



## Complete Summary

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### GUIDELINE TITLE

Docetaxel for the adjuvant treatment of early node-positive breast cancer.

### BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Docetaxel for the adjuvant treatment of early node-positive breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 21 p. (Technology appraisal guidance; no. 109).

### GUIDELINE STATUS

This is the current release of the guideline.

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## SCOPE

### DISEASE/CONDITION(S)

Early node-positive breast cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### CLINICAL SPECIALTY

Internal Medicine  
Obstetrics and Gynecology  
Oncology

## **INTENDED USERS**

Advanced Practice Nurses  
Nurses  
Physician Assistants  
Physicians

## **GUIDELINE OBJECTIVE(S)**

To evaluate the clinical effectiveness and cost-effectiveness of docetaxel for the adjuvant treatment of early node-positive cancer

## **TARGET POPULATION**

Women with early node-positive breast cancer

## **INTERVENTIONS AND PRACTICES CONSIDERED**

Docetaxel (Taxotere) concurrently with doxorubicin and cyclophosphamide (TAC regimen)

## **MAJOR OUTCOMES CONSIDERED**

- Clinical effectiveness
  - Disease-free survival
  - Overall survival
  - 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Searches of Unpublished Data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 an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (SchARR), University of Sheffield (see the "Availability of Companion Documents" field).

### **Clinical Effectiveness**

## **Critique of Manufacturer's Approach**

### *Was the Search Strategy Appropriate?*

Only four electronic databases were searched (Medline, Embase, the Cochrane Central Register, and American Society of Clinical Oncology [ASCO]). Other potentially relevant databases which were not searched include CINAHL, BIOSIS, the Science Citation Index, and the proceedings of the European Society for Medical Oncology (ESMO) and the San Antonio Breast Cancer Symposium. The most recent search was undertaken on 6th December 2005.

Sufficient detail was provided to allow the search strategies to be reproduced. The Medline search strategy was rerun: it did not identify the submission's key study, BCIRG 001, which was excluded by the attempt to limit the search to studies of early breast cancer (search string 14). As an equivalent search string was included in the search strategies used for the other databases, this would presumably have prevented the identification of that study, and possibly therefore other relevant studies, in those databases also; however, this was not tested.

The submission states that the electronic searches were supplemented by information from undescribed internal company data sources. The stated purpose of this was to try to identify unpublished studies. However, given the shortcomings of the electronic search strategies, it is likely that recourse to these data sources was necessary to identify published studies such as BCIRG 001.

### *Statement of the Inclusion/Exclusion Criteria Used in the Study Selection*

There is some ambiguity in terms of the statement of inclusion/exclusion criteria used in the study selection. The criteria used to identify the studies included in the list of all randomised controlled trials (RCTs) comparing docetaxel with alternative therapies were:

- Population: women with node-positive early (operable) breast cancer
- Intervention: docetaxel in any dose/regimen
- Comparator: any
- Outcome: not specified
- Study type: any RCT

However, the criteria used to identify studies for inclusion in the systematic review were more stringent:

- Population: women with node-positive early (operable) breast cancer
- Intervention: docetaxel in combination with anthracyclines
- Comparator: FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) or FEC (5-fluorouracil, epirubicin and cyclophosphamide)
- Outcome: not specified
- Study type: phase III RCTs

Only one study, BCIRG 001, was identified which fully met the submission's inclusion criteria by comparing the docetaxel-containing regimen recommended in the United Kingdom (UK) (TAC [docetaxel, doxorubicin, and cyclophosphamide])

with an anthracycline-containing regimen (FAC) in women with operable node-positive breast cancer.

The submission also draws data from a second study, PACS 01, which has not yet been published in full. This study did not meet the submission's inclusion criteria because it used an unlicensed docetaxel regimen (FEC100-T). Sanofi-Aventis (the manufacturer of docetaxel) did not have access to the full data from PACS 01, though they requested it.

The submission ignores data from four other potentially relevant studies which do not meet the inclusion criteria in full: these are the ECOG 2197, GEICAM 9805 and USO 9735 studies listed in Table 5 of the ERG Report (see the "Availability of Companion Documents" field), and the RAPP 01 trial. Although the populations of all four studies include women with high-risk node-negative disease, data from studies which include this patient group are not irrelevant since there is generally considered to be no evidence of heterogeneity of effect between node-positive and node-negative disease.

## **NUMBER OF SOURCE DOCUMENTS**

Sixty studies were identified which compared docetaxel with any comparator. Only five of these were said to have reported (Table 5 of the Assessment Report - see the "Availability of Companion Documents" field).

## **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**

Review of Published Meta-Analyses  
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 an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (SchARR), University of Sheffield (see the "Availability of Companion Documents" field).

## **Clinical Effectiveness**

## **Description and Critique of Manufacturer's Approach to Validity Assessment**

The submission does not reference a quality assessment tool. Quality is assessed in relation to the three criteria required by the single technology assessment (STA) specification: randomisation, blinding, and adequacy of follow-up.

It is not clear from published sources that a secure randomisation method was used in either BCIRG 001 or PACS 01. However, section 2.4.1 of the manufacturer's submission states that both studies used a secure randomisation method in which the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care. It is not clear how the manufacturer obtained this additional information in relation to PACS 01, given that they state that they did not have access to unpublished data from this trial, and that they state that information on the method of randomisation is not available for PACS 01.

The patients and clinical staff do not appear to have been blinded in either BCIRG 001 or PACS 01; this is claimed to be normal for cancer trials. It is not clear from the publications relating to either study whether the outcome assessors were blinded to treatment allocation, but the submission's response suggests that, in BCIRG 001, they were not. The US Food and Drug Administration (FDA) state that, although blinding is not essential when the outcome being measured is overall survival, it is preferred when the outcome is disease-free survival, and is necessary to minimise bias in the assessment of drug toxicity.

## **Description and Critique of Manufacturer's Outcome Selection**

The primary outcome measure used in BCIRG 001 was disease-free survival, defined as time from randomisation to date of a clinical relapse, a second cancer (except skin cancer other than melanoma, ductal or lobular carcinoma in situ of the breast, or in situ carcinoma of the cervix), or death, whichever occurred first. The secondary outcome measures were overall survival (defined as time from randomisation until death from any cause), health-related quality of life, and toxic effects.

These outcome measures are appropriate. In adjuvant therapy, the prolongation of disease-free survival appears to represent intrinsic benefit rather than acting only as a surrogate for overall survival. However, the FDA advises that the magnitude of that benefit should be carefully weighed against the toxicity of the treatment. As noted earlier, an overall survival gain is generally felt to be required to compensate for the toxicity of the therapy.

The tools used in BCIRG 001 to measure health-related quality of life, are appropriate for this purpose.

## **Description and Critique of the Statistical Approach Used**

The submission appears to contain unbiased estimates of relative treatment effects expressed in terms of hazard ratios, adjusted when necessary to take account of possible imbalances in prognostic factors. Meta-analysis was not

undertaken as only one trial was identified which used docetaxel in its licensed application.

Refer to Section 4.1 of the ERG Report (see the "Availability of Companion Documents" field) for more information.

## **Economic Evaluation**

### **Overview of Manufacturer's Economic Evaluation**

The economic evaluation model has three components:

- Adjuvant chemotherapy decision tree model

A decision tree is used to calculate expected cost and quality-adjusted life year (QALY) outcomes associated with the adjuvant chemotherapy treatments under consideration.

- Model of long term disease progression

A state transition model (Markov model) is used to generate estimates of disease free survival, quality adjusted life years, and monitoring costs. These outcomes are incurred up to disease relapse or death over the lifetime of the model defined as 40 years in the base case.

- Consequences of disease relapse

Recurrence of locoregional breast cancer or distant metastatic disease is assumed to be associated with constant cost, survival and quality of life outcomes.

Refer to Section 5 of the ERG Report (see the "Availability of Companion Documents" field) for a complete discussion of the modelling of survival effects, quality of life and costs within these three components as well as the sensitivity analysis.

## **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**

The Appraisal Committee discussed the Evidence Review Group's (ERG's) critique of the modelling between TAC (docetaxel given concurrently with doxorubicin and Cyclophosphamide) and FAC (5-fluorouracil, doxorubicin, and Cyclophosphamide). It concluded that although the ERG report raised valid and important issues regarding the modelling of long-term disease-free survival, post-relapse costs and survival, and the method used to input utilities, overall the structure and methodology of the manufacturer's model were acceptable for the purpose of decision making. The Committee accepted the ERG's view that the cost per quality-adjusted life year (QALY) gained in the comparison of TAC with FAC was unlikely to be greater than 35,000 pounds sterling.

The Committee considered evidence for the cost effectiveness of the TAC regimen compared with the FEC (5-fluorouracil, epirubicin, and cyclophosphamide) regimen, noting that FAC was used as a proxy for FEC in the manufacturer's economic model. The Committee discussed the indirect comparison between TAC and FEC put forward by the ERG, noting the scenario in which TAC could be economically dominated by the FEC100 regimen. The Committee agreed that this was not directly relevant to current standard care in England and Wales in the light of the quantitative survey provided by the manufacturer indicating that the FEC60 and FEC75 regimens are those most commonly used in the United Kingdom. The Committee further considered the additional economic modelling provided by the manufacturer on request regarding comparison of the TAC regimen with the FEC60 and FEC75 regimens. The Committee accepted that the TAC regimen is likely to be cost effective compared with the FEC regimen with doses of epirubicin used in current National Health Service (NHS) practice between the threshold incremental cost-effectiveness ratio (ICERs) of 20,000 pounds sterling and 30,000 pounds sterling presented in the manufacturer's additional modelling.

## **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**

Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is recommended as an option for the adjuvant treatment of women with early node-positive 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 docetaxel for the treatment of early node-positive breast cancer

### **POTENTIAL HARMS**

Docetaxel treatment is associated with a high incidence of myelosuppression and other significant side effects.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at <http://emc.medicines.org.uk/>.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. 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 appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

- The Healthcare Commission assesses the performance of National Health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by

National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- "Healthcare standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organizations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on NICE website ([www.nice.org.uk/TA109](http://www.nice.org.uk/TA109)) (also see the "Availability of Companion Documents" field).
  - Local costing template incorporating a costing report to estimate the savings and costs associated with implementation
  - Audit criteria to monitor local practice

## **IMPLEMENTATION TOOLS**

Audit Criteria/Indicators  
Patient Resources  
Quick Reference Guides/Physician Guides  
Resources

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 Health and Clinical Excellence (NICE). Docetaxel for the adjuvant treatment of early node-positive breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 21 p. (Technology appraisal guidance; no. 109).

**ADAPTATION**

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

**DATE RELEASED**

2006 Sep

**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**

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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:

- Docetaxel for the adjuvant treatment of early node-positive breast cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 2 p. (Technology appraisal 109). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Costing report and template: docetaxel for the adjuvant treatment of early node-positive breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. Various p. (Technology appraisal 109). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- Docetaxel for the adjuvant treatment of early node-positive breast cancer. Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 9 p. (Technology appraisal 109). Available in Portable Document Format (PDF) from the [NICE Web site](#).
- Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal. Evidence Review Group Report. The School of Health and Related Research (SchARR), University of Sheffield, UK. 2006 Mar 7. 85 p. Electronic copies: Available from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1101. 11 Strand, London, WC2N 5HR.

## **PATIENT RESOURCES**

The following is available:

- Docetaxel for the adjuvant treatment of early node-positive breast cancer. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 4 p. (Technology appraisal 109).

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

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1102. 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.

## **NGC STATUS**

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