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

Technology appraisal guidance
Published: 27 September 2006
nice.org.uk/guidance/ta108
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
# Paclitaxel for the adjuvant treatment of early node-positive breast cancer (TA108)

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This guidance is partially replaced by CG80.

1  Guidance

This guidance replaces paragraph 1.3 of Taxanes for the treatment of breast cancer (NICE technology appraisal guidance 30) issued in September 2001 [Replaced by NICE clinical guideline 81].

CG80 Early and locally advanced breast cancer updates the recommendations contained in this appraisal.

For details, see 'About this 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.
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:


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 109 (September 2006).


6.3 NICE has issued the following related clinical guidelines:


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 was considered for review in November 2007. Details can be found on the NICE website.

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

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 of Hygiene and Tropical Medicine

Professor Mike Campbell
Statistician, University
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 of Hygiene

Dr Fergus Gleeson  
Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch  
Former Director of Nursing & Workforce Development, Mid Essex 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

Professor Peter Jones  
Professor of Statistics & Dean Faculty of Natural Sciences, Keele
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

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
Professor Andrew Stevens
Professor of Public Health, University

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):


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
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.
Changes after publication

March 2014: minor maintenance

March 2012: minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

This guidance replaces paragraph 1.3 of Taxanes for the treatment of breast cancer (NICE technology appraisal guidance 30) issued in September 2001. [Replaced by NICE clinical guideline 81]

CG80 Early and locally advanced breast cancer updates the recommendations contained in this appraisal. NICE and the Department of Health are currently reviewing the future position on updating technology appraisals within clinical guidelines, with particular reference to implications for the funding direction on technology appraisals. In the meantime, the technology appraisal guidance remains available and should continue to be followed. The statutory funding direction remains in place for the recommendations contained in the technology appraisal guidance.

The recommendations from this guideline have been incorporated into a NICE Pathway. We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and 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. However, the guidance does not 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 this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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