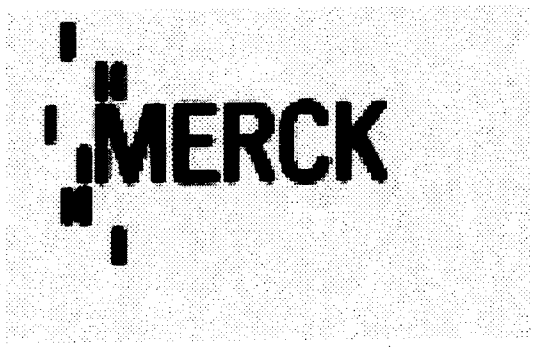

CETUXIMAB

(ERBITUX®)

100 mg solution for infusion (2 mg/mL)

"In combination with irinotecan for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy"

Submission to the
National Institute for Health and Clinical Excellence

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EXECUTIVE SUMMARY

Indication

Metastatic colorectal cancer (mCRC) is a significant cause of morbidity and mortality in England and Wales. Cetuximab, a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR), provides a unique approach for the treatment of patients with advanced disease. It is proposed that cetuximab is recommended primarily as:

- a new standard third-line therapy for all irinotecan-refractory colorectal cancer patients
- a further treatment option as second-line therapy in irinotecan-refractory EGFR-expressing colorectal cancer patients who are contraindicated to receive oxaliplatin.

Efficacy and safety

A controlled, randomised, phase II clinical study investigating the efficacy and safety of cetuximab in irinotecan-refractory advanced colorectal cancer patients has demonstrated that this patient group is responsive to both cetuximab monotherapy (10.8% of patients) and cetuximab/irinotecan combination therapy (22.9% of patients). Comparison of cetuximab with cetuximab/irinotecan has shown that combination therapy offers patients significantly enhanced time-to-progression rates (1.5 versus 4.1 months) and improved overall survival (6.9 versus 8.6 months), in addition to significantly increased overall response rates. No other therapies are presently recommended for the third-line treatment of colorectal cancer patients. Therefore, cetuximab/irinotecan combination therapy clearly offers benefits over active supportive care/best supportive care (ASC/BSC).

A qualitative review of published evidence has shown that the incidence of major adverse events with cetuximab/irinotecan (alopecia, nausea, leucopenia) is similar to that seen with irinotecan alone. Acne-like rash is associated with cetuximab administration. In approximately 5% of patients, hypersensitivity reactions may occur during treatment with cetuximab; approximately half of these reactions are severe. This is comparable to the toxicity profile of other chimeric monoclonal antibodies.

Demonstration of the efficacy and safety of cetuximab in patients with aggressive, chemotherapy-resistant, metastatic disease highlights the effectiveness of this agent, since individuals with advanced disease are unlikely to be responsive to chemotherapeutic regimens, compared with newly diagnosed patients. The significant increase in time to disease progression offered by cetuximab/irinotecan therapy means that patients will benefit from a significant extension in life-expectancy, as well as an enhanced quality of life through the reduction in disease-related symptoms.

Furthermore, the positive correlation of acne-like rash with disease response and survival in patients receiving cetuximab therapy provides a means of targeting chemotherapy to the patient population that is most likely to respond to treatment.

Proposed continuation rule

This submission proposes a treatment algorithm whereby patients with EGFR-expressing mCRC who commence therapy are assessed at 6 weeks for continuation or cessation of therapy. The continuation of therapy is based on an assessment of CT determined tumour response and grade of acne-like rash. The purpose of this continuation rule is to ensure that treatment with cetuximab/irinotecan is targeted towards patients most likely to benefit, while those who are unlikely to respond avoid exposure to the inevitable toxicities associated with cancer therapy. This also has the benefit of simultaneously maximising treatment cost-effectiveness.

The underlying basis for the proposed continuation rule is summarised as follows.

- The development of acne-like rash is correlated both to overall survival and to best overall response.
- Acne-like rash is simple to define for clinicians.
- Assessing patients at 6 weeks, rather than the standard 12 weeks, reduces treatment length by 6 weeks in patients who will have least benefit.

Cost-effectiveness

To date, there have been no economic evaluations published in the literature that assess the cost-effectiveness of cetuximab/irinotecan therapy in this indication. Consequently, the cost-effectiveness of cetuximab/irinotecan relative to ASC/BSC was assessed in a modelled economic evaluation. The modelled evaluation is based on the pivotal clinical trial in this submission and an important clinical trial assessing the outcomes of mCRC patients receiving chemotherapy relative to BSC.

The primary outcome measure for the economic evaluation is life-years gained. Consequently, the economic evaluation takes the form of a cost-effectiveness analysis and calculates the incremental cost per life-year gained with cetuximab/irinotecan therapy prescribed according to the proposed continuation rule, compared with ASC/BSC.

Over the duration of the model, patients treated with cetuximab/irinotecan accumulated mean additional costs of £13,971 per patient relative to those in the ASC/BSC group; £8924 of this is attributable to the acquisition cost of cetuximab. Based on the proposed continuation rule, the discounted life-expectancy of individuals treated with cetuximab/irinotecan was 0.89 life-years per patient. This contrasted with an estimated 0.47 life-years for patients receiving ASC/BSC in the model. The incremental cost per life-year gained with the proposed cetuximab/irinotecan algorithm was £33,263, relative to ASC/BSC.

Sensitivity analysis showed that the key drivers of the economic model included the continuation rule and the outcomes of chemotherapy relative to BSC. Probabilistic sensitivity analysis showed that cetuximab/irinotecan was consistently superior to ASC/BSC in terms of outcomes and had consistently higher costs.

Impact on the NHS

It is expected that cetuximab/irinotecan therapy will be used by 410 patients in England and Wales in 2006, rising to 1125 patients in 2008. This equates to 4–11% of the total population initiating first-line chemotherapy. It is estimated that the aggregate cost of cetuximab, if it is recommended for use as proposed in this submission, will be £3,656,117 in 2006, rising to £10,036,534 in 2008.

Conclusion

Cetuximab/irinotecan combination therapy is a proven active treatment for patients with few therapeutic alternatives. No other therapies are presently recommended for the third-line treatment of colorectal cancer patients. Hence, cetuximab/irinotecan combination therapy is unique and clearly offers patient benefits over the inactive treatment alternative of ASC/BSC.

The economic evaluation and estimation of financial impact on the NHS show that the proposed cetuximab/irinotecan algorithm can be applied cost-effectively and with a relatively minor budget impact. A decision to recommend cetuximab/irinotecan will improve the life-expectancy and quality of life of hundreds of patients with mCRC in England and Wales at an acceptable cost.