Scottish Medicines Consortium

cetuximab 2mg/ml intravenous infusion (Erbitux®) No (279/06)

MerckKGaA

9 June 2006

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

Cetuximab (Erbitux®) is accepted for restricted use within NHS Scotland in combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

It is restricted to patients who are not appropriate for or unable to tolerate chemo-radiotherapy and who are of good performance status with no evidence of distant metastases. It is also restricted to use by specialists in the management of head and neck cancer.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Cetuximab 2mg/ml intravenous infusion (Erbitux®)

Indication

In combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck (SCCHN).

Dosing information

Initial loading dose in week one of 400mg/m^2 followed by a weekly maintenance infusion of 250mg/m^2 for weeks 2-8. Radiotherapy starts in week 2.

UK launch date

April 2006

Comparator medications

Radiotherapy alone. This submission is for patients in whom chemoradiotherapy is not appropriate.

Cost of drug

Drug	Dose	Cost of treatment course
Cetuximab	**400mg/m^2 in week one followed by 250mg/m^2 for weeks 2-8**	**£4778 - £5873**

Costs are taken from the BNF no. 50 (September 2005) and with calculations for a body surface area range 1.6m^2 to 1.8m^2.

Summary of evidence on comparative efficacy

Cetuximab is a chimeric monoclonal antibody that binds to the extracellular domain of the epithelial growth factor receptor (EGFR), a member of the ErbB family of transmembrane tyrosine kinase receptors. EGFR expression is common in a number of normal epithelial tissues but is over-expressed in a wide variety of tumours including SCCHN. This expression appears to be directly correlated with aggressive tumour growth and reduced survival. Radiation increases the expression of EGFR in cancer cells and blockade of EGFR signalling sensitises cells to the effects of radiation.

There is one pivotal, phase lll, open-label, randomised, controlled trial in 424 patients with locally advanced SCCHN on which this extended licence indication is based. Eligible patients had to have measurable, stage lll/lV locally advanced non-metastatic SCCHN disease, Karnofsky Performance Status (KPS) of = 60, normal haematopoietic, hepatic and renal function and an expected survival of = 12 months, and be medically suitable for definitive radiotherapy (RT). Patients were excluded if they had previously received RT for head and neck cancer. Patients in both arms received one of three different RT schedules with curative intent. In the combination arm, patients received an initial loading dose of cetuximab 400mg/m^2 in the first week, followed by a weekly maintenance infusion of 250mg/m^2 in weeks 2-8 with RT starting in week 2. Patients were randomised using a minimisation technique,

with stratification according to KPS, nodal stage, tumour stage and RT regimen, in a ratio of 1:1, to radiotherapy alone (n=213) or radiotherapy plus cetuximab (n=211). The primary outcome was the duration of loco-regional control with secondary outcomes including overall survival, progression free survival (PFS), response rate, safety and quality of life. The median follow up was 54 months. Kaplan Meier estimates were used to calculate hazard ratios (HR). An independent committee of experts reviewed the results. For control of loco-regional disease, the primary outcome, the median duration was significantly longer in the cetuximab plus RT group, 24.4 months compared with 14.9 months for radiotherapy alone (HR for loco-regional progression or death 0.68 (95% CI, 0.52 to 0.89; p = 0.005 by the log rank test). At two years, the percentage of patients with loco-regional controlled disease was greater in the combination group (50% vs 41%). The secondary outcomes also favoured cetuximab. The median duration of overall survival was 49 months in the cetuximab plus RT group compared with 29 months for radiotherapy alone (HR 0.74; 95% CI: 0.56 - 0.97; p=0.03 by the log rank test) resulting in percentage survival rates at 3 years of 55% vs 45%, respectively; a 26% relative reduction in mortality for cetuximab plus RT compared with RT alone. PFS increased significantly from 12 months in the radiotherapy group to 17 months in the cetuximab plus RT group, HR 0.70, 95% CI 0.54; 0.90; p=0.006, with the percentage of patients progression free at 2 years, 37% and 46% respectively. Addition of cetuximab to RT was not found to have a negative effect on the global health status or quality of life scores, including social functioning, social eating and social contact.

Summary of evidence on comparative safety

No new safety concerns were raised during this study. Four patients discontinued cetuximab due to hypersensitivity reactions after the test dose or first dose. Nine patients discontinued cetuximab, eight due to the acneiform rash (grade 3). Acneiform rash was reported in 87% of cetuximab plus RT patients compared with 10% of patients with RT alone, (17% vs. 1% of patients reported the rash as grade 3-4, respectively). Fewer than 5% of patients required a dose reduction; with treatment delayed by at least four days in 14% of patients, most commonly because of cetuximab-induced rash. Twelve patients in the radiotherapy group and 11 patients in the combined-therapy group died within 60 days after the last radiotherapy or cetuximab treatment. No death was thought related to cetuximab.

Summary of clinical effectiveness issues

SCCHN is the generic term used for a heterogeneous group of malignant tumours including over 30 specific sites of cancer. Response to treatment varies depending on the site of the disease. An editorial accompanying the publication of the clinical trial in the New England Journal of Medicine made a number of observations: that cetuximab plus RT was not compared with chemoradiotherapy, the current recommended standard of care; local treatment will not affect the development of distant metastases; most of the benefit was seen in patients with oropharyngeal cancer, the diagnosis in more than half the patients; and that little improvement in survival was noted in patients with hypopharyngeal and laryngeal cancers.

The company have stated in the submission that the target population they wish considered are those patients for whom chemoradiotherapy is not appropriate. However, 50% of patients included in the study had a Karnofsky score of = 90 and many of these patients would be expected to be eligible for chemoradiotherapy. The patient population treated in practice may therefore differ from the study population, resulting in different outcomes, as patients with good prognosis (as indicated by tumour stage, Karnofsky score and age) had a pronounced

benefit. No clinical benefit was demonstrated in patients with Karnofsky score = 80 who were 65 or older.

As well as the addition of cetuximab to RT significantly improving the duration of overall survival, the different RT regimens also affect length of survival with the poorest outcomes seen in the once daily schedule (see appendix). The addition of cetuximab provided additional benefit when added to all schedules and did not exacerbate the common toxicities associated with radiotherapy. The different outcomes achieved with different radiotherapy regimens and different disease sites and the small numbers of patients included in the study who represent the target population in practice make assessment of clinical benefit difficult.

Summary of comparative health economic evidence

The manufacturer conducted a cost-utility analyses using a statistical "cure " model. The individual patient data was drawn from within the pivotal trial to estimate: progression free survival, overall survival, the costs of treatment and follow up and the costs of adverse events and final care.

Quality of life data is drawn from a separate EQ-5D study undertaken by the manufacturer among 50 UK oncology nurses. The drivers of modelling results are the projected years free of progression and years with progression. These are assigned quality of life values of 0.862 and 0.129 respectively. The imputed survival values yield an average lifetime QALY gain of 0.94. Coupled with an average incremental cost of £6,450 this allows the manufacturer to estimate a cost effectiveness of £6,870/QALY. Two-way senstitivity analysis shows that the incremental cost per QALY could increase up to £22,000.

Patient and public involvement

Patient Interest Group Submission: Mount Cancer Foundation

Budget impact

The manufacturer estimated that 180 people are thought to be intolerant of chemoradiotherapy and consequently receiving radiotherapy. The direct drug cost in year 1 is estimated as £292,700, based upon a market penetration of 30% or 53 patients, rising to £780,500 by year five, based upon a market penetration of 80% or 142 patients.

Given the additional costs associated with cetuximab the overall net cost is anticipated as £350,000 in year 1, rising to £900,000 by year 5.

Guidelines and protocols

SIGN guideline no.90: Diagnosis and Management of Head and Neck Cancer anticipated publication 2006.

NICE Single Technology Appraisal anticipated February 2007.

Additional information

In October 2005, following an Independent Review Panel, the Scottish Medicines Consortium concluded that cetuximab in combination with irinotecan for the treatment of patients with epidermal growth factor receptor–expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy should not be recommended for use within NHSScotland.

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 12 May 2006.

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

The undernoted references were supplied with the submission.

Baselga J.et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck Journal of Clinical Oncology.2005. 23(24):5568-77.

Bonner JA et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med.2006. 354(6):567-78.

Posner M et al, Cetuximab and Radiotherapy for Head and Neck Cancer. N Engl J Med 354; 6.634-636.