
# Xeloda® (capecitabine) NICE Submission

## ACHIEVING CLINICAL EXCELLENCE IN THE ADJUVANT TREATMENT OF COLORECTAL CANCER

**Roche Submission to the**
**National Institute for Health and Clinical Excellence**
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# 1. EXECUTIVE SUMMARY

**Background**

- As in most industrialised countries, the UK has a high rate of colorectal cancer. In 2000, there were 34,539 new cases of which 22,072 were cancers of the colon. Despite a steady increase in incidence, overall mortality has decreased slowly but steadily over the last 3 decades and around 40% of patients in this country are now still alive 5 years from initial diagnosis.
- Although it is clear from epidemiological studies that a family history of colorectal cancer contributes significantly to the risk of contracting the disease, the genetic basis of this increased susceptibility remains unclear, making early intervention generally impossible.
- Disease prevention remains an elusive strategy. The evidence that modifying currently understood risk factors will significantly alter the risk of developing colorectal cancer is weak and the type of lifestyle changes required to modify these risk factors are notoriously difficult to achieve in practice.
- Over the past 15 years, adjuvant chemotherapy has been established as a successful treatment strategy to reduce relapse and improve survival after surgical resection of localised colon cancer. The development of adjuvant chemotherapy has, generally, mirrored the evolution of chemotherapy for metastatic disease, with regimens first demonstrated to have activity in advanced disease then being applied in the adjuvant treatment setting.
- Numerous studies have over time confirmed the Mayo regimen of 5-FU/FA as the gold-standard adjuvant therapy. Mayo consists of 5-FU (425 $mg/m^2$ patient body surface area) plus FA (20 $mg/m^2$) given each day for five consecutive days every 28 days, for six cycles, i.e. a total of 30 days of treatment. Both drugs are given by IV injection almost always during hospital outpatient visits. To date, no other IV fluoropyrimidine-based adjuvant regimen has yet been formally demonstrated to be superior to the classical Mayo regimen in extending survival.
- Current NICE Guidelines on improving outcomes in colorectal cancer recommend that "systemic chemotherapy should be offered to all patients who after surgery for Dukes C colon or rectal cancer are fit enough to tolerate it standard treatment has been a course of 5-FU and FA given over 6 months". This guidance echoes that from the Association of Coloproctology of Great Britain and Ireland (ACGBI) and also that issued to health professionals in many other countries.
- However, the burden of IV adjuvant treatment is considerable both for patients and for the NHS itself. It is important to recognise that numerous visits to hospital for treatment administration are extremely disruptive to patients in their efforts to lead normal lives after the trauma of cancer diagnosis and surgery. Furthermore, IV adjuvant treatment requirements can often place a considerable burden on generally over-stretched NHS pharmacy and nursing staff and on chemotherapy delivery services in general.

## Xeloda® (capecitabine) – A Licenced Adjuvant Treatment for Colon Cancer Patients

- Capecitabine (*N*-[1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1.2-dihydro-2-oxo-4-pyrimidinyl]-m-pentyl carbamate; Ro 09-1978; Xeloda®) is an innovative cytototoxic fluoropyrimidine carbamate designed to overcome shortcomings with the prototypical fluoropyrimidine, 5-Fluorouracil (5-FU) which since its introduction in 1957 has been one of the most widely used anticancer drugs in the treatment of solid tumours.
- The initial approved indications for capecitabine were for:
  - First-line monotherapy of metastatic colorectal cancer
  - Use in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy that should have included an anthracycline
  - Monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.
- The clinical and cost effectiveness of capecitabine in the above indications was established by NICE in early 2003 which recommended that capecitabine should be offered as a treatment choice to all eligible patients according to the above indications.
- However in March 2005, the Marketing Authorisation for capecitabine was extended to now include the post-surgical adjuvant treatment of patients with Dukes C colon cancer.

## Demonstrating the Clinical Effectiveness of Xeloda® (capecitabine)

- The X-ACT study has provided the evidence necessary for registration purposes in the adjuvant treatment setting. X-ACT concluded that patients who received adjuvant chemotherapy with capecitabine benefited from equivalent efficacy with a trend to improved relapse-free and disease-free survival compared to the gold-standard Mayo regimen. In the same pivotal trial, patients receiving capecitabine also benefited from an improved safety and tolerability profile.
- Capecitabine, being an oral formulation, provides patients with an alternative to IV treatment offering improved convenience of administration and a tablet formulation that can be taken at home.
- In the search for increasing convenience for both the NHS and patients, 5FU/FA regimens other than the classical Mayo regimen are used in some centres. However, these regimens have never formally been demonstrated to have superior efficacy to Mayo. It is therefore reasonable to assume that the capecitabine regimen used in the X-ACT study matches the efficacy of these other alternative regimens.
- We conclude that capecitabine provides an efficacious, safe and convenient treatment alternative to the other adjuvant treatments currently used in England and Wales.

## Demonstrating the Cost Effectiveness of Xeloda® (capecitabine)

- Capecitabine costs on average an additional £1,500 when compared to the Mayo regimen. However, the costs associated with the administration of IV 5-FU/FA are £5,300 per patient compared to £450 for oral capecitabine. In addition, the costs associated with managing adverse events are approximately £300 higher for 5-FU/FA.
- We have concluded that capecitabine saves on average £3,608 per patient. Capecitabine is therefore cost-saving and due to the enhanced clinical outcomes achievable with capecitabine versus the Mayo regimen of 5-FU/FA is also a dominant strategy within the base case comparison.
- When compared to alternatives to the classical Mayo regimen, capecitabine remains cost-saving and based on threshold and extreme sensitivity analyses, capecitabine remains cost-saving in all cases and scenarios modeled.
- Finally, switching from the Mayo regimen of IV 5-FU/ FA to capecitabine has also been demonstrated to provide direct benefits to patients in the form of reduced hospital visits and time savings spent travelling to and from hospital.

## Freeing up Capacity within NHS Chemotherapy Services

- Subject to endorsement by NICE, the extension of the license for capecitabine to the adjuvant treatment setting presents a major opportunity for chemotherapy units in England and Wales to switch from IV to oral adjuvant treatment.
- Switching will free up capacity which can then be used to deliver other IV based treatments, including those presently recommended by NICE where uptake has been limited because of current capacity constraints. Such constraints have been clearly documented by the National Cancer Director in his investigation into the continued regional variations in access to some NICE appraised anti-cancer treatments.
- For example, if the 4,600 patients diagnosed with this condition each year in England and Wales were to receive 30 doses of IV bolus 5-FU and FA over the 6 months following surgery, around 138,000 chemotherapy day unit appointments would be needed to deliver approximately 276,000 IV drug doses. A majority of these appointments would be freed up through the use of oral capecitabine.

## Illustrating NHS Budget Impact

- Based on an incidence of 0.06%, we estimate that 30,600 patients are diagnosed with colorectal cancer every year in England and Wales. Of these patients, around 28% are diagnosed with Dukes C colon cancer. Around 85% of Dukes C colon cancer patients currently receive adjuvant chemotherapy which represents a total of about 4,600 patients presenting every year in England and Wales.
- Based on this eligible treatment population, we estimate that the annual budget impact for capecitabine usage will be approximately £9 million per annum.

## Conclusions

- Capecitabine is at least as effective and is less toxic than the current gold standard adjuvant treatment used in England and Wales and accords with expressed patient preference for an oral rather than an IV treatment.
- Capecitabine has been demonstrated to be a dominant treatment strategy compared with the present gold standard Mayo regimen and is cost-saving when compared to the other common treatment alternatives used in clinical practice.
- Pharmacy staff time, nursing staff time and chemotherapy delivery services are freed up every time a patient is treated with oral capecitabine as opposed to intravenous 5-FU/FA.