Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Paclitaxel for the adjuvant treatment of early node-positive breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 18 p. (Technology appraisal guidance; no. 108).

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 paclitaxel for the adjuvant treatment of early node-positive cancer

TARGET POPULATION

Women with early node-positive breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

The use of paclitaxel (Taxol) for adjuvant treatment of early node-positive breast cancer was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Disease-free survival
    - Overall survival
    - 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

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 Centre for Health Economics, University of York and Regional Drug and Therapeutic Centre, Newcastle (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Search Strategy

The Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) submission did not contain a systematic review of studies. A full search strategy was undertaken by the Evidence Review Group (ERG).

Inclusion Criteria

Participants: Female; operable node-positive early breast cancer.

Interventions: Paclitaxel, alone or in combination with anthracycline, administered adjuvant to surgical resection. Endocrine if consistent between groups.

Comparator: Chemotherapy regimens NOT including paclitaxel

Outcomes: Disease-free-survival; overall survival; recurrence, adverse events.

Exclusion Criteria

Participants: Male; advanced stage disease; neo-adjuvant chemotherapy.

Interventions: Paclitaxel administered in the adjuvant setting where the comparator is NOT the same underlying regimen as in the paclitaxel arm.

Study Selection

Peer review panel

Databases Searched

MEDLINE, EMBASE, CINAHL, EBM Reviews

Refer to Appendix 3 of the ERG Report (see the "Availability of Companion Documents" field) for detailed information on search strategy including search dates and terms.

Cost-Effectiveness

In the absence of a formal search strategy undertaken by the manufacturer, the ERG undertook a separate search for cost-effectiveness. The search conducted by the ERG identified 65 records.

Search Strategies Used to Identify Previously Published Economic Evaluations

This search has been a four-stage process. A similar unfocused strategy was used in all databases to ensure all potentially relevant searches were included in the search.

1. Search in National Health Service Economic Evaluation Database (NHS EED)

This includes economic evaluations and cost studies that have been identified in Medline, Embase, Cinahl and (previously) Current Contents since 1995, when the database was set up. The admin database (Cairs T) was searched so that all studies considered for the NHS EED database were included.

2. Search in Health Economic Evaluations Database

   (OHE HEED)

   This includes economic evaluations and cost studies that have been identified in Medline and Embase, and through hand-searching of around 50 journals.

3. Search in Medline (Silverplatter) for European studies since 2003

   European studies have not been included in NHS EED since 2003 (since the establishment of EuroNEED) so additional searches were done to ensure that all relevant European studies were captured.

4. Search in Embase (Ovid) for European studies since 2003

   European studies have not been included in NHS EED since 2003 (since the establishment of EuroNEED) so additional searches were done to ensure that all relevant European studies were captured.

Full details of the search strategies and databases used are shown in Appendix 10 of the ERG Report (see the "Availability of Companion Documents" field.)

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

The manufacturer identified 3 articles

Six systematic reviews were identified in the literature search performed by the Evidence Review Group (ERG).

Cost-Effectiveness

The search conducted by the ERG identified 65 records.

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

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 Centre for Health Economics, University of York and Regional Drug and Therapeutic Centre, Newcastle (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Structured critical appraisals of the identified studies are provided in Appendices 4 to 9 of the Assessment Report (see the "Availability of Companion Documents" field).

Economic Evaluation

Description of the Economic Model Submitted by Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

Sensitivity Analysis

The primary analysis focuses on the comparison of AC (doxorubicin and cyclophosphamide) with AC-P3 (AC followed by paclitaxel every 3 weeks). In secondary analyses comparisons are made between AC-P3, AC-P1 (AC followed by paclitaxel every week), AC-D3 (AC followed by docetaxel every 3 weeks) and AC-D1 (AC followed by docetaxel every week). An additional analysis was presented that compared the pooled paclitaxel arms to the pooled docetaxel arms. The interpretation of this sensitivity analysis is not clear. A sensitivity analysis is included that assessed the impact of reductions in the price of paclitaxel. The manufacturers also explored the sensitivity of the model to reductions in the cost of neutropenia events, and to altering the utility value for distant recurrences. A sensitivity analysis was conducted using a discount rate of 6% per annum for costs and 1.5% per annum for health outcomes. The manufacturers acknowledge that the use of external data sources for the probability of progression and survival following a recurrence resulted in the model underestimating overall survival in comparison to the included clinical trials. A threshold analysis was conducted to reduce the risks of progression to the point where overall survival matched that in Henderson et al. (2003). Results were presented for the time horizon varying to 5, 10 and 20 years. No sub-group analyses were conducted.

Model Validation

The manufacturers state that disease-free survival in the model matched that in the clinical trial used to inform the model baseline. They acknowledge that the model underestimates overall survival compared to the clinical trial, which results

from the use of an alternative data source to inform progression and survival. No further model validation is reported.

Critique of the Approach Used in the Manufacturer's Submission

Sensitivity Analysis

The inclusion of a sensitivity analysis around the discount rates used is appropriate. However, a mistake in this analysis meant that both costs and health outcomes were in fact discounted at 1.5% per annum when costs should have been discounted at 6%. The justification and interpretation of many of the other sensitivity analyses is unclear.

The lack of sub-group analyses may limit the generalisability of the model results. The baseline risk of progression varies among patients recruited to the clinical trials according to prognostic factors such as the number of involved nodes, tumour size, patient age and whether the tumour is oestrogen-receptor positive. In addition, some studies have suggested that the treatment effect could differ according to these prognostic factors and there has been the suggestion that concurrent rather than sequential use of tamoxifen may represent a confounder. By failing to consider these issues, the average results of the economic model could potentially conceal wide variation between sub-groups in the cost-effectiveness of paclitaxel.

Additional Work Undertaken by the Evidence Review Group (ERG)

The additional work undertaken by the ERG is intended to provide additional information on the qualitative impact of identified limitations. Given the restricted nature of these additional analyses only 3 areas are considered:

- Sub-group analysis
- Sensitivity analysis
- Additional comparator

Refer to Sections 5 and 6 of the ERG Report (see the "Availability of Companion Documents" field) for more information on the methods used to analyze the evidence.

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 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 [a combination of doxorubicin and cyclophosphamide]) with four cycles of AC alone. The reported cost per quality-adjusted life year (QALY) gained for this comparison was 4726 pounds sterling.

The Committee discussed the evidence provided by the manufacturer on the cost effectiveness of paclitaxel and considered the comments received from the Evidence Review group (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.

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

Paclitaxel, within its licensed indication, is not recommended 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 recommendation regarding the use of paclitaxel for the adjuvant treatment of early node-positive breast cancer

POTENTIAL HARMS

Paclitaxel treatment is associated with myelosuppression, hypersensitivity reactions 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.
- Weaknesses of cost effectiveness evidence submitted by the manufacturer:

  The Evidence Review group (ERG) felt that the Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) submission was generally of poor quality with key omissions. The major flaw in the submission was the absence of a systematic literature review, as instructed by the National Institute for Health and Clinical Excellence (NICE) in the draft guidance. BMS limited the clinical effectiveness in the submission to 3 studies, and it was unclear, without the ERG undertaking a full systematic review, whether they had considered all the relevant literature. This same selective use of available evidence was apparent in the economic evaluation. There was a tendency throughout the trials section to refer to relative risk rather than absolute risk and relevant *p* values were not quoted. This had the effect of exaggerating any possible benefits of treatment. Whilst the trial evidence around paclitaxel appears to show modest benefit, the trials themselves may not be directly applicable to the clinical situation that these patients are likely to face.

A further shortcoming of the submission was in not clearly defining the choice of comparator(s). This is important in determining relative efficacy and, if not clearly stated, affects the underlying discussions throughout the document. The comparators that were included in the cost-effectiveness analysis were not considered by the ERG to represent current treatment in the United Kingdom National Health Service (UK NHS) or relevant licensed alternatives, and 4 cycles AC (a combination of doxorubicin and cyclophosphamide) may be regarded as a weak comparator in this patient population.

Refer to Sections 1.4 and 1.5 of the Assessment Report (see the "Availability of Companion Documents" field) for additional information on the weaknesses, areas of uncertainty, and key issues of the manufacturer's submission.

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 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.

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

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Paclitaxel for the adjuvant treatment of early node-positive breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 18 p. (Technology appraisal guidance; no. 108).

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

Committee Members: 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

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:

- Paclitaxel 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 108). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

- The use of paclitaxel in the management of early stage breast cancer: a single technology appraisal. Evidence Review Group Report. Centre for Health Economics, University of York and Regional Drug and Therapeutics Centre, Newcastle, UK. 2006 Apr 28. 115 p. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1103. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Paclitaxel 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 108).

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: N1104. 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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