Sponsor submission to the National Institute for Health and Clinical Excellence:

Eloxatin® (oxaliplatin) for the adjuvant treatment of colon cancer

sanofi-aventis

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1. Executive summary

Introduction

- Colorectal cancer is the third most common form of cancer in the UK with over 35,000 new cases diagnosed annually, approximately 31,000 of which are in England and Wales alone. In turn, approximately two thirds of CRC patients in England and Wales have colon cancer alone (www.cancerresearchuk.org).
- The 5-year survival rate for CRC patients with stage III disease is between 25% and 60% depending on precise TNM (Tumour, Node, Metastasis) status at presentation, and for stage II disease 70% to 80%.
- The role of adjuvant systemic chemotherapy is to eliminate any occult micrometastases that might be present and reduce the incidence of disease recurrence, offering colon cancer patients the increased potential for cure.
- The use of 6 months adjuvant systemic 5-FU/FA chemotherapy is the current standard of care for patients with stage III colon cancer in England and Wales.
- The available evidence suggests that infusional 5-FU/FA regimens have better toxicity profiles and at least equivalent and possibly superior efficacy to bolus 5-FU/FA regimens in the adjuvant setting.
- Disease-free survival is felt to be the best indicator of efficacy in this clinical setting because it relates directly to the treatment under investigation at that time. Disease-free survival is defined as the time from randomisation to the appearance of local, regional or metastatic recurrence or the date of a secondary primary cancer or death from any cancer, whichever comes first.

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Clinical effectiveness

- The MOSAIC trial is the first trial to show a statistically significant DFS benefit for a new treatment regimen over standard 5-FU/FA therapy in the adjuvant setting.
- The MOSAIC trial randomised patients who had undergone curative resection for stage II and III colon cancer to receive either 5-FU/FA alone or the same infusional 5-FU/FA regimen plus oxaliplatin. The primary trial endpoint was DFS. Secondary trial endpoints included toxicity and overall survival.
- Oxaliplatin in combination with 5-FU/FA is effective in the adjuvant treatment of patients who have undergone complete surgical resection for stage II and III colon cancer.
    - At 4 years, the probability of remaining disease-free DFS rates for patients with stage III disease were 69.7% and 61.0% (p=0.002) for oxaliplatin/5-FU/FA and 5-FU/FA, respectively.
    - The hazard ratio for recurrence for the ITT population of patients with stage II and III colon cancer at 4 years was 0.76 [95%CI: 0.65;0.90], which corresponded to a 24% reduction in the risk of disease recurrence for the combination oxaliplatin/5-FU/FA compared with 5FU/FA alone.
- Oxaliplatin/5-FU/FA combination therapy has a predictable and manageable toxicity profile.

Cost-effectiveness

- A new economic evaluation was developed for this NICE submission. The evaluation uses patient level data from the MOSAIC trial, and presents a base case analysis that is modelled from treatment until death.
- Using observed mortality and DFS data, and the relationship between DFS and overall survival, a difference in overall survival was estimated.
- The estimated incremental lifetime cost per QALY of oxaliplatin plus 5-FU/FA compared with 5-FU/FA alone in patients who had undergone curative resection of stage III colon cancer is £4,805. Oxaliplatin/5-FU/FA may be considered a cost-effective intervention if the NHS is willing to pay £4,805 per QALY gained.
- It is estimated that oxaliplatin plus 5-FU/FA adds 0.68 QALYs (0.77 years of life) compared with 5-FU/FA, in a population of stage III patients over a lifetime, at an additional cost of £3,267.
- Probabilistic sensitivity analysis indicated that the probability of oxaliplatin plus 5-FU/FA being cost-effective compared with 5-FU/FA monotherapy would be 96.7%, given a threshold of £30,000 per QALY.
- The analysis showed that the ICER for oxaliplatin plus 5-FU/FA compared with 5-FU/FA fell below £30,000 per QALY after 5 years, 4 months of complete resection

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Overall conclusion

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a. ESMO Minimum clinical recommendations for diagnosis, treatment and follow-up of advanced colorectal cancer. Annals Oncol 12:1055, 2001

b. sanofi-aventis Market Research Data. 2005

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