

Drotrecogin alfa (activated) for severe sepsis

Technology Appraisal Guidance 84

Drotrecogin alfa (activated) for severe sepsis

Issue date: September 2004

Review date: September 2007

This document, which contains the Institute's full guidance for this appraisal, is available from the NICE website (www.nice.org.uk/TA084guidance).

An abridged version of this guidance (a 'quick reference guide') is also available from the NICE website (www.nice.org.uk/TA084quickrefguide). Printed copies of the quick reference guide can be obtained from the NHS Response Line: telephone 0870 1555 455 and quote reference number N0713.

Information for the Public is available from the NICE website or from the NHS Response Line (quote reference number N0714 for a version in English and N0715 for a version in English and Welsh).

This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the 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.

National Institute for Clinical Excellence

MidCity Place
71 High Holborn
London
WC1V 6NA

Web: www.nice.org.uk

Published by the National Institute for Clinical Excellence

September 2004

© National Institute for Clinical Excellence September 2004. All rights reserved. This material may be freely reproduced for educational and not for profit purposes within the NHS. No reproduction by or for commercial organisations is permitted without the express written permission of the Institute.

The quick reference guide has been distributed to the following:

- Primary care trust (PCT) chief executives
- Local health board (LHB) chief executives
- NHS trust chief executives in England and Wales
- Strategic health authority chief executives in England and Wales
- Medical and nursing directors in England and Wales
- Clinical governance leads in England and Wales
- Audit leads in England and Wales
- NHS trust, PCT and LHB libraries in England and Wales
- Patient advice and liaison co-ordinators in England
- ICU/ITU/critical care consultants in England and Wales
- Chief pharmacists, heads of drug purchasing, heads of drug information, GP prescribing advisors and purchase advisors in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- Chief medical, nursing and pharmaceutical officers in England and Wales
- Medical Director and Head of NHS Quality – Welsh Assembly Government
- Community health councils in Wales
- Commission for Healthcare Audit and Inspection
- NHS Clinical Governance Support Team
- Patient advocacy groups
- Representative bodies for health services, professional organisations and statutory bodies and the Royal Colleges

Contents

1	Guidance	5
2	Clinical need and practice	5
3	The technology	7
4	Evidence and interpretation	8
5	Recommendations for further research	19
6	Implications for the NHS	20
7	Implementation and audit	21
8	Related guidance	21
9	Review of guidance	21
	 Appendix A. Appraisal Committee members and NICE project team.....	 23
	A. Appraisal Committee members	23
	B. NICE Project Team	26
	 Appendix B. Sources of evidence considered by the Committee	 27
	 Appendix C. Detail on criteria for audit of the use of drotrecogin alfa (activated) for severe sepsis	 29

1 Guidance

- 1.1 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.
- 1.2 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.

2 Clinical need and practice

- 2.1 Sepsis is a clinical response to infection. This clinical response is referred to as the systemic inflammatory response syndrome. Sepsis is termed severe when it is associated with organ failure, tissue hypoperfusion or hypotension. It most commonly arises from bacterial infection but it can also be caused by a variety of other micro-organisms such as viruses and fungi.
- 2.2 The Intensive Care National Audit and Research Centre (ICNARC) carried out an observational cohort study comprising data from 91 adult general intensive care units (ICUs) in England, Wales and Northern Ireland between 1995 and 2000. From this, the prevalence of severe sepsis in the first 24 hours in intensive care in England, Wales and Northern Ireland was estimated to be 27%. This is equivalent to a little over 21,000 cases per annum in England and Wales. Severe sepsis usually develops as a consequence of infection in general medical and surgical wards, although it is usually managed after the patient has been transferred to an ICU. Despite advances in critical care, the mortality rate from severe sepsis is estimated to vary between 30% and 50%.
- 2.3 Several scoring systems have been developed to assess the severity of sepsis and to estimate the probability of certain outcomes (for example,

death) for groups of patients. These include the APACHE (Acute Physiology, Age and Chronic Health Evaluation) II and the SOFA (Sequential Organ Failure Assessment) scoring systems.

- 2.4 Most studies examine the burden of disease in the context of hospital resource use. While patients with severe sepsis represent an estimated 27% of ICU admissions (in the first 24 hours of intensive care), they account for 46% of all ICU bed days and 33% of all hospital bed days consumed by patients admitted to the ICU.
- 2.5 The cost of treating patients with sepsis is relatively high, as many of these patients require prolonged stays and complex treatment in an intensive care setting. A patient in an ICU is estimated to cost six times more per day than a patient in a general ward, and a patient in a high-dependency unit is estimated to cost three times more than a patient on a general ward. The average cost per bed day in a UK ICU was £1232 in 2002.
- 2.6 Many patients who survive severe sepsis are restored to good health. However, patients who survive an episode of severe sepsis may have permanent damage to organs or tissues, resulting in a significant, ongoing burden of ill health. In the years following their time in intensive care, patients may have poor health-related quality of life and an increased risk of death compared with the general population. For example, a high level of disability is often seen among survivors of severe meningococcal septicaemia because of amputations and organ failure. However, there is little published information on the quality of life after recovery from severe sepsis.
- 2.7 Current management of severe sepsis involves both treatment of the underlying infection, primarily with antibiotics, and supportive treatment according to the individual's assessed needs. The choice of antibiotic depends on the results of positive microbiological cultures (where available), the likely source of infection and the expected tissue uptake of the antibiotic.

- 2.8 Supportive treatment may include fluids, steroids, vasopressors, and ventilatory and renal support. Respiratory failure is very common during sepsis, with up to 85% of patients receiving ventilatory support during their illness. Up to 50% of these ventilated patients may develop adult (acute) respiratory distress syndrome, which is linked to a high mortality rate. Adequate fluid resuscitation with or without vasopressor support is also used to treat haemodynamic instability.

3 The technology

- 3.1 Drotrecogin alfa (activated) (Xigris, Eli Lilly), recombinant human activated protein C, is a new treatment for patients with severe sepsis. It is licensed in the European Union for the treatment of adult patients with severe sepsis with multiple organ failure, when added to best standard care.
- 3.2 Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis; it also has anti-inflammatory actions. Drotrecogin alfa (activated) is understood to exert its action by modulating the coagulation cascade and inflammatory responses associated with severe sepsis. In patients with sepsis, levels of protein C are depleted and the ability to produce endogenous activated protein C is impaired, shifting the balance towards greater systemic inflammation, intravascular coagulation and organ failure.
- 3.3 Drotrecogin alfa (activated) may increase bleeding, and consequently it is contraindicated in certain patients, such as those with active internal bleeding, chronic severe hepatic disease and intracranial pathology. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.4 The recommended standard treatment regimen for drotrecogin alfa (activated) is to infuse 24 micrograms/kg body weight/hour for 96 hours. The cost of a 5-mg vial of drotrecogin alfa (activated) is £152.05 (*Monthly Index of Medical Specialties [MIMS]*, March 2004). Therefore, the total acquisition cost of a full 96-hour course for a 70-kg patient is estimated to be £4905 excluding VAT.

Costs may vary in different settings because of negotiated procurement discounts. Drotrecogin alfa (activated) must be delivered through a dedicated lumen of a multilumen central venous catheter or a dedicated intravenous catheter.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 Clinical effectiveness

- 4.1.1 The Assessment Group (Southampton Health Technology Assessments Centre) only considered evidence from randomised controlled trials (RCTs) for its assessment of the effectiveness of drotrecogin alfa (activated). However, the Assessment Group considered a wider set of studies on the clinical use of drotrecogin alfa (activated) in its assessment of adverse effects. The generalisability of the available trial results to the UK context was estimated by comparing the participants, the care used and mortality rates in the available RCTs with UK data.
- 4.1.2 The non-RCT data considered included the open-label ENHANCE study, two compassionate-use studies (EVAS and EVBC), and the retrospective MERCURY study which comprised analyses related to the timing of drug administration.
- 4.1.3 Two RCTs were identified: EVAA (phase II) and the large phase III study, PROWESS. The evidence on the effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis has come primarily from PROWESS. The Assessment Group considered that, overall, this study had high internal validity and that the protocol changes that occurred during the course of the study did not appear to have biased the study's results in any way. The joint submission from the Intensive Care Society, the Scottish Intensive Care Society and others noted that it is generally believed that the protocol changes improved the study's power.

- 4.1.4 PROWESS randomised 1728 patients at centres across the world (1690 patients actually received the drug or placebo), although none were from the UK. The trial was designed to recruit 2280 patients, but enrolment was suspended after the second interim analysis when a statistically significant reduction in 28-day mortality was found in patients who received drotrecogin alfa (activated). The suspension fulfilled pre-determined stopping rules.
- 4.1.5 The proportion of patients with hypertension at baseline was slightly lower in the placebo arm than in the treatment group (35.0% versus 38.2%), but the proportions of those with previous myocardial infarction, congestive cardiomyopathy or diabetes were slightly higher in the placebo group. Higher proportions of patients in the placebo group also had septic shock (as defined by the sponsor), were being treated with vasopressors or were receiving mechanical ventilation. The US Food and Drug Administration concluded that these differences could slightly favour the group that received drotrecogin alfa (activated).
- 4.1.6 The primary efficacy endpoint in PROWESS was death from any cause and this was assessed 28 days after the initiation of the infusion. PROWESS demonstrated a statistically significant absolute risk reduction (absolute RR) in 28-day mortality of 6.5% (95% confidence interval [CI], 2.2 to 10.7: intention-to-treat result), which is equivalent to a relative risk of death of 0.79 (95% CI, 0.68 to 0.92). (Mortality in the placebo and treatment groups was 31.3% and 24.8%, respectively.) Longer-term follow-up of PROWESS patients (the EVBI study) showed that the survival benefit was maintained at 90 days ($p = 0.048$), although over the entire duration of follow-up (30-month data), the trend towards increased median survival was non-significant (log rank $p = 0.097$). However, the survival curves did not meet. (Long-term follow-up indicated an increase in median survival of about 9 months, from 846 days in the placebo group to 1113 days in the drotrecogin alfa [activated] group.)
- 4.1.7 Health-related quality of life was not assessed in either RCT.

Subgroup analyses

- 4.1.8 The PROWESS data have been further analysed by means of pre-specified and retrospective subgroup analyses. The results show that drotrecogin alfa (activated) may benefit some patient groups more than others.
- 4.1.9 Subgroup analyses planned a priori suggested that the relative risk of death (at 28 days) in patients treated with drotrecogin alfa (activated) was highest among those with one organ failure at baseline, and decreased progressively as the number of failed organs at baseline increased: the relative risk decreased from 0.92 (95% CI, 0.63 to 1.35) in patients with one organ failure at baseline to 0.60 (95% CI, 0.33 to 1.11) in those with five organ failures. Results for the individual subgroups did not show a statistically significant effect of drotrecogin alfa (activated) on the relative risk of death; however, when the subgroups of patients with two or more organ failures were combined, the relative risk of death was statistically significantly lower in those treated with drotrecogin alfa (activated) compared with placebo (0.78: 95% CI, 0.66 to 0.93). (Mortality in these combined placebo and treatment groups was 33.9% and 26.5%, respectively.) The corresponding results for a longer follow-up were marked 'academic in confidence'.
- 4.1.10 Patients in PROWESS were stratified at baseline according to the severity of disease as reflected by APACHE II score. Prospectively defined subgroup analyses found that lower mortality rates were observed for patients treated with drotrecogin alfa (activated) compared with placebo in all APACHE II quartile subgroups, with the exception of the first APACHE II score quartile (3 to 19). However, the mortality difference was only statistically significant for the third and fourth quartile subgroups (patients with an APACHE II score of 25 or more at baseline). When the patients in the third and fourth quartile subgroups were combined (this combined subgroup was not prospectively defined), the relative risk of death was 0.71 (95% CI, 0.59 to 0.85). (Mortality in the placebo and treatment groups was 44.7% and 30.9%, respectively.)

4.1.11 In a retrospective subgroup analysis, patients were stratified at baseline according to the SOFA scoring system. On the basis of the score obtained, patients were divided into SOFA quartiles. Patients in all subgroups experienced a survival benefit from drotrecogin alfa (activated), although the relative benefit was greatest for those in the first and fourth quartiles (the relative risk of death was 0.74 and 0.75, respectively). (The raw data required to calculate the confidence intervals for the relative risks according to SOFA quartile were not available to the Assessment Group.)

Adverse effects

4.1.12 There were no statistically significant differences in the incidence of serious adverse events between drotrecogin alfa (activated) and placebo in either RCT during the 28-day study period. In PROWESS, the incidence of bleeding events was statistically significantly higher in the intervention arm compared with the placebo group (24.9% compared with 17.7%, $p < 0.001$). In this study, the incidence of serious bleeding events was 3.5% in the intervention group and 2.0% in the placebo group ($p < 0.10$ for all serious bleeding events). During infusion, the incidence of serious bleeding events was 2.4% in the intervention group and 1.0% in the placebo group. In contrast, during the post-infusion period, the incidence was similar in both groups (1.2% and 1.1% in the intervention and placebo groups, respectively).

4.1.13 The incidence of serious bleeding events during infusion was higher in the open-label ENHANCE study (3.6% [$n = 2378$]) than in the RCTs. (This study used eligibility criteria similar to those used in PROWESS.) However, the incidence of serious bleeding events post-infusion was 2.9%. The incidence of intracranial haemorrhage during infusion was also higher in ENHANCE than in PROWESS (0.6% versus 0.2%), although the incidence of fatal intracranial haemorrhages was the same in these two studies (0.2%).

4.2 Cost effectiveness

- 4.2.1 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.
- 4.2.2 The published cost-effectiveness studies have applied a range of methods to the estimation of benefits. The cost-effectiveness abstracts did not provide very much detail on the methods used. Of the eight abstracts identified, seven applied analyses to European populations. All reported economic evaluations used the PROWESS data from those patients actually treated to estimate the benefits associated with drotrecogin alfa (activated).
- 4.2.3 The costs associated with drotrecogin alfa (activated) in patients with severe sepsis considered by the cost-effectiveness studies included the acquisition cost of the drug, an additional cost associated with an increased risk of severe bleeding events, hospitalisation costs associated with additional survivors of severe sepsis and, where it was thought appropriate, the long-term healthcare costs associated with additional survivors of severe sepsis. (Among the assessments described in sections 4.2.4 to 4.2.14, only the North American studies and the evaluation undertaken by the Assessment Group modelled the impact of long-term healthcare costs. In addition, not all the studies costed severe bleeding events explicitly.) With the exception of a recently published German study, all the economic evaluations detailed below (including that provided by the manufacturer and the model developed by the Assessment Group) valued the cost of inputs at 2000 to 2002 prices. The German study applied German-specific unit costs based on data from three

university hospitals for fiscal years 1998/1999 (or the nearest available year). The unit cost of drotrecogin alfa (activated) has remained unchanged since its launch in the UK.

4.2.4 The published US and Canadian papers estimated the incremental gain per treated patient to be between 0.38 and 0.68 life years for patients with severe sepsis. These studies estimated the incremental costs to be between US\$10,000 and US\$16,000 per patient treated. Estimates of cost per life year and cost per quality-adjusted life year (QALY) ranged from US\$15,801 to US\$33,000 and from US\$20,047 to US\$48,800, respectively. These estimates were for all the patients eligible for inclusion in PROWESS. For patients regarded to be at an increased risk of death, as indicated by an APACHE II score of 25 or more at baseline, the cost-effectiveness profile was more favourable (costs per life year and per QALY were lower). However, for patients with an APACHE II score of less than 25, the studies reported that treatment with drotrecogin alfa (activated) was associated with a very unfavourable cost-effectiveness profile: the technology was either dominated by conventional care or associated with an incremental cost per QALY of more than US\$400,000.

4.2.5 The terms of the licence dictate that the relevant patient group for any European analysis is patients with severe sepsis and multiple organ failure. The European studies have largely focused on this indication. As in the case of patients stratified by APACHE II score, the effectiveness of treatment was greater in the multiple organ failure group compared with the general 'all patients' group reported in PROWESS. Hence the cost-effectiveness profile in this subgroup was reported to be more favourable than the 'all patients' analysis.

4.2.6 A European analysis published after the Assessment Group's report, examined the cost effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis in Germany. For the base-case analysis it was assumed that the absolute RR at final patient discharge was the same as the

absolute RR in hospital mortality reported at 28 days (that is, 7.3% for patients with multiple organ failure). The discounted incremental gain in life years was reported to be 0.7 for patients with multiple organ failure (the discounted life expectancy per additional survivor was 9.5 years). The discounted incremental cost effectiveness was reported to be €12,880 per life year gained.

- 4.2.7 In a UK analysis published as an abstract only, the reported cost per life year gained for the full PROWESS patient group was between £7037 and £9519, depending on the method used to estimate life expectancy (with the cost per QALY estimate for this group being between £10,199 and £13,796). Costs per life year and per QALY for the patient group with multiple organ failure were reported as £4716 and £6385, respectively.
- 4.2.8 In general, the various published sensitivity analyses showed that the results were robust to variations in most assumptions.
- 4.2.9 In the analyses provided by the manufacturer, the discounted incremental life years gained were reported to be 1.1 life years per treated patient (PROWESS day-28 analysis) and 0.7 life years per treated patient (analysis based on follow-up data) for patients with severe sepsis and multiple organ failure (that is, the European licence indication). The additional mean costs per patient treated were estimated at £5106 based on 28-day effectiveness data and at £5331 based on longer-term follow-up data. This corresponded with incremental cost-effectiveness ratios of £6637 per QALY and £10,937 per QALY, respectively, based on a single health state value of 0.69 for survivors.
- 4.2.10 In its cost-effectiveness model, the Assessment Group used data on a baseline cohort of UK patients (from ICNARC), defined according to the criteria used in PROWESS, applying the same inclusion criteria as PROWESS but not the exclusion criteria used in that study. The Assessment Group did not apply the exclusion criteria used in PROWESS because it was thought that a different set of eligibility criteria would be applied in clinical

practice. The 28-day mortality for patients in the baseline cohort with severe sepsis was 41.5% (95% CI, 40.8% to 42.3%). This was much higher than the mortality rate reported in the placebo arm of PROWESS (31.3%). Among the subgroup of patients with multiple organ failure, the baseline 28-day mortality was 46.2% (95% CI, 45.3% to 47.1%). (The mortality of this subgroup in the placebo arm of PROWESS was 33.9%.) Long-term NHS costs were included in the base-case analysis.

4.2.11 The Assessment Group estimated a discounted incremental gain of 1.4 life years per treated patient (standard deviation, 0.4) in patients with severe sepsis and multiple organ failure. In terms of the incremental cost-effectiveness ratio, the Assessment Group estimated a base-case cost per QALY of £8228 in patients with severe sepsis and multiple organ failure (based on 28-day survival data and a single health state value of 0.60 for survivors). Excluding long-term NHS costs reduced the incremental cost per QALY to £6691.

4.2.12 The results of a probabilistic sensitivity analysis undertaken by the Assessment Group showed that if the NHS was willing to pay £20,000 per QALY, drotrecogin alfa (activated) would be a cost-effective use of resources in 98.7% of simulations (in patients with severe sepsis and multiple organ failure) compared with standard care.

4.2.13 In a sensitivity analysis, the Assessment Group examined the impact of varying the effectiveness of drotrecogin alfa (activated). The relative risk for the intervention was varied between 0.70 and 0.95 (the standard error was assumed to be the same as in the base-case model). The corresponding incremental cost per QALY in the group with severe sepsis and multiple organ failure was found to range from £6778 to £28,868.

4.2.14 In summary, the UK analyses indicate a cost per QALY of less than £11,000 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.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of drotrecogin alfa (activated), having considered evidence on the nature of the condition and the views of patients who had developed severe sepsis, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.
- 4.3.2 The Committee was mindful of the current licensed indication for the use of drotrecogin alfa (activated), which was based on a subgroup analysis of a single RCT. Patients were recruited to this trial in centres across the world but not in the UK. The Committee therefore considered carefully the generalisability of the study findings to the English and Welsh settings.
- 4.3.3 There is some evidence that the results of PROWESS are generalisable to a UK population. Submissions from professional organisations and experts for this appraisal stated that datasets from ICNARC and the Scottish Intensive Care Society Audit Group indicate that the characteristics of patients in the UK with severe sepsis are similar to those seen in PROWESS, if the full eligibility criteria of that trial are applied. In addition, the mortality rates observed in these surrogate UK populations are similar to those of the PROWESS control group. (Results from the ICNARC audit, for example, indicate a 28-day mortality of 32.7%.)
- 4.3.4 The results from the open-label ENHANCE study, which included UK centres, also lend some support to the generalisability of the PROWESS findings. (Mortality at 28 days was found to be 25.3%.) The Committee was therefore persuaded by the current evidence and by that presented by experts for this appraisal that the survival advantages seen in PROWESS are likely to be generalisable to the UK population.

- 4.3.5 The Committee noted that the cost-effectiveness analyses reviewed by the Assessment Group showed some variability in terms of the estimated incremental cost per QALY. In addition, the Committee noted that the Assessment Group's estimate of the incremental life years gained was generally higher than the estimates reported in the literature.
- 4.3.6 The Committee also noted that the trial analysis did not take account of possible bias introduced by stopping treatment early. The effect of any such bias would be to overestimate the absolute risk reduction in death. In addition, the Committee considered the impact of differences in baseline patient characteristics between the placebo and drotrecogin alfa (activated) arms of PROWESS that may have favoured the group that received drotrecogin alfa (activated).
- 4.3.7 The Assessment Group undertook a sensitivity analysis examining the variation in the incremental cost per QALY by relative risk, which showed that the magnitude of any potential bias identified would be unlikely to affect the conclusion that drotrecogin alfa (activated) is cost effective in patients with severe sepsis and multiple organ failure. The Committee was persuaded that, overall, the intervention was a cost-effective option for patients with severe sepsis whose risk of death was increased because of multiple organ failure.
- 4.3.8 The Committee also discussed the usefulness of the available scoring systems for selecting the patients most likely to benefit from treatment with drotrecogin alfa (activated). Both the experts for the appraisal and the Assessment Group advised against the use of the APACHE II or SOFA scoring systems. For example, it was argued that the APACHE II scoring system gives a high weighting to factors such as increased age and chronic ill health, and that it was not designed for individual prognostic use. In addition, it was noted that this tool was validated for use within the first 24 hours of admission into the ICU, although in PROWESS, the APACHE II score was determined at the point of study entry. The Committee was also advised that the SOFA scoring system was not developed to predict patient outcomes. The

Committee accepted that such tools would not be suitable aids for selecting patients for treatment with drotrecogin alfa (activated). However, the Committee considered that when selecting patients with sepsis and multiple organ failure for treatment with drotrecogin alfa (activated), the criteria used in defining organ failure should be based on those used in PROWESS and reflected in the Summary of Product Characteristics for drotrecogin alfa (activated). Overall, it was persuaded that the failure of two or more major organ systems (in particular, cardiovascular, respiratory and renal failure) was likely to indicate that drotrecogin alfa (activated) would be beneficial.

4.3.9 The Committee also considered the importance of taking into account several factors (for example, co-morbidities) when considering whether a patient would be likely to benefit from this treatment. The Committee was persuaded by the experts on the appraisal that patient selection was crucial in order to optimise the risk–benefit ratio for each patient.

4.3.10 The Committee also discussed who should supervise the use of drotrecogin alfa (activated) and the appropriate setting for its administration. It was strongly argued by the clinical experts that the administration of drotrecogin alfa (activated) should be confined to an ICU setting, but the Committee recognised that patients with severe sepsis are not always managed in an ICU. Nevertheless, the Committee considered that it was most important that any patient considered for treatment with drotrecogin alfa (activated) should also be provided with optimum intensive care support.

4.3.11 The Committee agreed, however, that the administration of drotrecogin alfa (activated) should only be initiated and supervised by a specialist consultant with intensive care skills. The Committee was persuaded that in defining the appropriate specialist consultant in this regard, appropriate competencies – rather than seniority and particular speciality – were crucial in determining who should have responsibility for supervising the use of drotrecogin alfa (activated). It was considered important by the Committee that the specialist be experienced in the care of patients with sepsis.

5 Recommendations for further research

- 5.1 Research is currently being undertaken by the manufacturer into the clinical effectiveness of drotrecogin alfa (activated) in a paediatric population. The manufacturer is also conducting research into the use of heparin prophylaxis during treatment with drotrecogin alfa (activated) in patients with severe sepsis at high risk of death. It is also in the process of setting up an extended dosing study in Europe.
- 5.2 Further research is required on the longer-term impact of drotrecogin alfa (activated) on mortality, morbidity, health-related quality of life and resource use among UK patients with severe sepsis and multiple organ failure. Survivors of severe sepsis may have a low health-related quality of life and an increased risk of death, at least in the initial few years following the septic episode. The potential of drotrecogin alfa (activated) to offset this burden of illness has yet to be adequately defined. In addition, little is known about the long-term costs incurred when patients survive sepsis. The longer-term impact of drotrecogin alfa (activated) could be assessed by means of case–control studies, observational research and clinical audit using high-quality databases.
- 5.3 Although there is some evidence to indicate that the prompt initiation of appropriate therapies leads to improved outcomes, further research is needed to characterise more fully the effect of the timing of treatment with drotrecogin alfa (activated) on outcomes in severe sepsis.
- 5.4 There is some evidence that the level of benefit achieved from treatment with drotrecogin alfa (activated) may vary according to the infecting organism and the site of infection. Further research is needed – by means of a national intensive care audit, for example – to clarify the benefit profile of drotrecogin alfa (activated) in these particular subgroups of patients.

6 Implications for the NHS

- 6.1 There is a marked variation in the incidence of severe sepsis cited in the literature. Data from ICNARC estimate the prevalence of severe sepsis (in the first 24 hours) at 27% of ICU admissions, with 84% of these patients having multiple organ failure. The experts for this appraisal stated that a much smaller proportion of patients admitted to ICUs would actually be appropriate for treatment with drotrecogin alfa (activated) once contraindications and individual patient characteristics were taken into account. They estimated that in the UK 3–5% of patients admitted to ICUs would receive drotrecogin alfa (activated). However, if the PROWESS eligibility criteria are applied to the ICNARC dataset, it is estimated that 12% of patients admitted to ICUs would be eligible for treatment with drotrecogin alfa (activated). The exact proportion of patients receiving treatment with drotrecogin alfa (activated) in any particular NHS Trust will depend on case-mix and other factors. Data from the Northern Ireland Intensive Care Group indicate that 7–8% of patients have been treated with drotrecogin alfa (activated) in general mixed surgical/medical units in the past year.
- 6.2 Assuming that approximately 78,000 adult patients are admitted to ICUs in England and Wales per annum, and taking account of the expert advice about the proportion of patients who would be eligible for treatment with drotrecogin alfa (activated), the annual cost of drug acquisition alone is estimated to be between £11 million and £19 million excluding VAT (£13 million to £22 million including VAT) – this is based on a treatment cost of £4905 per patient (excluding VAT). However, if the proportion of patients receiving treatment is estimated by applying the PROWESS eligibility criteria to the ICNARC dataset, the estimated annual drug acquisition cost increases to £46 million excluding VAT (£54 million including VAT).

7 Implementation and audit

- 7.1 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.
- 7.2 Intensive care units in NHS 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.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
 - 7.3.1 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.
 - 7.3.2 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.

8 Related guidance

- 8.1 There is no related guidance for this technology.

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed in September 2007.

Andrew Dillon
Chief Executive
September 2004

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE 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 three branches, with the chair, vice-chair and a number of other members between them attending meetings of all 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 Jane Adam

Radiologist, St George's Hospital, London

Professor Ron Akehurst

Dean of School of Health and Related Research, University of Sheffield

Dr Sunil Angris

General Practitioner, Waterhouses Medical Practice, Staffordshire

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Stirling Bryan

Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham

Professor John Cairns

Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor David Chadwick

Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool

Ms Ailsa Claire

Chief Executive, Barnsley Primary Care Trust, South Yorkshire

Dr Lorna Duggan

Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Mr Sanjay Gupta

Stroke Services Manager, Basildon & Thurrock University Hospitals NHS Trust

Professor Philip Home (Vice-Chair)

Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary,
Newcastle upon Tyne

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

Dr Virginia Pearson

Chief Executive, South Petherton Hospital, South Somerset PCT

Dr Christa Roberts

Industry Representative, UK Manager Vascular Intervention, Guidant Ltd,
Basingstoke, Hampshire

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, Westlake Surgery, Somerset

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Rod Taylor

Senior Lecturer, Department of Public Health & Epidemiology, University of
Birmingham

Professor Norman Waugh

Department of Public Health, University of Aberdeen

Mrs Miranda Wheatley-Price

Lay Representative, Director of Service Development, Colon Cancer Concern,
London

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Francis Ruiz

Technical Lead, NICE project team

Nina Pinwill

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

- A The Assessment Report for this appraisal was prepared by the Southampton Health Technology Assessments Centre (SHTAC), University of Southampton:

The Clinical and Cost-effectiveness of Drotrecogin Alfa (Activated) (Xigris) for the Treatment of Severe Sepsis in Adults: a Systematic Review and Economic Evaluation, December 2003

- B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Eli Lilly and Company

II Professional/specialist and patient/carer groups:

- British Association of Critical Care Nurses (BACCN)
- British Infection Society
- Department of Health (Critical Care Policy Team)
- Intensive Care Society
- Meningitis Research Foundation
- Royal College of Anaesthetists
- Royal College of Physicians
- Royal Society of Medicine
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- NHS Quality Improvement Scotland
- NHS Confederation

- Welsh Intensive Care Society
- Scottish Intensive Care Society

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on drotrecogin alfa (activated) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Julian Bion, Reader & Regional Advisor in Intensive Care Medicine, University Dept Anaesthesia and Intensive Care, Queen Elizabeth Hospital, Birmingham
- Dr Chris Garrard, Director of Adult Intensive Care Unit, John Radcliffe Hospital, Oxford
- Ms Linda Glennie, Head of Research and Medical Information, Meningitis Research Foundation
- Dr Simon Mackenzie, Consultant in Anaesthesia, Scottish Intensive Care Society, Royal Infirmary, Edinburgh
- Diane Moran, patient expert nominated by the Meningitis Research Foundation
- Dr Saxon Ridley, President of the Intensive Care Society
- Helen Esther Smith, patient expert nominated by the Meningitis Research Foundation
- Mr John Welch, Consultant Nurse, Department of Anaesthesia, Kingston Hospital, Surrey
- Dr Duncan Young, Adult Intensive Care Unit, John Radcliffe Hospital, Oxford

Appendix C. Detail on criteria for audit of the use of drotrecogin alfa (activated) for severe sepsis

Possible objectives for an audit

An audit could be carried out on the appropriateness of the use of drotrecogin alfa (activated) for severe sepsis.

Possible patients to be included in the audit

An audit could be carried out on people with severe sepsis that has resulted in multiple organ failure and who are receiving intensive care support in a reasonable time period for audit, for example, 6 months.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of drotrecogin alfa (activated) are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. Drotrecogin alfa (activated) is used for an adult who meets both of the following circumstances:</p> <p>a. the individual has severe sepsis that has resulted in multiple organ failure, and</p> <p>b. the individual is receiving optimum intensive care support</p>	<p>100% of people with severe sepsis that has resulted in multiple organ failure who are receiving optimum intensive care support</p>	<p>A. Drotrecogin alfa (activated) is contraindicated</p> <p>B. The individual's condition is not suitable for the use of drotrecogin alfa (activated)</p>	<p>Clinicians will need to agree locally on what constitutes evidence of use of the drug for audit purposes, e.g., prescription or documentation of administration.</p> <p>'Multiple organ failure' should be consistent with the PROWESS study and the Summary of Product Characteristics, and should include failure of two or more major organ systems – in particular, cardiovascular, respiratory and/or renal failure. 'Optimum intensive care support' means a level of supportive care that patients would receive in an ICU setting. It includes both treatment of the underlying infection, primarily with antibiotics, and supportive treatment according to the individual's assessed needs. The choice of antibiotic will depend on the results of any positive microbiological cultures, the likely source of infection and the expected tissue uptake of the antibiotic. Supportive treatment may include fluids, steroids, vasopressors, and ventilatory and renal support. Contraindications include active internal bleeding, chronic severe hepatic disease and intracranial pathology. See the Summary of Product Characteristics.</p> <p>Clinicians will need to agree locally on how to define optimum intensive care support and the conditions for which the use of drotrecogin alfa (activated) would be inappropriate (exceptions A and B), for audit purposes.</p>
<p>2. The administration of drotrecogin alfa (activated) is initiated and supervised only by a specialist consultant with intensive care skills and</p>	<p>100% of people who receive drotrecogin alfa (activated)</p>	<p>None</p>	<p>Clinicians will need to agree locally on the competencies needed to initiate and supervise, and what constitutes initiation and supervision of, the administration of drotrecogin alfa (activated), for audit purposes. Clinicians will also need to agree locally on how best this information should be recorded for audit</p>

experience in the care of patients with sepsis			purposes.
--	--	--	-----------

In addition, the following information may be useful to collect in an audit on the appropriate use of drotrecogin alfa (activated): the patient's length of stay in the ICU and in hospital; the patient's status at 28 days after the administration of the treatment; the time of administration of the treatment in relation to the onset of severe sepsis; whether or not the patient received the full 96-hour infusion, and if not, why not; the micro-organisms isolated and from which organ, before treatment; and the patient age and co-morbidities.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.