

Issue date: September 2006

Review date: June 2007

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

**Part review of NICE technology appraisal  
guidance 30**

**This guidance was developed using the  
Single Technology Appraisals process**

## **NICE technology appraisal guidance 109 Docetaxel for the adjuvant treatment of early node-positive breast cancer**

### **Ordering information**

You can download the following documents from [www.nice.org.uk/TA109](http://www.nice.org.uk/TA109)

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for women with breast cancer and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone the NHS Response Line on 0870 1555 455 and quote:

- N1101 (quick reference guide)
- N1102 ('Understanding NICE guidance').

### **This guidance is written in the following context**

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.

### **National Institute for Health and Clinical Excellence**

MidCity Place  
71 High Holborn  
London  
WC1V 6NA

[www.nice.org.uk](http://www.nice.org.uk)

© National Institute for Health and Clinical Excellence, September 2006. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the express written permission of the National Institute for Health and Clinical Excellence.

## Contents

1	Guidance.....	4
2	The technology.....	4
3	The manufacturer's submission .....	4
4	Consideration of the evidence.....	7
5	Implementation.....	10
6	Related guidance .....	11
7	Review of guidance.....	13
	Appendix A. Appraisal Committee members and NICE project team.....	14
	Appendix B. Sources of evidence considered by the Committee .....	18
	Appendix C. List of organisations involved in this appraisal .....	19

NOTE: This guidance replaces paragraph 1.3 in *NICE technology appraisal guidance* no. 30 issued in September 2001.

## **1 Guidance**

- 1.1 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.

## **2 The technology**

- 2.1 Docetaxel (Taxotere, Sanofi-Aventis) is an anticancer drug that belongs to a class of drugs known as taxanes. Docetaxel has a UK marketing authorisation for the adjuvant treatment of patients with operable node-positive breast cancer in combination with doxorubicin and cyclophosphamide. For further information about the drug please see the 'Summary of product characteristics' (SPC).
- 2.2 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 SPC.
- 2.3 The net price of docetaxel (40 mg/ml) is £162.75 for a 0.5 ml vial and £534.75 for a 2 ml vial (excluding VAT; 'British national formulary' 51). The cost per patient for six cycles of treatment would be approximately £6000. Costs may vary in different settings because of negotiated procurement discounts.

## **3 The manufacturer's submission**

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of docetaxel and a review of this submission by the evidence review group (ERG) (appendix B).

- 3.1 The manufacturer's submission approached the decision problem by comparing six cycles of the TAC regimen of docetaxel, doxorubicin and cyclophosphamide with six cycles of a combination regimen of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), both given 3-weekly in women with node-positive breast cancer. The outcomes were disease-free survival, overall survival, quality-of-life measures and adverse effects. The manufacturer provided data based on clinical opinion and survey data to identify the regimens most commonly used in the UK, and stated that no head-to-head trials have been reported that directly compare TAC with the regimens used commonly in the UK.
- 3.2 The main comparison in the manufacturer's submission, of TAC with FAC, was based on data from the randomised controlled trial (RCT) that underpinned the regulatory approval of docetaxel in this indication: BCIRG001. In the manufacturer's economic model, FAC was taken as a proxy for the combination regimen of 5-fluorouracil, epirubicin and cyclophosphamide (FEC), which has been reported in survey data to be the regimen most frequently used in the UK. The equivalence of FAC to FEC was suggested on the basis of clinical opinion, direct comparisons from therapy in metastatic disease, and a published indirect comparison. The base-case estimate of the cost per quality-adjusted life year (QALY) gained with six cycles of TAC compared with six cycles of FAC was £9800. The manufacturer also provided a comparison of the cost effectiveness of a regimen not specified in the SPC of three cycles of FEC followed by three cycles of docetaxel (FEC→T) with six cycles of FEC, based on the PACS01 study.
- 3.3 The manufacturer stated that a clinical panel had advised that the efficacy of the block sequential regimen of epirubicin followed by a combination of cyclophosphamide, methotrexate and 5-fluorouracil (E→CMF) may be superior to that of FAC. An indirect comparison, described as a 'simple threshold analysis' in the manufacturer's submission, was presented to explore the cost effectiveness of TAC compared with E→CMF. This analysis was based on a comparison of absolute disease-free survival rates across

trials, and the cost per QALY gained was estimated to be approximately £15,000 to £20,000.

- 3.4 The ERG report raised issues regarding the indirect comparisons necessary to estimate the clinical effectiveness of TAC compared with the regimens of FEC (with doses of epirubicin from 75 mg/m<sup>2</sup> to 100 mg/m<sup>2</sup>) and E→CMF, and concluded that the relative effectiveness remains unclear.
- 3.5 The ERG report included an in-depth critique of the manufacturer's modelling of TAC compared with FAC. Although the ERG identified issues regarding the long-term modelling of the disease-free period, the estimates of costs and survival post-relapse, the utility values used and the cost of prophylactic granulocyte colony-stimulating factor, the ERG estimated the base-case cost per QALY gained to be not substantially higher than the manufacturer's estimate, and unlikely to be greater than £35,000.
- 3.6 The ERG report also included indicative analyses in order to estimate the cost effectiveness of TAC compared with the FEC100 regimen, which contains epirubicin at a dose of 100 mg/m<sup>2</sup>, and of TAC compared with the E→CMF regimen. These analyses included scenarios in which the incremental cost-effectiveness ratio (ICER) of TAC was higher than the base-case in the manufacturer's submission, or in which TAC was even economically dominated by FEC100 or E→CMF. The ERG therefore concluded that the cost effectiveness in these circumstances remains unclear.
- 3.7 Following a request for clarification, the manufacturer provided data based on a survey of 272 patients which indicated that FEC60 and FEC75 are the most commonly used FEC regimens in the UK. The manufacturer also provided a systematic literature review which showed that there is no evidence that FEC60 or FEC75 are significantly different in efficacy from FAC50 or FEC50 in early breast cancer. This systematic review did suggest that FEC regimens with epirubicin doses above 90 mg/m<sup>2</sup> are more efficacious than those using lower doses. The manufacturer provided additional economic modelling to

estimate the improvement in efficacy that the FEC regimen would have to achieve over that of FAC for TAC to be expected not to be cost effective.

- 3.8 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from [www.nice.org.uk/TA109](http://www.nice.org.uk/TA109)

## **4 Consideration of the evidence**

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of docetaxel for the adjuvant treatment of early node-positive breast cancer, having considered evidence on the nature of the condition and the value placed on the benefits of docetaxel by women with early node-positive breast cancer, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.2 The Committee considered whether the decision problem had been adequately framed in the manufacturer's submission. It noted that the manufacturer's submission, the ERG and clinical specialists concurred that the relevant comparators in the context of the NHS in England and Wales are anthracycline-containing regimens, most commonly FEC and secondly E→CMF. The Committee did not accept that the FAC regimen is the principal comparator for this appraisal, because it is not frequently used in England and Wales.

### ***Clinical effectiveness***

- 4.3 The Committee discussed the BCIRG001 trial and accepted that the results demonstrated both a benefit in disease-free survival and that overall survival is improved by the use of TAC compared with FAC. The Committee were persuaded that the TAC regimen is associated with a significantly higher rate of grade 3 and 4 adverse events, in particular febrile neutropenia, but that this can be mitigated significantly with the use of granulocyte colony-stimulating factor. However, the Committee understood from clinical specialists' statements that docetaxel as a single agent carries a lower risk of

myelosuppression than docetaxel given in a combination regimen, and that the regimen preferred by the vast majority of breast cancer oncologists would be the block sequential regimen, FEC→T. The Committee was mindful of the fact that the licensed indication for the use of docetaxel in breast cancer does not include the FEC→T regimen, and that it would not be able to issue recommendations on this sequential regimen. The Committee appreciated that many patients with early node-positive breast cancer value the potential of docetaxel to reduce the rate of recurrence of their disease to the extent that they prefer to receive it, knowing that it is likely to cause adverse effects, some of which may be severe. The Committee concluded that the TAC regimen is more clinically effective than the FAC regimen.

- 4.4 The Committee considered the submission and further clarification provided by the manufacturer regarding the comparison of the TAC regimen with the FEC regimen. The Committee was persuaded that FEC60 and FEC75 are the most commonly used FEC regimens in the NHS in England and Wales, noting that the research provided by the manufacturer was in concurrence with clinical opinion. The manufacturer's systematic review and the statements from clinical specialists concurred that FEC75 can be assumed to be equivalent to FAC in terms of both efficacy and haematological toxicity. Because of this assumed equivalence, and the results of the BCIRG001 study showing TAC to be more clinically effective than FAC, the Committee accepted that the TAC regimen is likely to be more effective than FEC regimens with doses of epirubicin of 75 mg/m<sup>2</sup> or below.
- 4.5 The Committee discussed the rationale described in the manufacturer's submission for comparing the clinical effectiveness of the TAC regimen with that of the E→CMF regimen. The Committee noted the statement in the manufacturer's submission that an adjusted indirect comparison between TAC and E→CMF using the BCIRG001 study and the NEAT study (which compared E→CMF with CMF) was not considered appropriate because there was no comparator chemotherapy regimen that was common to the two trials, and there were marked differences in the characteristics of the trial

populations. The Committee considered the indirect approach discussed in the ERG report regarding the comparison of TAC with E→CMF. It noted that no evidence of a direct comparison between FAC and E→CMF regimens in the adjuvant setting had been identified. It discussed the uncertainty raised by the ERG about the comparison of TAC with E→CMF, noting that the manufacturer had found no further evidence following the request for further clarification. The Committee noted the issues raised by the manufacturer that there may be increased toxicity associated with the E→CMF regimen, and that this regimen requires more resources in terms of patient treatment time and specialist nurse time compared with the more commonly used FEC regimen. Additionally, the Committee noted that the E→CMF regimen requires patients to have more injections than other anthracycline regimens and is therefore not preferred by some patients. The Committee was aware that ongoing studies compare E→CMF with a block sequential regimen of docetaxel rather than the TAC regimen, and concluded that the existing uncertainty regarding the clinical effectiveness of the TAC regimen compared with the E→CMF regimen is likely to remain for the foreseeable future. The Committee recognised that information on the usage of E→CMF in the NHS is variable. The Committee concluded that, on balance, the current evidence on TAC compared with E→CMF and the degree of use of E→CMF in the NHS did not justify rejecting the use of TAC.

### ***Cost effectiveness***

- 4.6 The Committee discussed the ERG's critique of the modelling between TAC and FAC. 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 QALY gained in the comparison of TAC with FAC was unlikely to be greater than £35,000.

4.7 The Committee considered evidence for the cost effectiveness of the TAC regimen compared with the FEC 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 UK. 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 NHS practice between the threshold ICERs of £20,000 and £30,000 presented in the manufacturer's additional modelling.

### ***Summary of the considerations***

4.8 In summary, the Committee concluded that there was sufficient evidence to indicate that the TAC regimen is clinically and cost effective compared with standard practice in the NHS in England and Wales, and that it can be recommended as an alternative treatment option for the adjuvant treatment of early node-positive breast cancer.

## **5 Implementation**

5.1 The Healthcare Commission assesses the performance of 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 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.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations 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.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TA109](http://www.nice.org.uk/TA109)).

- Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice.

## 6 Related guidance

6.1 In 2001, NICE issued guidance on the use of taxanes (paclitaxel and docetaxel) for the treatment of breast cancer.

Guidance on the use of taxanes for the treatment of breast cancer (review). *NICE technology appraisal guidance* no. 30 (September 2001). Available from: [www.nice.org.uk/TA30](http://www.nice.org.uk/TA30)

Guidance in TA30 on the use of taxanes for the treatment of advanced breast cancer is still current (paragraphs 1.1. and 1.2). Guidance in TA30 on the use of taxanes for the adjuvant treatment of early breast cancer (paragraph 1.3) is

obsolete and replaced by this guidance and *Technology appraisal guidance* no. 108 ('Paclitaxel for the treatment of early node-positive breast cancer').

6.2 NICE has issued the following related technology appraisal guidance.

Paclitaxel for the adjuvant treatment of early node-positive breast cancer. *NICE technology appraisal guidance* no. 108 (September 2006). Available from: [www.nice.org.uk/TA108](http://www.nice.org.uk/TA108)

Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. *NICE technology appraisal guidance* no. 107 (August 2006). Available from: [www.nice.org.uk/TA107](http://www.nice.org.uk/TA107)

6.3 NICE has issued the following related clinical guideline.

Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. *NICE clinical guideline* no. 14 (May 2004). Available from: [www.nice.org.uk/CG014](http://www.nice.org.uk/CG014)

6.4 NICE is in the process of producing the following technology appraisal guidance.

Hormonal therapies for early breast cancer (publication expected November 2006).

6.5 NICE is in the process of producing the following clinical guidelines.

Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (partial update of CG14; publication expected October 2006).

Early breast cancer: diagnosis and treatment (publication expected July 2008).

Advanced breast cancer: diagnosis and treatment (publication expected July 2008).

## **7 Review of guidance**

- 7.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 7.2 The guidance on this technology will be considered for review in June 2007.

Andrew Dillon  
Chief Executive  
September 2006

## **Appendix A. Appraisal Committee members and NICE project team**

### **A. Appraisal Committee members**

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 ongoing topics are not moved between the branches.

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.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,  
University of Manchester

#### **Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

#### **Mr Brian Buckley**

Vice Chairman, InContact

**Professor John Cairns**

Public Health and Policy, London School of Hygiene and Tropical Medicine

**Professor Mike Campbell**

Statistician, University of Sheffield

**Dr Mark Chakravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble

Pharmaceuticals (UK) Ltd

**Dr Peter I Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology NHS Trust,

Merseyside

**Dr Mike Davies**

Consultant Physician, University Department of Medicine & Metabolism, Manchester

Royal Infirmary

**Mr Richard Devereaux-Phillips**

Public Affairs Manager, Medtronic Ltd

**Professor Jack Dowie**

Health Economist, London School of Hygiene

**Dr Fergus Gleeson**

Consultant Radiologist, The Churchill Hospital, Oxford

**Ms Sally Gooch**

Former Director of Nursing & Workforce Development, Mid Essex Hospital Services

NHS Trust

**Mr Sanjay Gupta**

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

**Professor Philip Home**

Professor of Diabetes Medicine, University of Newcastle upon Tyne

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Professor Peter Jones**

Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

**Dr Mike Laker**

Medical Director, Newcastle Hospitals NHS Trust

**Dr George Levvy**

Lay representative

**Ms Rachel Lewis**

Nurse Advisor to the Department of Health

**Mr Terence Lewis**

Mental Health Consultant, National Institute for Mental Health in England

**Professor Jonathan Michaels**

Professor of Vascular Surgery, University of Sheffield

**Dr Neil Milner**

General Medical Practitioner, Sheffield

**Dr Ruairidh Milne**

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

**Dr Rubin Minhas**

General Practitioner, CHD Clinical Lead, Medway PCT

**Mr Miles Scott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Professor Mark Sculpher**

Professor of Health Economics, University of York

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Mr Roderick Smith**

Finance Director, Adur, Arun and Worthing PCT

**Dr Ken Stein**

Senior Lecturer in Public Health, Peninsula Medical School, University of Exeter

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

The following individual, representing the National Collaborating Centre responsible for developing the Institute's clinical guideline related to this topic, attended the meeting to observe and to contribute as an adviser to the Committee.

**Dr Adrian Harnett**

Consultant in Clinical Oncology, Norfolk and Norwich University Hospital NHS Trust

## **B. NICE Project Team**

Each technology appraisal is assigned to a team consisting of one or more health technology analyst(s) (who act as technical leads for the appraisal) and a project manager.

**Helen Chung and Elisabeth George**

Technical Leads

**Emily Marschke**

Project Manager

## Appendix B. Sources of evidence considered by the Committee

- A The following manufacturer provided a submission for this appraisal.
- Sanofi-Aventis
- B The evidence review group (ERG) report for this appraisal was prepared by the School of Health and Related Research (SchHARR):
- Chilcott J, Lloyd Jones M, Wilkinson A (March 2006). Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology assessment.
- C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They gave their expert personal view on docetaxel for the adjuvant treatment of early node-positive breast cancer by providing written evidence to the Committee:
- Dr Sarah Rawlins, Head of Policy and Information, nominated by Breakthrough Breast Cancer – patient expert
  - Dr Andrew Wardley, Consultant Medical Oncologist, nominated by the Royal College of Physicians – clinical specialist
  - Dr Robert Stein, Consultant Medical Oncologist, nominated by the Royal College of Physicians – clinical specialist
  - Emma Kearns, nominated by Breast Cancer Care – patient expert

## Appendix C. List of organisations involved in this appraisal

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the Appraisal Consultation Document (ACD) and supporting evidence. Consultee organisations have the opportunity to appeal against the Final Appraisal Determination.

### I Professional/specialist and patient/carer groups:

- Association of Cancer Physicians
- Association of Surgeons of Great Britain and Ireland
- British Association of Surgical Oncology
- British Oncological Association
- British Oncology Pharmacy Association (BOPA)
- British Psychosocial Oncology Society
- Cancer Research UK
- Community Practitioners' and Health Visitors' Association
- Medical Women's Federation
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Breakthrough Breast Cancer
- Breast Cancer Care
- Cancerbackup
- Cancer Voices
- Long-Term Medical Conditions Alliance
- Macmillan Cancer Relief

- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Palliative Care
- Tenovus Cancer Information Centre
- Department of Health
- Eden Valley PCT
- North Liverpool PCT
- Welsh Assembly Government

## II Commentator organisations (without the right of appeal):

- British National Formulary
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Coordinating Centre for Health Technology Assessment
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Baxter Healthcare Ltd
- Bayer plc
- Genus Pharmaceuticals Ltd
- Goldshield Pharmaceuticals Ltd
- Mayne Pharma plc
- Medac UK
- Pfizer Ltd
- Teva UK Ltd
- Bristol-Myers Squibb Pharmaceuticals Ltd
- Diagnosis and treatment of breast cancer guideline development groups
- National Collaborating Centre for Cancer
- Cochrane Collaboration – Cochrane Breast Cancer Group
- Institute of Cancer Research

- MRC Clinical Trials Unit
- National Cancer Research Institute