



Complete Summary

GUIDELINE TITLE

Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 24 p. (Technology appraisal; no. 62).

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Locally advanced or metastatic breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the clinical effectiveness and cost effectiveness of oral capecitabine (Xeloda®) for locally advanced and metastatic breast cancer in relation to its licensed indications

TARGET POPULATION

Adults with locally advanced or metastatic breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Capecitabine
2. Capecitabine in combination with docetaxel

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
 - Survival (overall and progression free)
 - Response rate
 - Time to treatment failure
 - Symptom relief
 - Quality of life
 - Adverse events
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the National Health Service

(NHS) Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

Search Strategy

The following databases were searched for relevant published literature. Full details of the search strategy are reported in Appendix 1 of the Assessment Report (See the "Companion Documents" field.):

- BIOSIS
- CancerLit
- CCTR (Cochrane Controlled Trials Register)
- CINAHL (Cumulative Index for Nursing and Allied Health Literature)
- Conference Papers Index
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- HealthStar
- ISTP (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- Science Citation Index
- OHE Health Economic Evaluations Database

In addition the bibliographies of retrieved articles and industry submissions made to the National Institute for Clinical Excellence (NICE) were searched for further studies.

Inclusion and Exclusion Criteria

Two authors independently screened titles and abstracts (where available) of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained. The full paper copy of the study was assessed for inclusion by one reviewer and checked for accuracy by a second, using the criteria outlined below. Studies that did not meet the inclusion criteria were excluded. The bibliographic details of the excluded studies with reasons for exclusion are presented in tables in Appendix 6 of the assessment report. Any discrepancies were resolved by discussion and if necessary through consultation with the Reviews Manager.

Study Design

For the evaluation of clinical effectiveness the gold standard is the randomised controlled, Phase III clinical trial. The Assessment Groups did not identify any randomised, controlled trials to evaluate capecitabine monotherapy and so they included uncontrolled Phase II studies and other observational studies. For the evaluation of capecitabine in combination with docetaxel, a randomised controlled Phase III trial was identified. They also included uncontrolled Phase II studies.

Interventions

Oral capecitabine (Xeloda) used alone or in combination with docetaxel versus taxane monotherapy (paclitaxel or docetaxel), vinorelbine or best supportive care, as part of the following stages of treatment for locally advanced and/or metastatic breast cancer:

- As second or subsequent line therapy in combination with docetaxel for patients who have failed anthracycline-containing chemotherapy regimens
- As third or subsequent line monotherapy for patients who have failed taxanes and anthracycline-containing regimens or, who have failed taxanes and for whom further anthracycline therapy is not indicated.

Participants

Women with locally advanced or metastatic breast cancer were included. According to the UICC (International Union Against Cancer) staging system, locally advanced cancer refers to stages IIIa and IIIb, and metastatic cancer to stage IV (see Appendix 2 of the Assessment Report).

Outcome Measures

The following outcomes measures were included in the review:

- Overall survival
- Progression-free survival
- Tumour response (complete and partial)
- Time to treatment failure
- Adverse events/toxicity (diarrhoea, abdominal pain, nausea, vomiting, stomatitis, hand-foot syndrome (also known as hand-foot skin reaction or palmar-plantar erythrodysesthesia), hyperbilirubinaemia, fatigue, anaemia, thrombocytopenia, dermatitis and any other adverse effects judged to be appropriate.)
- Quality of life
- Costs from all reported perspectives

For capecitabine monotherapy we also considered patient preference for oral therapy as an additional outcome.

NUMBER OF SOURCE DOCUMENTS

Capecitabine Monotherapy

Twenty-three published reports of thirteen uncontrolled studies of clinical effectiveness were identified for inclusion. In addition, one economic evaluation was identified.

Capecitabine in Combination with Docetaxel

Five published reports of one randomised controlled trial investigating capecitabine in combination with docetaxel compared to single-agent docetaxel were identified. In addition, two uncontrolled studies were identified which investigated an alternative, low-dose docetaxel regimen. One economic evaluation

based on the randomised controlled trial (RCT) comparing capecitabine in combination with docetaxel to single-agent docetaxel was identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the National Health Service (NHS) Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

Data Extraction Strategy

One reviewer, using predefined data extraction forms, extracted data from studies meeting the inclusion criteria into an Access database. The forms were checked for accuracy by a second reviewer and any disagreements were resolved by discussion, or if necessary through consultation with the Reviews Manager.

Quality Assessment Strategy

Clinical effectiveness studies meeting the inclusion criteria for the review were assessed for quality by one reviewer, and checked for accuracy by a second. The quality of clinical effectiveness studies was assessed according to criteria based on NHS CRD Report No. 4.16. The same checklist was used to evaluate all of the effectiveness studies regardless of design in order to give a consistent summary of quality.

Economic evaluations were assessed for quality by one reviewer, and checked for accuracy by a second, using a checklist updated from that developed by Drummond and colleagues; additional commentary was provided where appropriate. Any disagreements were resolved by consensus or, if necessary, through consultation with a third reviewer. This checklist reflects the criteria for economic evaluations detailed in the methodological guidance developed by the National Institute for Clinical Excellence.

Methods of Analysis/Synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness were presented in structured tables and as a narrative summary. The possible effects of study quality on the findings of the review were discussed within the text. Due to the small number of studies included in the review and the heterogeneity between the studies, statistical pooling was not deemed appropriate. Consequently statistical chi-squared tests of heterogeneity have not been performed. Studies were grouped according to whether capecitabine was used alone or in combination with docetaxel.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Combination Therapy

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.

Monotherapy

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.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document

(ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- 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.
- 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.
- 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, and the clinical condition and preferences of the individual.
- The use of capecitabine to treat locally advanced or metastatic breast cancer should be supervised by oncologists who specialise in breast cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of oral capecitabine (Xeloda®) for locally advanced and metastatic breast cancer

POTENTIAL HARMS

Special warnings and special precautions for use of oral capecitabine:

- Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis, and hand-foot syndrome. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.
- Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with a history of significant cardiac disease.
- Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.
- Caution must be exercised in patients with central or peripheral nervous system disease, e.g., brain metastasis or neuropathy.
- Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.
- Patients receiving concomitant capecitabine and oral coumarin-derivative anti-coagulation therapy should have their anticoagulant response (International Normalized Ratio [INR] or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly.
- Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence of liver metastasis.
- The incidence of grade 3 or 4 adverse events in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) is increased compared to the overall population.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications for capecitabine use include:

- History of severe and unexpected reactions to fluoropyrimidine therapy
- Known hypersensitivity to capecitabine, fluorouracil, or any of the excipients
- Patients with severe hepatic impairment
- Patients with severe renal impairment (creatinine clearance below 30 mL/min)
- Treatment with sorivudine or its chemically related analogues, such as brivudine
- Contraindications for docetaxel also apply to the capecitabine plus docetaxel combination
- In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency
- During pregnancy and lactation
- Patients with severe leucopenia, neutropenia, or thrombocytopenia

QUALIFYING STATEMENTS

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This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- 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 (see the "Major Recommendations" field).
- Local guidelines, protocols, or care pathways that refer to the care of people with locally advanced or metastatic breast cancer should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix D of the original guideline document.
 - 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.
 - 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.
 - The individual and the clinician(s) responsible for treatment decide jointly on treatment after an informed discussion.
 - The use of capecitabine to treat locally advanced or metastatic breast cancer is supervised by an oncologist specialising in breast cancer.
- 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 of the original guideline document).

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. London (UK): National Institute for Clinical Excellence (NICE); 2003 May. 24 p. (Technology appraisal; no. 62).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 May

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr Jane Adam, Radiologist, St George's Hospital, London; Dr Sunil Angris, General Practitioner, Waterhouses Medical Practice, Staffordshire;

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 May. 1 p. (Technology appraisal 62). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- A rapid and systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or

metastatic breast cancer. NHS R&D HTA Programme. 2002 Sep 23. 156 p.
Available in Portable Document Format (PDF) from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line
0870 1555 455. ref: N0226. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix D of the [original guideline document](#).

PATIENT RESOURCES

The following is available:

- The use of capecitabine for locally advanced or metastatic breast cancer. Understanding NICE guidance - information for people with breast cancer and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 May. 9 p. (Technology appraisal 62).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the Department of Health Publications Order Line
0870 1555 455. ref: N0228. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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