated with gefitinib compared with platinum-doublet chemotherapy. There was no overall survival benefit demonstrated.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of gefitinib. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Vice-Chairman,
Scottish Medicines Consortium

Indication

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

The recommended dose is one 250mg tablet once a day. If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

The tablet may be taken orally with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as a dispersion in water (non-carbonated). No other liquids should be used. Without crushing it, the tablet should be dropped in half a glass of drinking water. The glass should be swirled occasionally, until the tablet is dispersed (this may take up to 20 minutes). The dispersion should be drunk immediately after dispersion is complete (i.e. within 60 minutes). The glass should be rinsed with half a glass of water, which should also be drunk. The dispersion can also be administered through a naso-gastric or gastrostomy tube.

Patients with poorly tolerated diarrhoea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250mg dose. For patients unable to tolerate treatment after a therapy interruption, gefitinib should be discontinued and an alternative treatment should be considered.

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

Product availability date

September 2009
Gefitinib meets SMC end of life criteria.

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.[1]

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product in those patients with previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR-TK mutations i.e. as a first-line therapy. SMC has previously accepted both afatinib and erlotinib for use in NHSScotland at this stage in the disease.

The evidence for this indication comprises four multi-centre, randomised, controlled, open-label phase III studies conducted predominantly in Asia (IPASS, NEJ002, WJTOG3405, and First-SIGNAL) and a post-marketing, single-arm phase IV study conducted in a Caucasian population (IFUM).[2-9]

The phase III studies recruited adults with advanced NSCLC. NEJ002 and WJTOG3405 specifically recruited patients with activating mutations of EGFR-TK, whereas these patients were a subgroup in

IPASS (21%, 261/1,217) and First-SIGNAL (13%, 42/313). Patients were required to have an Eastern Cooperative Oncology Group (ECOG) or World Health Organisation (WHO) performance status of 0 to 2 in IPASS and First-SIGNAL and 0 or 1 in NEJ002 and WJTOG3405. All studies randomly assigned patients in a 1:1 ratio to either gefitinib 250mg orally once daily or to intravenous platinum doublet chemotherapy. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent or protocol stipulated maximum number of 21-day chemotherapy cycles. Post-progression treatment was at local investigator discretion and crossover was permitted. The platinum regimens and duration of treatment for each study are presented in Table 1.

Table 1: Platinum-doublet regimens of the phase III studies

Study	Platinum doublet regimen	Duration of chemotherapy
IPASS [2, 3]	Day 1: Carboplatin (AUC 5 or 6) Paclitaxel 200mg/m^2	Maximum six cycles
NEJ002 [4, 5]	Day 1: Carboplatin (AUC 6) Paclitaxel 200mg/m^2	At least three cycles
WJTOG3405 [6, 7]	Day 1: Cisplatin 80mg/m^2 Docetaxel 60mg/m^2	Maximum of three to six cycles
First-SIGNAL [8]	Day 1: Cisplatin 75mg/m^2 Day 1 and 8: Gemcitabine 1,250mg/m^2	Maximum of nine cycles

In IPASS, NEJ002, and WJTOG3405, the primary outcome was progression-free survival (PFS), defined as the time from randomisation to the first observed disease progression, according to Response Evaluation Criteria in Solid Tumours (RECIST) or patient death. Overall survival was the primary outcome in First-SIGNAL. Survival outcomes were analysed using Kaplan-Meier curves with hazard ratios estimated using Cox proportional hazard models and compared with log-rank tests. A secondary outcome assessed in the studies was overall response rate (ORR), defined as complete or partial response according to RECIST. Gefitinib was associated with statistically significant improvements in PFS and larger ORRs compared with platinum doublet regimens; however there was no statistically significant benefit with overall survival.[2-8] Outcomes for patients with activating mutations of EGFR TK are presented in Table 2. Survival data from the most recent data cut are presented.

The IFUM study, a phase IV, open-label, single-arm study, was conducted to characterise the efficacy and safety of gefitinib in Caucasian patients as a post-marketing requirement stipulated by the European Medicines Agency. The study recruited Caucasian adults with confirmed advanced NSCLC and activating mutations of EGFR-TK, WHO performance status 0 to 2 who were eligible for standard first-line treatment. All patients (n=106) received gefitinib 250mg orally once daily until disease progression, unacceptable toxicity or other reason. Subsequent treatment was at the investigator's discretion. At a median follow up of 13.0 months, the investigator-assessed ORR was 70% (partial response 72/106, complete response 2/106). Central, independent assessment of tumour response resulted in an ORR of 50%. Median PFS was estimated at 9.7 months based on 61 events (58% of study population). The 12-month PFS rate was estimated to be 38%. Overall survival data are still immature; at the data cut-off 27% of patients had died, median overall survival was estimated at 19.2 months, and 12-month overall survival rate was 70%.[9]

Table 2: Outcomes from the phase III studies[2-8]

Outcome		Study			
		IPASS (n=261)*	NEJ002 (n=228)	WJTOG3405 (n=177)	First-SIGNAL (n=42)*
PFS	Event rate	80% (208/261)	87% (199/228)	66% (116/177)	NR
	Median (gefitinib)	9.5 months	10.8 months	9.2 months	8.0 months
	Median (platinum)	6.3 months	5.4 months	6.3 months	6.3 months
	HR (95%CI)	0.48 (0.36 to 0.64)	0.32 (0.24 to 0.44)	0.49 (0.34 to 0.71)	0.54 (0.27 to 1.10)
OS	Event rate	76% (199/261)	61% (138/228)	46% (82/177)	NR
	Median (gefitinib)	21.6 months	27.7 months	35.5 months	27.2 months
	Median (platinum)	21.9 months	26.6 months	38.8 months	25.6 months
	HR (95%CI)	1.00 (0.76 to 1.33)	0.89 (0.63 to 1.24)	1.19 (0.77 to 1.83)	1.04 (0.50 to 2.18)
ORR	Gefitinib	71%	74%	62%	85%
	Platinum	47%	31%	32%	38%
	p-value for difference	p=0.0001	p<0.001	p<0.0001	p=0.002

PFS = progression-free survival, OS = overall survival, ORR = overall response rate, HR = hazard ratio, CI = confidence interval, NR = not reported. *sub-group of the full study population with activating mutation of EGFR-TK.

IPASS assessed quality of life and symptoms using the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire. The questionnaire was completed until disease progression and study drug discontinuation. Post-hoc exploratory analysis in the subgroup of patients with activating mutations of EGFR-TK suggested that gefitinib treatment was associated with a statistically significantly greater proportion of patients achieving a sustained clinically important improvement in total FACT-L score, trial outcome index (TOI) and lung cancer subscale (LCS) scores (table 3).[2]

Table 3: Quality of life outcomes for EGFR mutation-positive patients in IPASS (Post-hoc exploratory analysis).

Quality of life outcome (definition of clinically relevant improvement)	Proportion with sustained clinically relevant improvement		Odds ratio (95% CI), p-value
	Gefitinib (n=131)	Platinum (n=128)	
Total FACT-L score (6 points on a 0 to 136 scale)	70%	44%	3.01 (1.79 to 5.07), p<0.0001
TOI (6 points on a 0 to 84 scale)	70%	38%	3.96 (2.33 to 6.71), p<0.0001
LCS (2 points on a 0 to 28 scale)	76%	54%	2.70 (1.58 to 4.62), p=0.0003

FACT-L = functional assessment of cancer treatment – lung, TOI = trial outcome index, LCS = lung cancer scale, CI = confidence interval.

Summary of evidence on comparative safety

Adverse events (AEs) in patients treated with gefitinib tended to be mild in severity (grade 1 or 2). In IPASS, dose modification to manage toxicity was required in 16% of gefitinib patients and in the platinum group, 35% for carboplatin and 38% for paclitaxel.[2] Grade 3 or 4 AEs were experienced in smaller proportions of patients treated with gefitinib compared with platinum-doublet treatment. In IPASS the proportions were 29% and 61% respectively, and in NEJ002 the proportions were 41% versus 72%.[2, 5]

In the total study population of IPASS, the most commonly reported AEs in the gefitinib group were: rash or acne (66% versus 22% in the platinum group), diarrhoea (47% versus 22%), dry skin (24% versus 2.9%), anorexia (22% versus 43%), pruritus (19% versus 13%) and stomatitis (17% versus 8.7%).[2] Liver transaminase elevation was also a commonly reported AE in the studies. [4, 6]

Interstitial lung disease events such as acute respiratory distress syndrome or pneumonitis occurred in 2.6% of gefitinib patients and in 1.4% of platinum patients in the IPASS study. Four patients died as a result of this AE, three in the gefitinib group and one with platinum doublet therapy.[2] In NEJ002 there were six cases of interstitial lung disease reported in the gefitinib group; three were severe including one that was fatal.[4] In WJTOG3405, two patients in the gefitinib group developed interstitial lung disease, one case of which was fatal.[6]

In Caucasian patients the side effect profile of gefitinib was similar to that observed in the comparative Asian studies. AEs were reported in most patients (93%), and the most common were rash (45%), diarrhoea (31%) and vomiting (13%). AEs tended to be mild in severity. AEs at least grade 3 in severity were reported in 15% of patients; diarrhoea (3.7%), pneumonia (2.8%), cardiac failure (1.9%), and liver transaminase elevation (0.9%).[9]

Summary of clinical effectiveness issues

Currently there are three EGFR-TK inhibitors licensed for use in patients with advanced NSCLC; gefitinib, afatinib and erlotinib. The submitting company has requested that SMC considers the use of gefitinib in those patients with previously untreated locally advanced or metastatic NSCLC with activating EGFR-TK mutations i.e. as a first-line therapy. SMC has previously accepted both afatinib and erlotinib for use in NHSScotland at this stage in the disease. Gefitinib meets SMC end-of-life criteria.

The evidence comes from four phase III studies which compared gefitinib with doublet chemotherapy. The relevant results from the IPASS and First-SIGNAL studies come from sub-groups of patients with EGFR positive mutations from the overall study patient populations. The primary outcome was PFS in three of the four comparative studies, and overall survival in the fourth, First-SIGNAL. PFS is considered to be a surrogate endpoint. In the three larger studies, gefitinib in comparison with platinum-doublet therapy was associated with a significant improvement in PFS, with an extension of median PFS of 2.9 to 5.4 months in patients with activating mutations of EGFR-TK. In the relevant sub-group in First-SIGNAL there was no significant difference between gefitinib and platinum treatment for PFS. The sample size was small for this sub-group and the study was not powered for this comparison. In all four studies the benefits from gefitinib in terms of tumour response (ORR) and PFS did not translate into an observed overall survival advantage.[2-8] None of the studies were

powered to demonstrate an advantage in overall survival in patients with activating mutations of EGFR-TK. Furthermore, analyses of overall survival were confounded by patient crossover following disease progression. The proportion of patients randomised to platinum-doublet therapy who subsequently received gefitinib or other EGFR-TK inhibitors was 64% in IPASS, 98% in NEJ002 and 91% in WJTOG3405.[3, 5, 7]

Post hoc subgroup analysis of IPASS suggests a benefit for global quality of life as well as for lung cancer associated symptoms with gefitinib treatment compared with platinum-doublet therapy.[2] Responses to the quality of life questionnaires used in IPASS may have been biased by the open-label nature of the study.

The comparative studies were conducted in an Asian population. The phase IV study IFUM, characterised the efficacy and safety of gefitinib in a Caucasian population and the outcomes in this study were similar to the Asian-based studies. Comparator regimens used in the Asian studies are similar to those employed in NHSScotland with the notable exception of any pemetrexed-platinum combination, which is recommended in patients with adenocarcinoma.

Interstitial lung disease was reported in small numbers of patients in the studies. This uncommon but severe AE has also been reported in patients treated with afatinib and erlotinib.[1, 10, 11]

There are currently no direct comparisons of gefitinib with afatinib or erlotinib but there is an ongoing multicentre, randomised, open-label, phase IIb study (LUX-Lung 7) comparing afatinib with gefitinib as first-line treatment and this is expected to be completed by December 2016.[12] To support the economic case, the company presented a summary of the findings of eight systematic reviews of the EGFR-TK inhibitors in the treatment of NSCLC. Varying methodologies were used from naive indirect comparisons to Bucher indirect comparisons, while four reviews were Bayesian network meta-analyses (NMA, two of which were published in full).[13-20]

In a NMA of 16 studies of first-line treatment, Liang et al found that with wide credible intervals for the comparisons between gefitinib and afatinib and erlotinib, there was insufficient evidence of a difference between treatments for ORR, one-year PFS rates and one- and two-year overall survival rates.

The NMA by Popat et al comprised 21 studies. Credible intervals for the hazard ratios of treatment effect between gefitinib and afatinib and erlotinib overlapped one so there was insufficient evidence of a difference in treatment effect between the EGFR-TK inhibitors for overall survival (fixed-effects model) and PFS (random-effects model). [19]

There were limitations associated with the other six analyses. However, there was no evidence of significant differences in efficacy between the three agents.[13-16, 18, 20]

Clinical experts consulted by SMC considered that the introduction of gefitinib has no significant service implications.

The EGFR TK inhibitors are orally administered; gefitinib in contrast with afatinib and erlotinib does not require to be taken at a specific time in relation to food. While there is dose adjustment recommended for toxicity for afatinib and erlotinib, gefitinib is recommended to be withheld for up to 14 days.[1, 10, 11]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing gefitinib with afatinib and erlotinib for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s). The results were presented over a five year time horizon. SMC clinical experts confirmed erlotinib and afatinib are appropriate comparators for NHS Scotland.

The efficacy data to support the cost-minimisation analysis came from findings of the systematic reviews, described above. The company presented the results stating that the ORRs were similar for the intervention and the two comparators, suggesting there were no statistically significant differences in PFS or overall survival. On the basis of no significant differences between the treatments, the company asserted that a cost-minimisation analysis was appropriate.

No adverse events were considered in the analysis and the only costs in the model related to drug acquisition costs. Treatment was assumed to be until progression, and this was assumed to be the same in both treatment arms at 10 months. Administration, monitoring and EGFR testing costs were common to both arms and thus excluded. A patient access scheme (PAS) is in place in NHS Scotland for both erlotinib and afatinib and was incorporated into the analysis using an estimate of the relevant price for both treatments.

A PAS was also submitted for gefitinib and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was given on the price of gefitinib. With the PAS, gefinitib would be considered a cost-effective treatment option.

The company provided one- and two-way sensitivity analyses, varying the treatment duration, including adverse events and varying both simultaneously. Considering the with- PAS results, none of these scenarios changed the conclusion that gefitinib is cost-effective.

Based on the assumption of comparative efficacy, gefitinib with the PAS price is a cost-effective treatment option and, thus the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from the Roy Castle Lung Cancer Foundation, which is a registered charity.
- The Roy Castle Lung Cancer Foundation has received pharmaceutical company funding in the past two years, including from the submitting company.
- Late stage lung cancer has a number of impacts on daily living. Breathlessness and weight loss can affect people's ability to manage day to day activities such as dressing, preparing food and taking part in social activities. As the disease progresses affected people become more dependent on family members or formal services for day to day care.

- The EGFR+ patients are more likely to be younger, female and non-smokers than the average lung cancer population. As a result; perception of lung cancer as a risk is lower and those with symptoms are unlikely to meet referral guideline, leading to later diagnosis by which time the cancer has few if any curative treatments.

- Gefitinib offers another targeted therapy for EGFR+ patients that may give increased longevity in survival as well as better quality of life experience. Additional months or years of life can be a significant bonus. Effective and evidence based treatment options which open this opportunity to more patients are valuable.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN 137 "Management of lung cancer: a national clinical guideline" in February 2014.[21] This includes recommendations for first-line systemic therapy for patients with stage IIIB and IV NSCLC. For patients with EGFR mutations with advanced NSCLC, the guideline recommends first-line single agent tyrosine kinase inhibitors (TKI). It states that adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used. This was a Grade A recommendation based upon high quality evidence.

The National Institute for Health and Care Excellence (NICE) published NICE Clinical Guideline 121 "The diagnosis and treatment of lung cancer" in April 2011 (revision due December 2015).[22] The guideline refers to NICE single technology appraisals TA192 "Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer" and TA162 "Erlotinib for the treatment of non-small-cell lung cancer" (superseded by TA258 in June 2012). Gefitinib, erlotinib and afatinib (TA310 published April 2014) were each recommended as options for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the EGFR-TK mutation.

The European Society for Medical Oncology (ESMO) published "Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in August 2014.[23] The guidelines recommend that NSCLC patients should be tested for EGFR mutations prior to initiation of first-line therapy. The guideline notes that in patients with activating EGFR mutations, first-line therapy with EGFR-TKIs (afatinib, erlotinib or gefitinib) increases PFS and has also been associated with significantly higher response rates and better quality of life when compared with first-line chemotherapy in EGFR mutation (L858R, exon 19 deletion)-positive NSCLC patients. Consequently, the guideline recommends that TKIs are the preferred first-line therapy in this population.

Additional information: comparators

Afatinib or erlotinib.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Gefitinib	**250mg orally once daily**	**26,302**
Afatinib	40mg orally once daily	26,303
Erlotinib	150mg orally once daily	19,796

Doses are for general comparison and do not imply therapeutic equivalence. Costs from www.mims.co.uk on 31 August 2015. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 469 patients per year to which confidential estimates of treatment uptake were applied. Based upon SMC clinical expert responses, the company's figures appeared to be a large overestimation of the patient population eligible for treatment in Scotland.

Without PAS: The gross impact on the medicines budget was estimated to be £3m in year 1 rising to £4m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £529k in year 1 rising to £704k in year 5. Note that these figures do not include the PAS discounts for erlotinib and afatinib.

*Other data were also assessed but remain commercially confidential.**

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The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 16 October, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.