Complete Summary

GUIDELINE TITLE

Gemcitabine for the treatment of metastatic breast cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Gemcitabine for the treatment of metastatic breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 24 p. (Technology appraisal guidance; no. 116).

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Metastatic 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 gemcitabine for the treatment of metastatic breast cancer

TARGET POPULATION

Patients with metastatic breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Gemcitabine (Gemzar) in combination with paclitaxel

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Overall survival
    - Time to documented progression of disease
    - Tumour response
    - Health-related quality of life (measured by brief pain inventory [BPI] and Rotterdam Symptom checklist [RSCL])
    - Adverse effects
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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 assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessment Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Manufacturer's Approach

Description of Manufacturer's Search Strategy and Comment on whether the Search Strategy Was Appropriate

The sources used by the manufacturer for the search (Embase, Medline, Medline in Process, NICE, Cochrane, NCCHTA, American Society of Clinical Oncology [ASCO], National Health Service (NHS) CRD, Internal databases, internet), are appropriate and comprehensive. Additional databases that could have been used to obtain the clinical evidence are Biosis and Web of Science, although it is unlikely that they would have yielded any additional key results. The manufacturer has documented the use of ASCO, which is the key source of information for sourcing ongoing cancer trials. The search documentation could have been widened or clarified to include mention of sources such as the national research register, controlled clinical trials, clinicaltrials.gov, in order to track any ongoing trials.

The search strategies in the manufacturer's submission (MS) are transparent, fully documented, and reproducible. The ERG reproduced components of the search on 23rd May 2006. The main search (Search 1, MS) yielded similar results, but the ERG identified 457 citations with the paclitaxel search (after amending to take account of extra references since November 2005), compared with 84 in the manufacturer's search. The manufacturer's Embase search was from 1988, whereas the ERG's was from 1980, but searches were otherwise as similar as was feasible. A brief scan of the identified references suggested that none of the 'extra' references were relevant to the systematic review.

The MS states that the search included data up until the 28th November 2005. For the sake of completeness, the ERG considers that an update search should have been re-run for all the study drugs.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on whether They Were Appropriate

The MS describes an appropriate method of identifying and screening references for inclusion in the systematic review. Three independent reviewers applied pre-specified inclusion/exclusion criteria to citations identified by the searches, and discussed any unclear references until agreement was reached.

The MS specified the following inclusion criteria for the systematic review of the literature:

1. Study design - original studies reporting final results of phase III clinical trials
2. Interventions - gemcitabine/paclitaxel, docetaxel/capecitabine, paclitaxel monotherapy or docetaxel monotherapy
3. Population - patients with metastatic breast cancer (MBC) who have been treated and failed on prior anthracycline treatment in an adjuvant or neoadjuvant setting
4. Outcome measures - no outcome measures were specified in the inclusion/exclusion criteria

Phase I and II trials, observational studies, letters to the editor and editorials were excluded from the systematic review. The manufacturer did not state whether published systematic reviews would be considered in the review, and did

not state clearly whether conference abstracts would be included or excluded. The specified inclusion/exclusion criteria were appropriate and reflect the information given in the decision problem.

Economic Evaluation

Cost Effectiveness Searches

The searches for cost-effectiveness studies are not clearly described in the MS. The searches described in the clinical effectiveness section of MS appear to have covered cost-effectiveness, since the reviewers identified studies from these which were only applicable to the economic model. However, the cost-effectiveness section then describes a separate search (dated 8th September 2005) of all the key databases. This search is not well documented, and only basic keywords are included in table 19 of the MS. The citations identified by this search are different from those identified in the earlier stage of the review, and appear to have been used to inform the design of the economic model.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

The manufacturer's submission presented evidence on the clinical effectiveness of gemcitabine plus paclitaxel based on a single randomized controlled trial.

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

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessment Centre (see the "Availability of Companion Documents" field).

Description and Critique of Manufacturer's Approach to Validity Assessment

The manufacturer applied the quality assessment criteria recommended by NICE to the B9E-MC-JHQG (JHQG) study, but it is not clear whether this was done by a single reviewer or consensus of multiple reviewers. The manufacturer did not apply any quality assessment criteria to the comparator studies which were included for indirect comparison, and did not quality assess the studies included to provide data for the economic model.

Since the JHQG trial has only been published in abstract format, it was not possible for the ERG to check the validity of the manufacturer's quality assessment. On the basis of information presented in the manufacturer's submission (MS), the quality assessment criteria appear to have been applied adequately for questions relating to randomisation and follow-up. The trial was open-label, so observers were not kept fully blinded to treatment assignment. The text in the MS does not score the question on blinding, although the MS text suggests that a mixture of A and B should apply. Whilst the primary outcome (survival) is clearly free from observer bias, outcomes involving tumour response could be affected by bias. Although standard oncology criteria are stated to have been used, there is still a difference between investigator-assessed response and independently assessed response, so there is a degree of subjective interpretation in these outcome measures. As such, the ERG considers that the quality assessment question on blinding should be scored as 'A' (refer to Table 2 of the Assessment Report - see the "Availability of Companion Documents" field).

No formal assessment was made in the MS of the quality of reporting and methodology of the two randomized controlled trial (RCTs) of the alternative comparisons (docetaxel versus paclitaxel; capecitabine/docetaxel combination versus docetaxel). Using the NICE guideline for manufacturers, the ERG has assessed these two trials to be of reasonable methodological quality (refer to Table 3 of the ERG Report - see the "Availability of Companion Documents" field).

Critique of Submitted Evidence Syntheses

No meta-analysis was undertaken by the manufacturer due to the differences in the comparators in the included trials. The manufacturer tabulated results from comparator trials, but did not perform a full indirect comparison or narrative synthesis of key outcomes for these. No formal statistical assessment of heterogeneity was performed, possibly owing to the lack of a standard comparator arm across trials. The ERG requested further details of heterogeneity, and the manufacturer supplied a table of patient characteristics for the different trials.

Refer to Sections 5 and 6 of the ERG Report (see the "Availability of Companion Documents" field) for more information on description of 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

Evidence on cost effectiveness presented in the manufacturer's submission was based on a Markov state-transition model with a 3-year horizon, equivalent to the typical life expectancy of people diagnosed with metastatic breast cancer. A series of pairwise economic analyses comparing gemcitabine plus paclitaxel with docetaxel monotherapy, paclitaxel monotherapy and docetaxel plus capecitabine was presented by the manufacturer. All these analyses were based on an indirect comparison in which weighted absolute treatment outcomes (including survival data) were pooled from single arms of different trials in published literature. In order to compare gemcitabine plus paclitaxel with paclitaxel monotherapy, the median overall survival estimate for gemcitabine plus paclitaxel was taken from the randomized controlled trial (RCT) comparing gemcitabine plus paclitaxel with paclitaxel monotherapy. However, for paclitaxel monotherapy, the manufacturer did not use overall survival estimates from this comparative study, but instead used the average of the pooled, weighted absolute survival data from single arms of different studies.

The base-case analysis compared gemcitabine plus paclitaxel with docetaxel monotherapy and resulted in an incremental cost-effectiveness ratio (ICER) of 17,200 pounds sterling per quality-adjusted life year (QALY). A comparison of gemcitabine plus paclitaxel with paclitaxel monotherapy resulted in an ICER of 30,100 pounds sterling per QALY. A comparison of gemcitabine plus paclitaxel with docetaxel plus capecitabine resulted in an ICER of 23,200 pounds sterling per QALY. The manufacturer presented a scenario analysis for gemcitabine plus paclitaxel against docetaxel monotherapy where the price of non-proprietary paclitaxel is assumed to be 55% less than that of proprietary paclitaxel: the ICER in this case fell from 17,200 pounds sterling per QALY to 4700 pounds sterling per QALY.

The Evidence Review Group (ERG) reviewed the economic model and judged its structure to be reasonable and based on previous economic studies. The main drivers of cost effectiveness are the estimates of overall survival, the cost of paclitaxel, and the utilities assigned to the health states in the model. The ERG's main source of concern was the indirect comparison method used by the manufacturer to generate the survival estimates for the economic model, which involved pooling treatment outcome data from single arms of different trials. The ERG commented that the method used by the manufacturer ignored the fact that RCTs are designed to measure relative treatment effects. The indirect comparison method used does not preserve the benefits of randomisation and it is at best equivalent to observational studies.

By using the treatment efficacy data from both arms of the RCT comparing gemcitabine plus paclitaxel with paclitaxel monotherapy instead of the pooled estimates from the manufacturer's indirect comparisons, the ERG estimated the ICER for a comparison between gemcitabine plus paclitaxel and paclitaxel monotherapy to be 42,800 pounds sterling per QALY. In an illustrative analysis, the ERG found that using relative treatment effects to estimate overall survival for

docetaxel monotherapy resulted in an ICER of 45,800 pounds sterling per QALY for a comparison of gemcitabine plus paclitaxel against docetaxel monotherapy.

Refer to Sections 3 and 4 of the original guideline document for more information on cost-effectiveness.

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

Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of gemcitabine for the treatment of metastatic breast cancer

POTENTIAL HARMS

The side-effect profile of gemcitabine plus paclitaxel is similar to that of other chemotherapeutic agents. The most common haematological adverse effect reported is neutropenia and the most common non-haematological adverse effects reported include fatigue and diarrhoea.

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

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare 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.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on NICE website (www.nice.org.uk) (see also the "Availability of Companion Documents" field).
    - Costing report and costing template to estimate the savings and costs associated with implementation
    - Audit criteria to monitor local practice

IMPLEMENTATION TOOLS

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

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

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Gemcitabine for the treatment of metastatic breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 24 p. (Technology appraisal guidance; no. 116).

ADAPTATION

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

DATE RELEASED

2007 Jan

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 Jane Adam, Radiologist, St George's Hospital, London; Professor A E Ades, MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol; Dr Amanda Adler, Consultant Physician, Addenbrooke's Hospital, Cambridge; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Vice Chair*) Professor of Clinical Pharmacology, University of Leicester; Mrs Elizabeth Brain, Lay Member; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia; Mrs Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Dr Paul Ewings, Statistician, Taunton and Somerset NHS Trust, Taunton; Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Mr Adrian Griffin, Health Outcomes Manager, Johnson & Johnson Medical Ltd; Ms Linda Hands, Consultant Surgeon, John Radcliffe Hospital; Dr Rowan Hillson, Consultant Physician, Diabeticare, The Hillingdon Hospital; Professor Philip Home (*Vice Chair*) Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Terry John, General Practitioner, The Firs, London; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham; Dr Simon Mitchell, Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester; Ms Judith Paget, Chief Executive, Caerphilly Local Health Board, Wales; Dr Ann Richardson, Lay Member; Mr Mike Spencer, General Manager, Clinical Support Services, Cardiff and Vale NHS Trust; Dr Simon Thomas, Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust; Mr David Thomson, Lay Member; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Professor Mary Watkins, Professor of Nursing, University of Plymouth

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:

- Gemcitabine for the treatment of metastatic breast cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 116). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Costing statement: gemcitabine for the treatment of metastatic breast cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 116). Available in Portable Document Format (PDF) from the NICE Web site.
- Gemcitabine for the treatment of metastatic breast cancer. Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 8 p. (Technology appraisal 116). Available in Portable Document Format (PDF) from the NICE Web site.
- Gemcitabine for metastatic breast cancer. Evidence Review Group Report. Southampton Health Technology Assessments Centre. 2006 Jul 24. 81 p. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1178. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Gemcitabine for the treatment of metastatic breast cancer. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 4 p. (Technology appraisal 116).

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: N1179. 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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