Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

erlotinib, 25, 100 and 150mg film-coated tablets (Tarceva®)

SMC No. (664/10)

Roche

17 December 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

erlotinib (Tarceva®) is not recommended for use within NHS Scotland.

Indication under review: as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Erlotinib maintenance treatment provided a statistically significant increase in progression free survival and overall survival in patients treated with standard first-line platinum-based chemotherapy, both in the whole study population and in a *post hoc* analysis in patients with stable disease. In the whole study population the changes in these outcomes were considered to be of modest size.

The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Dosing Information

150mg daily, taken at least 1 hour before or 2 hours after food intake.

Erlotinib treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Product availability date

April 2010

Summary of evidence on comparative efficacy

Epidermal growth factor receptor (EGFR) is expressed on the cell surface of normal cells but is elevated in several solid tumours including a high proportion of non-small cell lung cancers (NSCLC). Erlotinib is an oral EGFR tyrosine kinase inhibitor, inhibiting the intracellular phosphorylation of EGFR preventing the triggering of the biochemical cascade.

SMC has previously accepted erlotinib for restricted use for second-line treatment in locally advanced or metastatic NSCLC. This submission relates to an extension to the marketing authorisation to include maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after standard platinum-based first-line chemotherapy. Maintenance treatment is a new approach in the treatment of NSCLC. The extension to the marketing authorisation is based on one pivotal phase lll study, supported by a *post hoc* analysis of the study population.

In a double-blind, placebo-controlled, maintenance study, 889 patients with NSCLC whose disease had not progressed following four cycles of platinum-based chemotherapy, were randomised to treatment with erlotinib 150 mg daily (n=438) or placebo (n=451), until disease progression, unacceptable toxicity or death. Randomisation was stratified by EGFR immunohistochemistry (IHC) status, disease stage (IIIB or IV), Eastern Cooperative Oncology Group (ECOG) performance status, prior chemotherapy regimen, smoking history and region. Included patients were aged ≥ 18 years, with unresectable or metastatic NSCLC, ECOG performance status of 0 or 1, at least 12 weeks life expectancy, and had not to have been treated previously with an EGFR inhibitor. The co-primary outcome was duration of progression free survival (PFS) in both the intention to treat (ITT) population and in the EGFR IHC-positive population. Tumour response was classified using Response Evaluation Criteria In Solid Tumours [RECIST] and assessments were done at baseline and at 6-weekly intervals until week 48. Interim PFS analyses were performed after 731 events (disease progression or death). A two-sided log-rank test was used to compare the two treatment groups and median PFS was estimated using the Kaplan-Meier method, with hazard ratios (HR) and 95%

confidence intervals (CI) estimated using Cox regression analysis. The alpha level of 5% was split between the two co-primary outcomes: 3% for all patients and 2% for patients with EGFR IHC-positive tumours. Secondary outcomes included overall survival (OS), best tumour response and quality of life measures based on the Functional Assessment of Cancer Therapy-Lung (FACT-L) instrument.

At the time of data cut off, 749 events had occurred, 349 in the erlotinib group and 400 in the placebo group. Median follow-up was 11.4 months in the erlotinib group and 11.5 months in the placebo group. Median PFS was statistically significantly longer in the erlotinib compared with placebo group, 12.3 weeks versus 11.1 weeks, HR 0.71 (95% CI: 0.62 to 0.82), with a similar HR in patients with EGFR IHC-positive tumours, representing around 70% of the patient population, 0.69 (95% CI: 0.58 to 0.82).

In the ITT population at 6 months, the number of patients who remained on treatment and had neither progressed nor died was 83 (25%) in the erlotinib group and 53 (15%) in the placebo group.

The secondary endpoints provided similar outcomes. Median OS in the ITT population was statistically significantly extended in the erlotinib group compared with placebo, 12 months versus 11 months, HR 0.81 (95% CI: 0.70 to 0.95) and in the EGFR IHC-positive population the HR was 0·77 (95% CI: 0·64 to 0·93). A best tumour response was achieved by a significantly higher number of erlotinib patients, 12% compared with 5.4% of placebo patients. Based on results from the FACT-L instrument, there were no differences between the treatment groups with respect to time to symptom progression, time to deterioration in Trial Outcome Index, and time to deterioration in quality of life.

At the request of the European Medicines Agency (EMA), an analysis of PFS and OS was undertaken in patients who had stable disease (rather than objective response) at the end of their first-line platinum-based chemotherapy (n=487; 55% of the ITT population). The median PFS was 12 weeks in the erlotinib group and 11 weeks in the placebo group, HR 0.68 (95% CI: 0.56 to 0.83) and the median OS was 12 months and 9.6 months for the erlotinib and placebo groups respectively, HR 0.72 (95% CI: 0.59 to 0.89). In total, 61% of erlotinib and 63% of placebo patients received second-line and subsequent systemic therapy, which included docetaxel, pemetrexed, vinorelbine, erlotinib and gefitinib.

Summary of evidence on comparative safety

No new adverse events were reported with erlotinib in this treatment setting. In the stable disease population, serious adverse events were reported in 33 (13%) of erlotinib patients and 23 (10%) of placebo patients.

In the whole study population, the most frequently reported serious adverse event was pneumonia, reported in seven patients in the erlotinib group and four in the placebo group. There was a higher rate of skin rash (49% versus 5.8%) and diarrhoea (20% versus 4.5%) in the erlotinib group.

In the whole study population, twenty (4.6%) patients withdrew due to adverse events in the erlotinib group (12 considered related to study drug) compared with 7 (1.6%) in the placebo

group. A dose reduction or interruption due to an adverse event was required in 70 (16%) patients in the erlotinib group and 15 (3.4%) patients in the placebo group.

Summary of clinical effectiveness issues

Erlotinib maintenance treatment provided a statistically significant increase in PFS and OS in patients treated with standard first line platinum-based chemotherapy, both in the whole study population and in the *post hoc* analysis in patients with stable disease. In the whole study population the increases in both these outcomes were considered modest by the European Medicines Agency (EMA). The alternative strategy to using erlotinib maintenance therapy immediately after first-line chemotherapy is second-line treatment with erlotinib initiated on disease progression. The relative effects of these two strategies on OS outcomes are unclear.

The *post hoc* analysis for stable disease formed the basis of the marketing authorisation as the EMA concluded that the benefit of treatment in the whole study population in the phase lll study did not outweigh the risks. The manufacturer was asked to identify a restricted population for which the risk-benefit ratio could be found to be beneficial. The stable disease population was identified, but patients were not stratified within the study for these criteria. Therefore the patient population for which the licence was finally granted was from a *post hoc* analysis of a secondary endpoint.

The EMA also noted that in a *post hoc* subgroup analysis of patients with epidermal growth factor receptor (EGFR) activating mutations these patients did dramatically better than the whole study population, but the sample size was not big enough to provide robust analysis.

The patient population in the study may not be representative of the population treated in Scotland as most patients were recruited outside of Western Europe. Patients studied had performance status 0 or 1 and patients in the Scottish population may have poorer performance status.

The initial platinum-based therapy in the study may differ from that now used currently in Scottish practice and second-line and subsequent systemic treatments used on disease progression may have impacted on the OS outcomes. No improvement in quality of life or cancer symptom control was demonstrated. Although conducted under double-blind conditions, the investigators blinding may have been compromised due to the high incidence of rash and diarrhoea in erlotinib patients.

Erlotinib is an oral therapy and is generally well tolerated.

One possible comparator for erlotinib maintenance treatment in NSCLC patients who have not progressed on standard first line platinum-based chemotherapy is pemetrexed. Although the patient populations eligible for treatment with pemetrexed and erlotinib overlap, they differ in some respects. Pemetrexed is licensed for maintenance therapy in patients with non-squamous cell histology and includes those with an objective response. Erlotinib is licensed for both squamous and non-squamous histology, but in patients with stable disease only (not objective response).

SMC has previously accepted pemetrexed in combination with cisplatin for restricted use as first-line therapy in locally advanced or metastatic NSCLC of predominantly non-squamous

histology. Clinical experts have indicated that this is expected to increase the use of pemetrexed as first-line therapy and in these patients erlotinib would be the only licensed option for maintenance as the pemetrexed marketing authorisation excludes this. In the pivotal study with erlotinib maintenance, patients who had previously received pemetrexed were excluded therefore the benefits of erlotinib maintenance treatment in this group are unknown.

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility analysis of erlotinib maintenance therapy compared to:

- best supportive care (BSC) ie a 'watch and wait' strategy where no active treatment is undertaken until disease progresses; and,
- pemetrexed maintenance therapy

among patients with stable disease (SD) subsequent to first-line chemotherapy.

As pemetrexed is licensed only for the non-squamous NSCLC patient population, this led the manufacturer to consider patient subgroups for squamous and non-squamous disease. However, as pemetrexed has recently received a negative recommendation from SMC for this indication it is less relevant as a comparator and results differentiated for squamous and non-squamous patients are also of less relevance.

For the main comparison of erlotinib against BSC among SD patients, the manufacturer calculated the time spent in progression free survival (PFS) and overall survival (OS) as estimated by the Liverpool Evidence Review Group (ERG) for the NICE Single Technology Assessment (STA) of erlotinib maintenance therapy from the pivotal trial. The time spent in progressive disease (PD) was then calculated as the residual of OS minus PFS.

Utility values were also drawn from the ERG report for the NICE STA of erlotinib maintenance therapy. The utility for PFS was slightly higher for erlotinib than for BSC, this apparently being due to the Grade 3/4 adverse event profile.

The direct drug costs for erlotinib were based upon a 'Time To Complete Cessation' analysis estimated by the manufacturer. In effect, this appears to have applied a Kaplan Meier plot to patient level data on 30 day prescriptions rates, qualified by prescription rates being no higher than the estimated proportion in PFS. In contrast, the ERG used the PFS curve to calculate prescription rates. The manufacturer made a reasonable case that since some patients cease treatment prior to progression the 'Time To Complete Cessation' analysis was the appropriate method for the base case.

Other costs and inputs were largely drawn from a range of submissions to NICE, though few details were supplied within the submission or subsequent clarifications.

For the main comparison of erlotinib with BSC among SD patients, erlotinib was estimated to cost an additional £8,361, to yield an additional 0.325 years survival and an additional 0.196 quality adjusted life years (QALYs). This resulted in a cost effectiveness estimate of £46,132 per QALY.

Results were sensitive to the method used to calculate the erlotinib drug costs. Applying the ERG dosing calculations resulted in cost effectiveness estimates of £51,980 per QALY. Clinical effectiveness estimates were not explored in the sensitivity analysis, which was a key weakness.

Other weaknesses of the main analysis comparing erlotinib with BSC included:

- limited detail of the calculations underlying parameter values being presented; and,
- no consideration of possible sequencing of erlotinib e.g. comparing maintenance erlotinib to second-line treatment with erlotinib initiated on disease progression.

Given the relatively high cost-effectiveness ratios and the weaknesses highlighted above, the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Summary of patient and public involvement

Patient Interest Group Submission: Roy Castle Lung Cancer Foundation.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) have published Guideline 80: Management of patients with lung cancer, in February 2005. The guideline recommends treatment with a platinum-based doublet regimen in all patients with stage IIIb/IV NSCLC not suitable for curative resection or radical radiotherapy, and are fit enough to receive it. Second line treatment with 3-weekly docetaxel should be considered for patients with good performance status. The need for an update is currently being considered.

The National Institute for Health and Clinical Excellence (NICE) has published Clinical Guideline (CG) 24: The diagnosis and treatment of lung cancer, in February 2005. The guideline recommends a range of first-line and second-line treatment options for stage III/IV NSCLC depending on patient factors. An update is in progress with a publication date of March 2011.

Neither guideline includes a statement regarding maintenance treatment of NSCLC, as they predate the licensing of erlotinib and pemetrexed for this indication.

Additional information: comparators

Best supportive care is the comparator in patients with poorer performance status. Pemetrexed has a marketing authorisation as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. This indication has not been recommended by SMC but as the only other licensed maintenance therapy has been included as a comparator.

An alternative approach to treatment in patients who have responded to first line platinum-based chemotherapy would be to treat with either erlotinib, pemetrexed or docetaxel on disease progression.

Cost of relevant comparators

Drug	Dose Regimen	Cost per maintenance treatment (£)
erlotinib	**150mg orally daily**	**4,568***
pemetrexed	500mg/m^2 intravenous infusion every 3 weeks	7,200*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 October 2010 from September MIMS and based on a body surface area of 1.8m^2. Cost for pemetrexed does not include treatment with vitamin B_{12}, folic acid supplementation and dexamethasone. *The median time to PFS in the pivotal study was about 12 weeks and therefore the costs for erlotinib are based on 12 weeks treatment. In the pivotal study of pemetrexed maintenance, median treatment was for 5 cycles and the costs presented in the table reflect this and are for 5 cycles of pemetrexed treatment.

Additional information: budget impact

Based on the assumption that 26% of advanced NSCLC patients would receive first line treatment and that 25% of these would have stable disease as best response to induction, the manufacturer estimated that around 220 patients would be eligible for erlotinib annually. Given a market share of 55 patients (25%) in the first year rising to 202 patients (90%) by the fifth year, the manufacturer estimated a gross erlotinib drug cost of £446k in the first year rising to £1.7m by the fifth year. Use of pemetrexed as a maintenance treatment would not displace use of any existing medicines and therefore no cost-offsets from reduced prescribing of other treatments would be applicable. SMC experts suggest that these estimates may be conservative.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

Federico Cappuzzo, Tudor Ciuleanu, Lilia Stelmakh et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010; 11: 521

The European Medicines Agency (EMA) European Public Assessment Report erlotinib (Tarceva®) EMA/CHMP/298837/2010

This assessment is based on data submitted by the applicant company up to and including 12 November 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.

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.