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Paclitaxel 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 108 Paclitaxel for the adjuvant treatment of early node-positive breast cancer

Ordering information

You can download the following documents from www.nice.org.uk/TA108

- 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:

- N1103 (quick reference guide)
- N1104 ('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.

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

1 Guidance

- 1.1 Paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer.

2 The technology

- 2.1 Paclitaxel is an anticancer drug that belongs to a class of drugs known as taxanes. Paclitaxel has a UK marketing authorisation for the adjuvant treatment of node-positive breast carcinoma following anthracycline and cyclophosphamide therapy. The 'Summary of product characteristics' (SPC) states that adjuvant treatment with paclitaxel should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy. For further information about the drug see the SPC.
- 2.2 Paclitaxel treatment is associated with myelosuppression, hypersensitivity reactions and other significant side effects. For full details of side effects and contraindications, see the SPC.
- 2.3 Paclitaxel is available in the NHS as a branded (Taxol, Bristol-Myers Squibb Pharmaceuticals) and a non-proprietary generic drug. The net prices of Taxol (6 mg/ml) are £116.05 (5 ml vial), £347.82 (16.7 ml vial), £521.73 (25 ml vial) and £1043.46 (50 ml vial) (excluding VAT; 'British national formulary' [BNF] 51). The net non-proprietary price of paclitaxel (6 mg/ml) is £112.20 (5 ml vial), £336.60 (16.7 ml vial), £561.00 (25 ml vial) and £1009.80 (50 ml vial) (excluding VAT; BNF 51). The cost per patient, assuming an average of four cycles of treatment, is approximately £4000. 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 Taxol (Bristol-Myers Squibb) 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 providing evidence about the clinical and cost effectiveness of the regimen, specified in the SPC, of four cycles of the anthracycline doxorubicin and cyclophosphamide (a chemotherapy combination known as AC) followed by four cycles of paclitaxel, compared with four cycles of AC alone. It also provided evidence from comparisons of four cycles of AC followed by four cycles of paclitaxel or docetaxel (another taxane) using regimens that are not currently covered by a marketing authorisation in the UK. The clinical studies included in the manufacturer's submission were not identified through a systematic review of the relevant literature. In the studies which included four cycles of AC as comparator, the addition of four cycles of paclitaxel after four cycles of AC resulted in statistically significant improvements in disease-free survival (hazard ratio [HR] in both studies 0.83). One of the studies also showed a statistically significant improvement in overall survival (HR 0.82) whereas the other did not.
- 3.2 The manufacturer's submission provided economic evidence based on a probabilistic Markov state-transition model that compared four cycles of paclitaxel (following four cycles of AC) with four cycles of AC alone. The reported cost per quality-adjusted life year (QALY) gained for this comparison was £4726.
- 3.3 The ERG raised a number of issues related to the manufacturer's submission.
 - There was no systematic review of the effectiveness evidence or the cost-effectiveness evidence, or to inform inputs for the economic model.

- The comparator used in the economic analysis (four cycles of AC) is not commonly used in the NHS for the adjuvant treatment of early node-positive breast cancer and is considered less effective than the most commonly used regimens, including extended anthracycline therapy of six to eight cycles.
- No patient subgroups stratified according to prognostic characteristics were considered.
- Utility data were not adjusted for patient age or chemotherapy-specific toxicities.
- The costs of adverse events in the first four cycles with AC were not included in the model, and neutropenia was the only adverse event for which costs were included in the model.

3.4 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TA108.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of paclitaxel 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 paclitaxel 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. The Committee noted the clinical specialists' statements that the regimens most commonly used in the NHS are six cycles of polychemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC), or four cycles of epirubicin followed by four cycles of cyclophosphamide, methotrexate and 5-fluorouracil (E→CMF), and that

both FEC and E→CMF are considered to be clinically more effective than four cycles of AC.

Clinical effectiveness

- 4.3 The Committee noted that no systematic review of the clinical effectiveness of paclitaxel in the adjuvant treatment of early node-positive breast cancer was carried out by the manufacturer. However, it noted that the ERG considered that results from other potentially relevant trials would be unlikely to affect their conclusion about the clinical effectiveness of paclitaxel. The Committee agreed that the evidence provided by the manufacturer demonstrated that adding four cycles of paclitaxel after four cycles of AC provides a clinical benefit over four cycles of AC. However, the Committee noted that the comparator used, four cycles of AC, is not a commonly used chemotherapy regimen for adjuvant treatment of early breast cancer in the NHS. The Committee further heard from the clinical specialists that treatment with four cycles of AC is considered only for women who cannot tolerate longer durations of treatment. Therefore the Committee was persuaded that adding four cycles of paclitaxel after four cycles of AC would not be a treatment option considered for this group of women.
- 4.4 The Committee noted that there was no evidence of a comparison of paclitaxel, within its licensed indication, with extended AC therapy, FEC or E→CMF regimens. The Committee noted the clinical specialists' statements that the magnitude of the benefit of FEC (six cycles) or E→CMF (four cycles of E followed by four cycles of CMF) over four cycles of AC was considered to be at least as high as the benefit of adding four cycles of paclitaxel after four cycles of AC. The Committee was therefore not persuaded that paclitaxel using the regimen recommended in the SPC (four cycles of AC followed by four cycles of paclitaxel; all cycles three weeks apart) is proven to be clinically more effective than current standard care in the NHS.

Cost effectiveness

- 4.5 The Committee discussed the evidence provided by the manufacturer on the cost effectiveness of paclitaxel and considered the comments received from the ERG. The Committee was not persuaded that the economic model provided by the manufacturer was sufficiently robust to make a case for the cost effectiveness of paclitaxel, because of the issues raised by the ERG. These included the lack of a systematic review to identify and critique inputs to the model, without which the choice of inputs for the model was not sufficiently justified for the ERG and the Committee to judge their validity. Other issues were the inadequate consideration of chemotherapy toxicities and, more importantly, the choice of a comparator that was not relevant to standard practice in England and Wales, and that no modelling was attempted that compared paclitaxel with standard practice in England and Wales.

Summary of the considerations

- 4.6 The Committee concluded that paclitaxel, within its licensed indication, should not be recommended for the adjuvant treatment of early node-positive breast cancer. The Committee reached this conclusion because of the lack of evidence of the clinical and cost effectiveness of paclitaxel compared with current standard practice in the NHS.

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 As there are no implementation or cost implications related to this technology appraisal guidance, no tools will be issued.

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

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. 109 ('Docetaxel for the treatment of early node-positive breast cancer').

- 6.2 NICE has issued the following related technology appraisal guidance.

Docetaxel for the adjuvant treatment of early node-positive breast cancer. *NICE technology appraisal guidance* no. 109 (September 2006). Available from: www.nice.org.uk/TA109

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

- 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

- 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

Professor David Chadwick

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

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

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 first 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.

Elisabeth George and Helen Chung

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.
- Bristol-Myers Squibb Pharmaceuticals Ltd
- B The evidence review group (ERG) report for this appraisal was prepared by the Centre for Health Economics, University of York, and the Regional Drug and Therapeutics Centre (Newcastle):
- Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, Erhorn S, Humphries C, White S, Horsley W, Ferrie L, Thomas S (March 2006). The use of paclitaxel in the management of early stage breast cancer.
- 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 paclitaxel 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
- 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.