Complete Summary

GUIDELINE TITLE

Drotrecogin alfa (activated) for severe sepsis.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Drotrecogin alfa (activated) for severe sepsis. London (UK): National Institute for Clinical Excellence (NICE); 2004 Sep. 31 p. (Technology appraisal; no. 84).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 21, 2005, Xigris: Eli Lilly and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of the stopping of enrollment in a randomized, double-blind, placebo-controlled trial of Xigris in pediatric patients with severe sepsis. Xigris is not indicated for use in pediatric severe sepsis.
- March 2005, Xigris (drotrecogin alfa [activated]): Eli Lilly and the FDA notified healthcare professionals about revisions to the WARNINGS section of labeling for Xigris [drotrecogin alfa (activated)], a biological therapeutic product indicated for the treatment of adult patients with severe sepsis who are at high risk of death.
- April 21, 2005, Drotrecogin alfa (activated): The European Medicines Evaluation Agency (EMEA) recommended that drotrecogin alfa (activated) should only be used in high-risk patients, mainly in situations when therapy can be started within 24 hours of the onset of organ failure. In addition, it should only be used by experienced doctors in institutions skilled in the care of patients with severe sepsis. Drotrecogin alfa (activated) should not be used in patients with single organ dysfunction, especially if they have had recent surgery (within 30 days).

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SCOPE

DISEASE/CONDITION(S)

Severe sepsis with multiple organ failure (i.e., sepsis associated with organ dysfunction, tissue hypoperfusion, or hypotension)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Infectious Diseases
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical and cost-effectiveness of drotrecogin alfa (activated) for the treatment of adults with severe sepsis

TARGET POPULATION

Adults with severe sepsis

INTERVENTIONS AND PRACTICES CONSIDERED

Drotrecogin alfa (activated) (recombinant human activated protein C [rhAPC]) (Xigris™)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness

  The primary outcome measure was all-cause mortality at the end of study follow-up. The side effect profile of drotrecogin alfa (activated) was also covered. Additional secondary outcome measures that were considered include:

  - Death from septic shock
  - Length of hospital and/or ICU stay
  - Functional status (quality of life)
  - Acute Physiology Age and Chronic Health Evaluation (APACHE) II scores
  - Number of organ failures
  - Organ dysfunction
  - Duration of assisted ventilation
  - Nosocomial infection
- 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
Searches of Unpublished Data

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 a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessments Centre (SHTAC) (see the "Companion Documents" field).

Search Strategy

Extensive electronic searches were conducted by an experienced information scientist, to identify both published and unpublished literature including existing systematic reviews and primary studies evaluating the effectiveness of drotrecogin alfa (activated), relevant quality of life literature, and economic evaluations.

The databases searched, and search strategy used, are documented in Appendix 3 of the assessment report.

Further useful citations were retrieved through scanning the reference lists of all retrieved studies and contact with experts. Sponsor and other submissions were also checked for:

- Any additional studies, or additional unpublished data relating to previously identified studies, meeting the inclusion criteria
- Relevant cost data
- Data on current use of drotrecogin alfa (activated) for severe sepsis in England and Wales

The titles and abstracts retrieved by the electronic searches were screened independently by two reviewers; the full papers for each study selected were obtained and assessed for inclusion again by two reviewers. Any disagreements were resolved through discussion, with referral to a third reviewer where necessary. Reasons for exclusion of full papers were formally documented. Any "commercial in confidence" data taken from sponsor's submission has been clearly marked (underlined) in the report submitted to the Health Technology Assessment (HTA programme and to the National Institute for Health and Clinical Excellence (NICE). A separate version with any such data removed has also been submitted.

Inclusion Criteria and Exclusion Criteria

Participants

Hospitalised adult patients with severe sepsis or septic shock acquired either in the community or in the hospital. Severe sepsis is defined according to internationally accepted guidelines, as set out by American College of Chest Physicians/Society of Critical Care Medicine in 1992. Studies conducted in children (aged <18 years) were excluded.

Interventions

Drotrecogin alfa (activated) (i.e., recombinant human activated protein C) plus conventional care compared to conventional care alone.

Study Design

In order to establish the effectiveness of the intervention, only randomised controlled trials (RCTs) were included. To establish the safety of the drug all studies conducted in relevant participants were included. The generalisability of the available trial results to the United Kingdom (UK) context were estimated by comparing the participants and care used in the available RCT(s) to that in the UK.

Outcome Measures

The expert panel for the review were consulted to determine the most appropriate outcome measures for the review. See the "Major Outcomes Considered" field in this summary.

Quality Assessment and Data Extraction Strategy

Quality assessment of RCTs was conducted according to the guidelines of the Cochrane Infectious Diseases Group, with the addition of some topic-specific items relevant to trials conducted in people with sepsis (see Appendix 4 of the Assessment Report).

Data extraction and quality assessment were conducted independently by two reviewers using pre-designed forms. Any disagreements were resolved through discussion, with referral to a third reviewer if necessary.

NUMBER OF SOURCE DOCUMENTS

Quantity of Research Available

A total of 1,016 titles and abstracts were retrieved from the literature searches and from screening the reference lists. The Assessment Centre obtained 108 full papers and from these seven full papers and three abstracts were selected for inclusion in the review. A flowchart of the results of the search and inclusion/exclusion decisions is provided at Figure 1, and a list of excluded studies is provided in Appendix 5 of the assessment report.

Two randomised controlled trials (RCTs) assessing the effectiveness of drotrecogin alfa (activated) were identified, results for one having been published in five subsequent papers. The U.S. Food and Drug Administration (FDA) have also published a clinical review of recombinant human activated protein C (rhAPC) to support their licensing decision. This includes data not available in the other trial publications and also reports some exploratory analyses of the trial data. A cumulative safety review provides data from the two RCTs plus three otherwise unpublished prospective open-label studies and data from the commercial use of the drug up to April 2002.

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 a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessments Centre (SHTAC) (see the "Companion Documents" field).

Methods of Analysis/Synthesis

For the primary endpoint, trial data are presented as relative risks and 95% confidence intervals (CI). Continuous data, such as length of hospital stay, are presented as mean and standard deviation. Data for the following subgroups are thought to be of particular relevance: severity of disease at baseline, e.g., Acute Physiology Age and Chronic Health Evaluation (APACHE) II score; number of organ failures; source and site of infection, e.g., hospital vs. community acquired.

For the assessment of side effects incidence, all available data on the clinical use of drotrecogin alfa (activated) in patients with severe sepsis was included.

Prospective observational data from Intensive Care National Audit and Research Centre (ICNARC) was obtained and used to examine the generalisability of the trial results to the United Kingdom setting.

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

Literature Search and Methods

The literature search undertaken by the Assessment Group identified three published cost-effectiveness analyses that were performed from a North American perspective. The Assessment Group also identified six published abstracts and two unpublished abstracts. The manufacturer provided two economic evaluations (one based on PROWESS day-28 data and one on the follow-up information available) and a model as part of its submission. In addition, the Assessment Group developed a model to assess the cost effectiveness of drotrecogin alfa (activated) plus conventional care versus conventional care alone in a UK cohort of adult patients with severe sepsis.

Summary

The United Kingdom analyses indicate a cost per quality-adjusted life year (QALY) of less than 11,000 pounds sterling for patients with severe sepsis and multiple organ failure treated with drotrecogin alfa (activated). If all patients are considered, the cost per QALY profile becomes less favourable. Other available studies are broadly consistent with these findings, although North American estimates of cost per QALY are higher.

See Section 4.2 of the original guideline document for a detailed discussion and more information.

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

Note from the National Guideline Clearinghouse (NGC) and the National Institute for Health and Clinical Excellence (NICE): Since the NICE guidance on drotrecogin alpha (activated) was issued, the European Medicines Evaluation Agency (EMEA) has recommended changes to the way that drotrecogin alpha (activated) should be used. Please see the "Regulatory Alert" field for more information. NICE advises that clinicians wishing to prescribe drotrecogin alpha (activated) should take the EMEA advice into account alongside the guidance from NICE when deciding whether or not to prescribe drotrecogin alpha (activated).

- Drotrecogin alfa (activated) is recommended for use in adult patients who have severe sepsis that has resulted in multiple organ failure (that is, two or more major organs have failed) and who are being provided with optimum intensive care support.
- The use of drotrecogin alfa (activated) should only be initiated and supervised by a specialist consultant with intensive care skills and experience in the care of patients with sepsis.

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 drotrecogin alfa (activated) for the treatment of severe sepsis

POTENTIAL HARMS

Drotrecogin alfa (activated) may increase bleeding.

For full details of side effects and contraindications, see the Summaries of Product Characteristics, available at http://emc.medicines.org.uk/.

CONTRAINDICATIONS

CONTRAINDICATIONS

Drotrecogin alfa (activated) may increase bleeding, and consequently it is contraindicated in certain patients, such as those with active internal bleeding.

For full details of side effects and contraindications, see the Summaries of Product Characteristics, 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. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health 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

Implementation and Audit

- All clinicians who care for adults with severe sepsis and multiple organ failure should review their current practice and policies to take account of the guidance set out in Section 1 of the original guideline document (and the "Major Recommendations" field).
- Intensive care units in National Health Service hospitals should define the clinical circumstances in which drotrecogin alfa (activated) is to be used and

the training and experience of consultants who are authorised to initiate and supervise the treatment.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - Drotrecogin alfa (activated) is used for an adult with severe sepsis that has resulted in multiple organ failure and who is being provided with optimum intensive care support.
    - The use of drotrecogin alfa (activated) is initiated and supervised only by a specialist consultant with intensive care skills and experience in the care of patients with sepsis.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
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

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Drotrecogin alfa (activated) for severe sepsis. London (UK): National Institute for Clinical Excellence (NICE); 2004 Sep. 31 p. (Technology appraisal; no. 84).

ADAPTATION

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

DATE RELEASED

2004 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

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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) from the National Institute for Health and Clinical Excellence (NICE) Web site.

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

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Drotrecogin alfa (activated) for severe sepsis. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Sep. 2 p. (Technology appraisal 84). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- The clinical and cost-effectiveness of drotrecogin alfa (activated) (Xigris™) for the treatment of severe sepsis in adults: a systematic review and economic evaluation (excluding commercial in confidence data). Assessment report. Southampton (UK): Southampton Health Technology Assessments Centre (SHTAC); 2003 Dec. 157 p. (Technology appraisal 84). Electronic copies: Available in PDF from the National Institute for Health and Clinical Excellence (NICE) Web site.

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

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Drotrecogin alfa (activated) for severe sepsis: understanding NICE guidance - information for the families and carers of people with severe sepsis, and the public. London: National Institute for Health and Clinical Excellence. 2004 Sep. 10 p. Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

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

This NGC summary was completed by ECRI on November 10, 2005. This summary was updated by ECRI on November 14, 2006, following the U.S. Food and Drug Administration (FDA) advisory on Xigris.

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