NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Capecitabine for the treatment of locally advanced or metastatic breast cancer

1 Guidance

1.1 In the treatment of locally advanced or metastatic breast cancer, capecitabine in combination with docetaxel is recommended in preference to single-agent docetaxel in people for whom anthracycline-containing regimens are unsuitable or have failed.

1.2 Capecitabine monotherapy is recommended as an option for people with locally advanced or metastatic breast cancer who have not previously received capecitabine in combination therapy and for whom anthracycline and taxane-containing regimens have failed or further anthracycline therapy is contraindicated.

1.3 The decision regarding treatment should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents, alternative treatments for locally advanced or metastatic breast cancer, as well as the clinical condition and preferences of the individual.

1.4 The use of capecitabine to treat locally advanced or metastatic breast cancer should be supervised by oncologists who specialise in breast cancer.

2 Clinical need and practice

2.1 In England and Wales in 1999 there were approximately 33,000 new cases of breast cancer, with more than 12,000 reported deaths.
2.2 Locally advanced and metastatic breast cancers are defined by clinical staging based on the tumour, node and metastasis staging system. Stage III denotes locally advanced disease, and stage IV indicates metastatic breast cancer.

2.3 Between 16% and 20% of people initially presenting with breast cancer have advanced disease with distant metastases, and around 50% of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer.

2.4 Therapy for locally advanced or metastatic breast cancer aims to manage the symptoms and prolong life, with resection being considered on a palliative basis. Cure is generally not possible with current regimens, and although the choice of therapy is often determined by what the individual has previously received, it is sometimes appropriate to select therapy on the basis of the side-effect profile.

2.5 First-line systemic therapy for locally advanced or metastatic breast cancer is chemotherapy for oestrogen receptor-negative individuals (usually an anthracycline-containing regimen, or sometimes a combination of cyclophosphamide, methotrexate and fluorouracil) and hormone manipulation therapy for oestrogen receptor-positive individuals. Chemotherapy is also generally preferred for aggressive disease, particularly when it has metastasised to critical visceral sites, or when the interval since previous treatment for early-stage disease is short.

3 The technology

3.1 Capecitabine (Xeloda) is a fluoropyrimidine carbamate precursor of 5-fluorouracil (5-FU). It is given orally and is converted via several enzymatic steps to give intratumoural release of 5-FU. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase, is found at higher levels in some tumour tissues than in normal tissue, thereby reducing systemic exposure to 5-FU.
3.2 Capecitabine in combination with docetaxel is licensed for the treatment of individuals with locally advanced or metastatic breast cancer for whom anthracycline-containing regimens have failed. The recommended dose of capecitabine is 1250 mg/m² twice daily for 2 weeks, followed by a 1-week rest period, combined with docetaxel at 75 mg/m² as a 1-hour intravenous infusion on the first day of every 3-week cycle.

3.3 Capecitabine monotherapy is licensed for the treatment of individuals with locally advanced or metastatic breast cancer for whom taxane- and anthracycline-containing chemotherapy has failed or for whom further anthracycline therapy is not indicated. The recommended dose of capecitabine is 1250 mg/m² administered twice daily for 2 weeks, followed by a 1-week rest period before another cycle of treatment.

3.4 The listed costs of 60 150-mg tablets and 120 500-mg tablets of capecitabine are £44 and £295, respectively (excluding VAT; British National Formulary 44, September 2002). The listed cost (excluding VAT) for docetaxel (40 mg/ml) is £175 (0.5 ml vial) and £575 (2 ml vial). Based on an assumed body surface area of 1.7 m², the acquisition cost (excluding VAT) of treating an individual for one 3-week cycle is therefore £1393 for combination therapy and £293 for monotherapy. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 Clinical effectiveness

Combination therapy

4.1.1 One phase III randomised controlled trial (RCT) of combination therapy (capecitabine plus docetaxel vs docetaxel) was identified. All 511 individuals enrolled in this study had relapsed after anthracycline-based therapies and
were followed for a minimum of 15 months. Capecitabine was given in 3-week cycles, at a dose of 1250 mg/m² twice daily for 2 weeks, followed by a 1-week rest period. Docetaxel was given as a 1-hour intravenous infusion on the first day of each 3-week cycle at a dose of 75 mg/m² in the combination group and 100 mg/m² in the monotherapy group. Patients in both arms of the trial received at least two cycles of treatment.

4.1.2 Two uncontrolled studies were also identified, but were of limited use because they used lower-dose combination therapy and contained small numbers of individuals (n = 21 and n = 19).

4.1.3 In the RCT, the median overall survival times in the capecitabine/docetaxel combination and docetaxel monotherapy arms were 14.5 and 11.5 months, respectively (p = 0.013 for difference). A significant difference in the median time to disease progression was also reported, which favoured combination therapy (6.1 vs 4.2 months, p = 0.0001). The median time to treatment failure also favoured the combination arm (4.0 vs 2.8 months, p = 0.0002), while the median duration of response (which was assessed according to the World Health Organization guidelines) was similar in both groups (7.3 months for combination therapy vs 7.0 months for monotherapy, not statistically significant). The rate of overall (complete plus partial) response was significantly greater in individuals who received combination treatment, but there was no statistically significant difference in the rate of people achieving a complete response.

4.1.4 Health-related quality of life was measured in the RCT. No statistically significant differences were reported between the two treatment groups in any of the domains. For example, mean global health status, assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at 18 weeks, was 51.6 for combination therapy and 48.7 for monotherapy (p = 0.83 for change from baseline).

4.1.5 The overall incidence of treatment-related adverse events was higher in the combination group than in the monotherapy group (98.0% vs 93.7%), but this
difference could have arisen by chance (relative risk [RR] 1.0, 95% CI, 0.9 to 1.1). Individuals in the combination group experienced significantly more hand–foot syndrome, stomatitis, vomiting, diarrhoea, dyspepsia, lacrimation and appetite reduction, whereas those in the monotherapy group experienced more myalgia, peripheral neuropathy and pyrexia, which may be related to the higher dose of docetaxel used. The incidences of grade III/IV hand–foot syndrome (RR 20.7, 95% CI, 6.6 to 65.0), diarrhoea (RR 2.4, 95% CI, 1.3 to 4.2), nausea (RR 3.3, 95% CI, 1.2 to 8.8) and stomatitis (RR 3.7, 95% CI, 2.0 to 6.9) were significantly higher in the combination therapy group than in the monotherapy group.

Monotherapy

4.1.6 No RCTs of capecitabine monotherapy were available. In all, 13 uncontrolled studies were identified that investigated the use of monotherapy in individuals for whom anthracycline and/or taxane therapy was reported to have failed. Eight of these were phase II studies (two were available as full manuscripts and six as abstracts) and two were case-series (both available as abstracts only). The final three studies investigated the use of capecitabine monotherapy following relapse after high-dose chemotherapy and autologous stem cell support, which is considered to be experimental and is not in line with the licence. These three studies are not considered further in this document.

4.1.7 Median overall survival was reported in five studies, and ranged from 8.1 to 15.2 months. Six studies reported median times to disease progression (2.8–6.2 months) and five recorded duration of response (5.0–8.3 months). The median time to treatment failure was reported in only one study (3.2 months).

4.1.8 Overall, tumour response rates in the 12 studies that provided data ranged from 15% to 28%.
4.1.9 Only one study formally assessed health-related quality of life. Individuals showed an improvement on a number of the questionnaire’s domains. However, only a relatively small number of individuals (46 out of 126, 37%) were included in this analysis, and the effect of selection bias on these results is unknown.

4.1.10 In the two studies that reported adverse event data in full, 10% and 22% of individuals reported grade III/IV hand–foot syndrome and 14% and 19% reported grade III/IV diarrhoea. These were the most commonly reported serious side effects.

4.2 Cost effectiveness

Combination therapy

4.2.1 The manufacturer provided an economic model of the cost effectiveness of capecitabine plus docetaxel compared with docetaxel monotherapy, which was tested by the Assessment Group. A second economic evaluation was identified, but was not reviewed in the Assessment Report because it was only available as an abstract.

4.2.2 The manufacturer’s model was based on the results from the single RCT. The costs of purchasing and administering the drugs were included in the analysis, as were the costs of treating adverse events. Health outcomes were expressed in terms of quality-adjusted life years (QALYs), which were estimated from published utilities for stable and progressive disease obtained from oncology nurses. The health impact of side effects on morbidity levels was not incorporated into the analysis.

4.2.3 In the manufacturer’s baseline analysis, capecitabine combination therapy was argued to be less costly and more effective than docetaxel (combination therapy £9090, 0.82 QALYs; docetaxel £9250, 0.67 QALYs).

4.2.4 In its report, the Assessment Group tested a number of the assumptions in the manufacturer’s analysis of combination therapy. Despite these changes to
the analysis, capecitabine combination therapy remained cost saving and more effective than docetaxel monotherapy (combination therapy £9090, 0.78–0.98 QALYs; docetaxel £9250, 0.58–0.82 QALYs).

**Monotherapy**

4.2.5 The manufacturer provided an economic model, which was tested by the Assessment Group, of the cost effectiveness of capecitabine monotherapy compared with vinorelbine monotherapy. The model was based on indirect comparison of data. A second economic evaluation was identified, but was not reviewed in the Assessment Report because it was only available as an abstract.

4.2.6 The manufacturer’s model included only the costs of drug acquisition and administration in the analysis, and health outcomes were presented in the form of life-years and QALYs. The health outcomes of side effects were not incorporated into the analysis.

4.2.7 In the baseline analysis, capecitabine was less costly and more effective than vinorelbine (capecitabine £400–£600, 0.45–0.65 QALYs; vinorelbine £670–£990, 0.38–0.41 QALYs).

4.2.8 Additional analysis of the manufacturer’s model was undertaken by the Assessment Group as set out in their report. It was found that after making changes to the assumptions used in the manufacturer’s analysis, capecitabine remained less costly and more effective than vinorelbine (capecitabine £1300, 0.73 QALYs; vinorelbine £1500, 0.55 QALYs).

4.3 **Consideration of the evidence**

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of capecitabine, having considered evidence on the nature of the condition and the value placed on the benefits of capecitabine by people with breast cancer, those who represent them, and clinical experts. It was
also mindful of the need to take account of the effective use of NHS resources.

Combination therapy

4.3.2 The Committee considered that evidence from the RCT demonstrated that capecitabine combination therapy is likely to be more effective than docetaxel monotherapy in terms of several outcomes, including overall survival. However, the side-effect profile of combination therapy may be less acceptable, and the final choice of therapy may be influenced by factors such as contraindications to the different regimens and the clinical condition and preference of individuals. The Committee therefore concluded that, for the majority of individuals, capecitabine combination therapy should be the preferred clinical option over single-agent docetaxel but that taxane monotherapy (docetaxel or paclitaxel) should be considered as an alternative.

Monotherapy

4.3.3 The Committee considered that the evidence for the effectiveness of capecitabine as a monotherapy was less convincing, given that there were no controlled trials.

4.3.4 Although the Committee agreed that vinorelbine was likely to be the most appropriate comparator, it was unable to ascertain the relative clinical and cost effectiveness of the two agents because of the lack of robust evidence from direct comparisons. The Committee acknowledged the limitations of indirect comparisons, but concluded that the evidence presented suggested that it was unlikely that capecitabine was less effective than vinorelbine. The Committee also noted that orally administered drugs may be preferred by many individuals over intravenous regimens. In addition, capecitabine monotherapy was likely to be no more costly than vinorelbine monotherapy.

4.3.5 The Committee was also mindful that, although over time the increased use of capecitabine/docetaxel combination therapy will result in fewer individuals
being eligible for subsequent capecitabine monotherapy, there will still be a group for whom it should be considered.

5 Recommendations for further research

5.1 There was only limited high-quality evidence available for the consideration of the use of capecitabine as monotherapy in people with locally advanced or metastatic breast cancer. An RCT comparing this use of capecitabine with vinorelbine (and intravenous 5-FU) and with symptomatic control alone is needed to provide evidence for the review of the guidance in Section 1.2. This should include an economic evaluation and an assessment of health-related quality of life.

6 Implications for the NHS

6.1 The net cost of capecitabine combination therapy compared with docetaxel monotherapy, assuming that 7500 individuals receiving combination therapy would have received docetaxel monotherapy, is a saving of £1.2 million (excluding VAT). This assumes a total cost of treatment (including all items considered in the evaluation) of £9090 for combination therapy and £9250 for docetaxel monotherapy. However, the exact cost saving will largely depend on the proportion of individuals who receive combination therapy and the proportion who receive monotherapy; the Committee was unable to quantify these numbers.

6.2 It is unlikely that this cost-saving would be realised in terms of ‘cash’ for two reasons: the estimates represent amounts of resources that would remain within the system (but might nevertheless be redeployed); and the estimates are based on average costs (for example, of days in hospital avoided), some of which are fixed costs and therefore will not be saved, but could be available for other purposes.
7 Implementation and audit

7.1 Clinicians with responsibility for treating people with locally advanced or metastatic breast cancer should review their current practice and policies to take account of the guidance set out in Section 1.

7.2 Local guidelines, protocols or care pathways that refer to the care of people with locally advanced or metastatic breast cancer should incorporate the guidance.

7.3 To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix C.

7.3.1 An individual with locally advanced or metastatic breast cancer for whom anthracycline-containing regimens are unsuitable or have failed is provided with capecitabine in combination with docetaxel.

7.3.2 An individual with locally advanced or metastatic breast cancer who has not previously received capecitabine in combination therapy, and for whom anthracycline- and taxane-containing regimens have failed, or for whom further anthracycline therapy is contraindicated, is offered capecitabine monotherapy as an option.

7.3.3 The individual and the clinician(s) responsible for treatment decide jointly on treatment after an informed discussion.

7.3.4 The use of capecitabine to treat locally advanced or metastatic breast cancer is supervised by an oncologist specialising in breast cancer.

7.4 Local clinical audits on the care of people with advanced breast cancer could also include measurement of compliance with accepted clinical guidelines or protocols including ‘Improving outcomes in breast cancer’ (see Section 8.1).
8 Related guidance

8.1 The Institute has issued guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. All issued guidance and details of appraisals and guidelines in progress are available on the NICE website (www.nice.org.uk).


9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed in the light of new evidence in January 2006 or sooner, contingent on the results of any ongoing trials and any ongoing technology appraisals.
David Barnett
Chair, Appraisal Committee
March 2003
Appendix A. Appraisal Committee members

NOTE 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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies, and topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If 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 declaration of interests, are posted on the NICE website.

**Dr Jane Adam**
Radiologist, St George’s Hospital, London

**Dr Sunil Angris**
General Practitioner, Waterhouses Medical Practice, Staffordshire

**Dr Darren Ashcroft**
Senior Clinical Lecturer, School of Pharmacy & Pharmaceutical Sciences, University of Manchester

**Professor David Barnett (Chair)**
Professor of Clinical Pharmacology, University of Leicester

**Professor John Brazier**
Health Economist, University of Sheffield
**Professor Mike Campbell**  
Statistician, Institute of General Practice & Primary Care, Sheffield

**Dr Mike Davies**  
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

**Dr Cam Donaldson**  
PPP Foundation Professor of Health Economics, School of Population and Health Sciences & Business School, Business School – Economics, University of Newcastle upon Tyne

**Professor Jack Dowie**  
Health Economist, London School of Hygiene & Tropical Medicine

**Dr Paul Ewings**  
Statistician, Taunton & Somerset NHS Trust, Taunton

**Ms Sally Gooch**  
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

**Miss Linda Hands**  
Clinical Reader in Surgery, University of Oxford

**Ms Ruth Lesirge**  
Lay Representative, previously Director, Mental Health Foundation, London

**Dr George Levvy**  
Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

**Dr Gill Morgan**  
Chief Executive, NHS Confederation, London

**Professor Philip Routledge**  
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff
Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

Professor Andrew Stevens (Vice-Chair)
Professor of Public Health, University of Birmingham

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Senior Lecturer & Public Health Consultant, University of Southampton
Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the NHS Centre for Reviews and Dissemination/Centre for Health Economics, University of York:


B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document. Consultee organisations were provided with the opportunity to appeal against the FAD:

I Manufacturer/sponsors:

- Roche Products Limited

II Professional/specialist and patient/carer group:

- Association of Surgeons of Great Britain and Ireland
- Breakthrough Breast Cancer
- Breast Cancer Care
- British Psychosocial Oncology Society
- British Oncology Pharmacy Association
- CancerBACUP
- Department of Health
- Hyndburn and Ribble Valley PCT
- Long Term Medical Conditions Alliance
- Macmillan Cancer Relief
- Medical Women's Federation
- National Cancer Alliance
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists
- Royal Pharmaceutical Society of Great Britain
- UK Breast Cancer Coalition
- Welsh Assembly Government
- Welsh Cancer Network

III Commentator organisations (without the right of appeal):
- NHS Quality Improvement Scotland
- Hyndburn and Ribble Valley Primary Care Trust
- Institute of Cancer Research

C The following individuals were selected from clinical expert 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 capecitabine for the treatment of locally advanced or metastatic breast cancer by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD:
- Dr David Miles, ICRF Department of Clinical Oncology, Guy’s Hospital, London
- Dr Stephen R D Johnston, Consultant Medical Oncologist, Royal Marsden Hospital, London
- Dr Chris Twelves, Beatson Oncology Centre, Western Infirmary, University of Glasgow
- Anna Wood, Policy Analyst, Breast Cancer Care
- Elisabeth Davies, Director, UK Breast Cancer Coalition
Appendix C. Detail on criteria for audit of the use of capecitabine for the treatment of locally advanced or metastatic breast cancer

Possible objectives for an audit

An audit on the treatment of people with locally advanced or metastatic breast cancer could be carried out to ensure that capecitabine is being used appropriately.

Possible people to be included in an audit

An audit could be carried out on people with locally advanced or metastatic breast cancer referred over a suitable time period, for example, 6 months or a year.

Measures that could be used as a basis for audit

The measures that could be used in an audit of capecitabine for the treatment of locally advanced or metastatic breast cancer are as follows.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Standard</th>
<th>Exceptions</th>
<th>Definition of terms</th>
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<tbody>
<tr>
<td>1. The individual is provided with capecitabine in combination with docetaxel if anthracycline-containing regimens are unsuitable or have failed</td>
<td>100% of the people for whom anthracycline-containing regimens are unsuitable or have failed</td>
<td>None</td>
<td>Clinicians will have to agree locally on definitions for suitability for treatment with and failure of anthracycline-containing regimens.</td>
</tr>
<tr>
<td>2. The individual is offered capecitabine monotherapy as an option if:</td>
<td>100% of the people who have not received capecitabine in combination therapy previously and for whom anthracycline and taxane-containing regimens have failed, or for whom further anthracycline therapy is contraindicated</td>
<td>None</td>
<td>Clinicians will have to agree locally on how failure of anthracycline and taxane-containing regimens and contraindications to anthracycline therapy are documented for audit purposes.</td>
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<tr>
<td>a. he or she has not previously received capecitabine in combination therapy and</td>
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<tr>
<td>b. anthracycline and taxane-containing regimens have failed or further anthracycline therapy is contraindicated</td>
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<tr>
<td>3. The individual and the clinician(s) responsible for treatment decide jointly on treatment after an informed discussion of the following:</td>
<td>100% of the people included in the audit</td>
<td>None</td>
<td>Clinicians will have to agree locally on how the joint decision and informed discussion are documented for audit purposes.</td>
</tr>
</tbody>
</table>
a. the contraindications of the agents and
b. the side-effect profile of the agents and
c. alternative treatments for locally advanced or metastatic breast cancer and
d. the clinical condition of the individual and
e. the preferences of the individual

| 4. An oncologist specialising in breast cancer supervises the use of capecitabine | 100% of the people receiving capecitabine | None | Clinicians will have to agree locally on how supervision of the use of capecitabine is defined and documented for audit purposes. |
**Calculation of compliance with the measures**

Compliance (%) with each measure described in the table is calculated as follows.

\[
\text{Number of people whose care is consistent with the criterion plus the number of people who meet any exception} \times 100
\]

Number of people to whom the measure applies

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement, and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.