NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck

1 Guidance

This guidance on the use of cetixumab in combination with radiotherapy, for patients with locally advanced squamous cell cancer of the head and neck, is based on evidence submitted by the manufacturer. The evidence submitted was insufficient to enable a recommendation to be made on the use of cetuximab in combination with radiotherapy, as an alternative in patients for whom chemoradiotherapy is inappropriate.

1.1 Cetuximab in combination with radiotherapy is not recommended for patients with locally advanced squamous cell cancer of the head and neck.

1.2 People currently receiving cetuximab should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Cetuximab (Erbitux, Merck Pharmaceuticals) is a chimeric immunoglobulin G monoclonal antibody that competes for epidermal growth factor receptor (EGFR) binding sites on the external surface of the cell membrane. Binding of cetuximab to EGFR prevents activation of tyrosine kinase within cells, eventually resulting in apoptosis. Cetuximab, in combination with radiotherapy, is indicated for the treatment of patients with locally advanced

squamous cell cancer of the head and neck. For further information see the summary of product characteristics.

2.2 The most common side effects of cetuximab are mild or moderate infusion-related reactions such as fever, chills, nausea, vomiting, headache, dizziness or dyspnoea that occur soon after the first cetuximab infusion. Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis or nail disorders (for example, paronychia). The majority of skin reactions develop within the first 3 weeks of therapy.

2.3 The acquisition cost of cetuximab is £136.50 for a 2-mg/ml, 50-ml vial (excluding VAT; 'British national formulary', 52nd edition). The first dose is 400 mg/m^2 body surface area. Subsequent weekly doses are 250 mg/m^2 each. A course of treatment can range from 2 to 8 weeks. Assuming a body surface area range of between 1.6 m^2 and 1.8 m^2, the drug-cost of a course of treatment comprising two to eight cycles is £4778 to £5873. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of cetuximab and a review of this submission by the Evidence Review Group (ERG) (appendix B).

3.1 The manufacturer's submission approached the decision problem by comparing cetuximab plus radiotherapy with radiotherapy alone. The manufacturer specified that the population under consideration consisted of people with locally advanced squamous cell cancer of the head and neck for whom chemotherapy is considered inappropriate but for whom radiotherapy is suitable. The outcome measures specified in the decision problem were duration of

locoregional control, overall survival, progression-free survival and safety.

3.2 The manufacturer's submission presented evidence on the clinical effectiveness of cetuximab plus radiotherapy based on a single randomised controlled trial (RCT) (the Bonner trial) that compared cetuximab plus radiotherapy with radiotherapy alone in people with stage III or IV nonmetastatic squamous cell cancer of the oropharynx, hypopharynx or larynx. Criteria for eligibility included medical suitability for definitive radiotherapy, a Karnofsky performance score of at least 60, and normal haematopoietic, hepatic and renal function. Patients were not included in the trial if they had undergone surgery or had previously received radiotherapy for head and neck cancer. The primary outcome measure was the duration of control of locoregional disease. The secondary endpoints were overall survival, progression-free survival, response rate and safety.

3.3 Final analyses of the trial showed that the 211 people in the cetuximab plus radiotherapy arm had a longer median duration of locoregional control than the 213 people in the radiotherapy-alone arm (24.4 months versus 14.9 months, p = 0.005; hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.52 to 0.89), and greater median overall survival (49.0 months versus 29.3 months, p = 0.03, HR 0.74, 95% CI 0.57 to 0.97).

3.4 The manufacturer's submission presented a de novo economic analysis that compared cetuximab plus radiotherapy with radiotherapy alone. The model used individual patient data from the RCT to estimate costs and health effects during the trial period for each patient. Where trial observations were censored, the model extrapolated costs and health effects.

3.5 The base-case analysis compared cetuximab plus radiotherapy with radiotherapy alone and resulted in an incremental cost effectiveness ratio (ICER) of £6390 per quality-adjusted life year (QALY). The manufacturer undertook a univariate sensitivity analysis, which demonstrated that the model was not sensitive to change when assessing uncertainty in a variety of inputs. Relatively large variability was observed when the timeframe of the analysis changed from a lifetime to the period of the trial follow-up, resulting in an ICER of £19,951 per QALY gained.

3.6 The Evidence Review Group (ERG) reviewed the evidence on clinical and cost effectiveness submitted by the manufacturer. The ERG judged that the one trial included in the manufacturer's submission was well conducted and that the results for the primary endpoints appeared robust. However, the ERG noted that the trial population included a majority of patients with good performance status (Karnofsky performance score ranged from 60 to 100 but was most commonly 90), who would be expected to be suitable for chemoradiotherapy. Therefore, the population of the trial did not match the population described in the decision problem, that is, patients for whom chemoradiotherapy is considered inappropriate. Furthermore, there are differences between the radiotherapy regimens used predominantly in UK clinical practice and those that were used in the trial.

3.7 The ERG reviewed the economic model and identified a number of concerns. The most important of these was that the only RCT (the Bonner trial) informing the economic analysis did not match the population in the decision problem. The manufacturer was requested to clarify the definition and criteria for identifying patients for whom chemoradiotherapy would be considered inappropriate but for whom radiotherapy would be considered suitable. The manufacturer provided a list of possible criteria for defining patients

for whom chemoradiotherapy is inappropriate, based on consultation with a small number of oncologists. In addition the manufacturer was requested to provide information on the number of patients in the trial for whom chemoradiotherapy was considered inappropriate. However, the manufacturer stated that it was unable to provide analyses based on these criteria because the RCT was not designed or statistically powered to assess for subgroups of patients for whom chemoradiotherapy may be considered inappropriate.

3.8 In addition, the ERG identified a series of concerns and uncertainties about the methods for extrapolation of the trial data, assessment of health-related quality of life (HRQoL) and estimation of resource use and costs. The ERG concluded that the methods used were probably appropriate and concluded that altering the method of extrapolation would be unlikely to cause the ICER to increase above £20,000.

3.9 The ERG undertook additional work to examine the robustness of the base-case results to the assumptions made in the manufacturer's cost-effectiveness model for HRQoL, resource use and cost. The ERG concluded that any inaccuracies would have to be very large to have a material effect on the conclusions of the manufacturer's cost-effectiveness analysis.

3.10 The ERG felt that although the economic analyses undertaken by the manufacturer demonstrated that cetuximab in combination with radiotherapy was cost-effective compared with radiotherapy alone under a broad range of different assumptions, assuming a threshold of £20,000 per QALY, the cost effectiveness estimates may not be directly applicable to the population specified in the manufacturer's decision problem (that is, patients for whom chemoradiotherapy is considered an inappropriate option). This

was because the clinical study, on which the economic analysis was based, included a substantial proportion of patients for whom chemoradiotherapy would be expected to be suitable.

3.11 Full details of all the evidence are in the manufacturer's submission and the ERG report, both of which are available from www.nice.org.uk/page.aspx?o=260234

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck, having considered evidence on the nature of the condition and the value placed on the benefits of cetuximab by people with locally advanced squamous cell cancer of the head and neck, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee considered the decision problem described in the manufacturer's submission to be reasonable, but noted that the population specified in the decision problem excluded people for whom chemotherapy would be suitable. Therefore the decision problem did not reflect the entire population of people with locally advanced squamous cell cancer of the head and neck for whom cetuximab might be considered as a treatment option according to its licensed indication. (See section 2.1).

4.3 The Committee considered current clinical practice in the treatment of locally advanced squamous cell cancer of the head and neck. It heard from the clinical specialist that chemoradiotherapy is the standard care for patients with stage lll and IV squamous cell cancer of the head and neck. However, there are patients for whom chemoradiotherapy is considered inappropriate, for example,

because of coexisting medical conditions and poor performance status. Chemoradiotherapy carries a high risk of adverse effects and patients need to be willing and fit enough to cope with these. The clinical specialist and patient experts were of the opinion that for patients whose condition required an alternative to chemoradiotherapy, cetuximab plus radiotherapy was a useful option because of its relatively low toxicity profile compared with chemotherapy.

4.4 The Committee heard from the clinical specialist that there are considerable differences in practice across the UK. There are no clear definitions or criteria for patients for whom chemoradiotherapy is considered inappropriate, and there are differences in the selection of initial treatment modality (surgery versus chemoradiotherapy), radiation dose intensities and the means of delivery of chemotherapy. More intensive radiotherapy regimens require suitable infrastructure and patients need to attend hospital all day (which some are unable to do).

4.5 The Committee considered the evidence on the clinical effectiveness of cetuximab in combination with radiotherapy for the treatment of locally advanced squamous cell cancer of the head and neck. It noted that there was only one relevant RCT, which compared cetuximab plus radiotherapy with radiotherapy alone in people with non-resected disease. The Committee noted that the trial had been initiated at a time when radiotherapy rather than chemoradiotherapy was the standard treatment. The Committee accepted that cetuximab with radiotherapy had been shown to be more effective than radiotherapy alone in the relatively fit patient population represented in the trial.

4.6 The Committee noted that there were no trials that compared cetuximab plus radiotherapy directly with chemoradiotherapy. The

Committee understood that chemoradiotherapy is considered to be standard treatment in patients with good performance status, and that cetuximab plus radiotherapy might have advantages over chemoradiotherapy in terms of reduced toxicity. However, the Committee was not presented with any evidence comparing cetuximab plus radiotherapy with chemoradiotherapy.

4.7 The Committee considered the use of cetuximab in combination with radiotherapy according to the population specified in the manufacturer's decision problem, that is, the subgroup of patients for whom chemoradiotherapy was unsuitable. The Committee noted that the manufacturer was unable to provide information on the number of patients in the RCT for whom chemoradiotherapy was considered inappropriate but for whom radiotherapy was considered suitable, or on the effectiveness of cetuximab plus radiotherapy in this group.

4.8 The Committee considered that patients with lower performance status would form most, if not all, of the population for whom chemoradiotherapy would be considered inappropriate in clinical practice. However, it noted that no clinical benefit had been demonstrated for cetuximab plus radiotherapy in patients with a Karnofsky performance score of 80 or less, based on evaluation of the principal registration trial data in the 'European public assessment report' published by the European Medicines Agency. The Committee noted that the manufacturer had stated that the Bonner trial was not designed or statistically powered to identify the subgroups of patients for whom chemoradiotherapy would be inappropriate. However, given the absence of benefit (albeit with wide confidence intervals) it could not make the subgroup of patients with a Karnofsky performance score of 80 or less the basis for a recommendation to use cetuximab plus radiotherapy. Indeed the Committee noted that the 'European public assessment report'

stated that the 'overall impression of all subgroup analyses is that the add-on effect of cetuximab tends to be small or absent irrespective of outcome measure in patients with poor prognosis (estimated from median overall survival)'.

4.9 The Committee also heard from the clinical specialist that those patients for whom chemoradiotherapy is contraindicated would represent a higher-risk population with shorter median survival than for those for whom chemoradiotherapy was an option. It concluded that the absolute benefit, and therefore the cost-effectiveness of treatment, in this subgroup might be expected to be considerably less than suggested by the economic modelling. The Committee concluded that there was no evidence to support the use of cetuximab in combination with radiotherapy for people with low performance status.

4.10 The Committee then considered patients with a Karnofsky performance score of 90 or more and explored situations in which chemoradiotherapy might be unsuitable for patients in this category. It reviewed the following criteria proposed by the consultees for identifying patients for whom cisplatin-based chemoradiotherapy would be inappropriate.

- **Active peripheral, cerebral or coronary vascular disease and any form of myelosuppression.** The Committee considered that patients with active disease meeting these criteria would always have a Karnofsky performance score of less than 90 and therefore the Committee concluded that cetuximab in combination with radiotherapy could not be recommended for this group of patients. (See section 4.8.).
- **Contraindications to cisplatin (conditions predisposing the patient to thrombocytopaenia, impaired renal function, impaired hearing and peripheral neuropathy).** The Committee

noted that patients meeting these criteria had either been excluded from the Bonner trial (criteria for eligibility included normal haematopoietic, hepatic and renal function) or (if they had impaired hearing, peripheral neuropathy or risk of thrombocytopaenia) could be treated with carboplatin. The Committee was aware that although carboplatin does not have a UK marketing authorisation for the treatment of locally advanced squamous cell cancer of the head and neck, it is being used to treat this condition in UK clinical practice and has an evidence base for its use in chemoradiotherapy. The Committee concluded that because carboplatin-based chemoradiotherapy can be given as an alternative to cisplatin-based chemoradiotherapy in the group of patients for which there is an evidence base, it could not recommend cetuximab as a treatment for patients with contraindications to cisplatin. (See section 4.6.).

- **Previous cisplatin therapy for any malignancy.** The Committee noted that patients who had received chemotherapy within the prior 3 years were excluded from the Bonner trial, and that those treated more than 3 years before their presenting episode may receive further platinum therapy.

Overall the Committee was not presented with any robust data justifying the use of cetuximab in combination with radiotherapy relating to groups of patients with a Karnofsky performance score of 90 or more and for whom chemoradiotherapy is considered an inappropriate option.

4.11 In the absence of robust data on the clinical effectiveness of cetuximab plus radiotherapy for patients for whom chemoradiotherapy is considered inappropriate, the Committee was unable to conclude on the basis of the evidence currently

before it that cetuximab is a cost-effective option for these patients.

.

Summary of the considerations

4.12 For patients for whom chemoradiotherapy is not indicated, the evidence did not provide a robust demonstration of the clinical effectiveness of cetuximab combined with radiotherapy compared with radiotherapy alone. **[Paragraph 1.1]**

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health bbards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAxxx). *[Note: tools will be available when the final guidance is issued]*

6 Recommendations for further research

6.1 The Committee recommended further research on:

- the use of cetuximab in combination with radiotherapy compared with radiotherapy alone in patients with low Karnofsky performance score
- the use of cetuximab in combination with radiotherapy compared with chemoradiotherapy in patients with high Karnofsky performance score. A clinical trial on radiation therapy and cisplatin with or without cetuximab in treating patients with stage III or stage IV head and neck cancer (RTOG-0522) is currently recruiting patients.

7 Related guidance

7.1 NICE has issued the following cancer service guidance.

Improving outcomes in head and neck cancer. NICE cancer service guidance (2004). Available from: www.nice.org.uk/csghn

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in May 2009.

Andrew Stephens

Chair, Appraisal Committee

April 2007

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice chair and a number of other members attending meetings of all three branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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.

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

Dr David W Black
Director of Public Health, Chesterfield Primary Care Trust

Mr Brian Buckley
Vice Chairman, Incontact

Dr Carol Campbell
Senior Lecturer, University of Teesside

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Professor David Chadwick

Professor of Neurology,

Dr Peter Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Ms Jude Cohen

Chief Executive, Women's Nationwide Cancer Control Campaign

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance Research and Development Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic

Dr Rachel A Elliott

Clinical Senior Lecturer, University of Manchester

Mrs Eleanor Grey

Lay member

Dr Dyfrig Hughes

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of Health and Policy in Health, University of Wales

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Mark Sculpher

Professor of Health Economics, University of York

Professor Andrew Stevens

Chair of Appraisal Committee C

B. NICE project team

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

Nicola Hay

Technical Lead

Janet Robertson

Technical Adviser

Christopher Feinmann

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The following manufacturer/sponsor provided a submission for this appraisal:

- Merck Pharmaceuticals UK

B The evidence review group (ERG) report for this appraisal was prepared by the Centre for Health Technology, University of York and NHS Northern and Yorkshire Regional Drug and Therapeutics Centre:

- Griffin S, Walker S, Sculpher M, White S et al. Cetuximab for the treatment of locally advanced squamous cell carcinoma of the head and neck, September 2006.

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on cetuximab by providing written and oral evidence to the Committee. They were also invited to comment on the Appraisal Consultation Document (ACD).

- Dr Nick Slevin, Consultant Clinical Oncologist, Christie Hospital NHS Trust, nominated by the Royal College of Radiologists – clinical expert
- Dr Kevin Harrington, Mayo Clinic College of Medicine, nominated by the Royal College of Radiologists – clinical expert (written statement only)
- Ms Brenda Brady, nominated by the Mouth Cancer Foundation – patient expert
- Mrs Jean Fraser, nominated by the National Association of Laryngectomee Clubs – patient expert

Appendix C. List of organisations involved in this appraisal

The following organisations accepted the invitation to participate in this appraisal. They are also invited to comment on the ACD and consultee organisations are provided with the opportunity to appeal against the FAD:

I Professional/specialist and patient/carer groups:

- British Association of Head and Neck Oncologists
- British Association of Head and Neck Oncology Nurses
- British Association of Oral and Maxillofacial Surgeons
- Cancer Networks Pharmacists forum (BOPA)
- Cancer Research UK
- Cancerbackup
- Get A-Head
- Let's Face it
- Mouth Cancer Foundation
- National Association Of Laryngectomee Clubs
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal Pharmaceutical Society

II Commentator organisations (without the right of appeal):

- British National Formulary
- Centre for Health Economics, University of York and the Regional Drug and Therapeutics Centre, Newcastle
- Department of Health, Social Services and Public Safety for Northern Ireland
- King's College Hospital Maxillofacial Unit – The Head and Neck Oncology Group
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement