Recombinant Human Activated Protein C (rhAPC) or Drotrecogin Alfa (Activated)
Michelle Leady, PharmD, Michael Kraft, PharmD, Cesar Alaniz, PharmD

SUMMARY AND CRITICAL ISSUES
Drotrecogin alfa (activated) or recombinant human activated protein C (rhAPC) is approved for the reduction of mortality in adult patients with severe sepsis who have a high risk of death. A reduction in endogenous protein C has previously been implicated as a risk factor in septic patients. Sepsis is a systemic inflammatory response syndrome (SIRS) occurring in response to infection. SIRS or inflammatory activation can lead to severe sepsis, SIRS with accompanying organ failure, which is associated with a mortality rate of up to approximately 50%. Severe sepsis typically progresses with lung dysfunction and shock occurring immediately, and then with further organ dysfunction involving the kidneys, liver, or central nervous system (CNS).

Currently, there are no other drugs approved for the treatment of sepsis; management consists primarily of supportive treatments, such as fluid resuscitation and antimicrobials, blood products, vasopressors to improve the systolic blood pressure and mean arterial pressure, inotropes to improve cardiac index (CI), and mechanical ventilation.

The cascade of events resulting in sepsis has been described elsewhere. Microbial infections induce endotoxin release, resulting in the production of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1), and interleukin-6 (IL-6). These cytokines have been implicated in the stimulation of tissue factor and in the activation of neutrophils. The presence of tissue factor results in initiation of the coagulation process by producing thrombin, which eventually results in a fibrin clot. Activation of neutrophils can result in vasculature damage. Fibrinolysis, the destruction of a fibrin clot, is also impaired in sepsis because of the release of plasminogen-activator inhibitor (PAI-1) by both thrombin and inflammatory cytokines.

Previous trials involving corticosteroids or monoclonal antibodies to endotoxin or TNF-α were effective only in subsets of patients with sepsis because of their limited scopes of action. However, drotrecogin alfa (activated) is a novel therapeutic agent in the treatment of sepsis. It inhibits both inflammation and coagulation while promoting fibrinolysis. Drotrecogin alfa (activated) inhibits thrombin formation by inactivating coagulation factors Va and VIIa. It also inhibits the production of the inflammatory mediators TNF-α, IL-1, and IL-6, and promotes fibrinolysis by inhibiting PAI-1.

The safety and efficacy data with use of drotrecogin alfa (activated) are currently limited (see Table 1). The agent has been evaluated in only two published trials and in one unpublished trial still in abstract form.

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CLINICAL TRIALS
Bernard, Vincent, Laterre et al.5

The phase III published trial, termed PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Sepsis) demonstrated that treatment with drotrecogin alfa (activated) significantly reduced the primary endpoint of all cause 28-day mortality compared to those treated with placebo in patients with severe sepsis. Patients included in the study were those with severe sepsis, defined as known or suspected infection with three or more signs of systemic inflammation, and sepsis-induced dysfunction of at least one organ or system within the past 24 hours. Study exclusionary criteria were extensive and included the following: patients at increased risk of bleeding; patients with known hypercoagulable conditions; pediatric patients; thrombocytopenic patients (platelet count<30,000/mm³); patients not expected to survive; as well as patients receiving heparin (low-molecular-weight or unfractionated), warfarin, acetylsalicylic acid, thrombolytics, glycoprotein IIb/IIIa inhibitors or antithrombin III. Patients fitting the inclusion criteria were initiated within 24 hours of diagnosis with either a continuous infusion of rhAPC at a dose of 24 mg/kg/hr, or a continuous infusion of normal saline with or without albumin. Patients in both the treatment group and the placebo group were treated for a total of 96 hours.

The mortality rate was found to be 30.8% in the placebo group and 24.7% in the rhAPC-treated group (P=0.005). These results indicate that the absolute reduction and the relative reduction in risk of mortality are 6.1% and 19.4%, respectively, and that the number needed to treat to save one life was 16.

The incidence of serious bleeding (defined as any intracranial hemorrhage, life-threatening bleeding, bleeding classified as serious by the investigator or bleeding requiring three units of packed red blood cells on two consecutive days) during administration of the infusions, was higher in the rhAPC group at 28 days than in the placebo group; 3.5% (29 patients) versus 2% (16 patients), respectively, P=0.06. In both groups, serious bleeding was more frequent in high-risk patients, such as those with gastrointestinal ulceration, traumatic injury of a blood vessel, or a prolonged prothrombin time. Two patients treated with rhAPC experienced fatal intracranial hemorrhage during the infusion (days one and four), as did one patient given placebo six days after the infusion. There were no differences between the groups in terms of blood-transfusion requirements, and combining the agent with heparin had no effect on the incidence of bleeding.

The incidence of new infections between the groups was comparable. No other adverse events were associated with treatment with drotrecogin alfa (activated).

Limitations of this study include the severely restrictive inclusionary criteria, the lack of evaluation of mortality after 28 days, the lack of information about incidence of bleeding during infusion, and the lack of evaluation of quality of life at 28 days.
Recombinant Human Activated Protein C

Bernard, Ely, Wright, et al. 6

This was a placebo-controlled phase II dose-ranging trial for drotrecogin alfa (activated) in patients with severe sepsis. One hundred thirty-one patients were administered either placebo or drotrecogin alfa in low (12 or 18 mcg/kg/min) or high (24 or 30 mcg/kg/hr) doses. Outcomes evaluated included: 28-day mortality; improvement in SIRS; ventilator use; shock; number of days in the ICU; and number of hospital-free days. Although no statistically significant differences were observed for any endpoints when low- or high-dose rhAPC were compared to placebo, patients treated with high-dose rhAPC did demonstrate a trend toward improvement in outcomes of number of SIRS-free days, failure-free days for certain organ systems (respiratory and central nervous system), and in the number of circulatory-failure-free days, along with reduction in 28-day mortality. With regard to 28-day mortality, a reduction in relative risk of 40% (P=0.21) was determined when high-dose rhAPC and placebo were compared.

A serious bleeding event was defined as a bleed resulting in intracranial hemorrhage, transfusion of two or more units of packed red blood cells on two consecutive days, or a bleed that put the patient at risk of death. Serious bleeding events were seen in four rhAPC-treated patients during the 28-day study period, with two of these events occurring during the infusion itself. There were no statistical differences between rhAPC and placebo in adverse events identified during the study; however, a greater number of rhAPC-treated patients experienced skin rash.

Nearly half of patients initiated on rhAPC in this trial did not receive the assigned infusion dose or were not treated for the anticipated infusion duration because of elevations in APTT over 95 seconds or the need for invasive procedures. The majority of patients requiring a dose alteration were those receiving the highest infusion dose of rhAPC, 24 mcg/kg/hr. Other outcomes identified by this study included the ability of rhAPC to significantly reduce D-dimer and IL-6 levels.

Kinasewitz, Marolis, Freebairn, et al. 7

This further evaluation expanded on the PROWESS trial results to determine the effects of rhAPC in patients with sepsis. In this evaluation, the percent changes in biomarker values (protein c, protein s, antithrombin, D-dimer, PT, APTT, IL-6 and additional markers) prior to and after infusion of the agent were compared. Results of the study indicated that change in D-dimer and IL-6 were significantly lower, and PC activity was significantly increased in patients treated with rhAPC compared to patients who received placebo. This result supports the determination that rhAPC primarily affects the inflammatory and coagulation pathways in patients with severe sepsis. The risk of bleeding with rhAPC is a concern, and although the authors indicate that APTT and PT normalized during the study, these values were significantly elevated compared to placebo during study infusion, indicating that there might be a greater potential for hemorrhage in rhAPC-treated patients.

ADVERSE REACTIONS 1

Bleeding was the most prevalent adverse event with drotrecogin alfa activated in the PROWESS trial.

**Table 1 Contraindications/Warnings/Precautions 1**

<table>
<thead>
<tr>
<th>Contraindications</th>
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<tbody>
<tr>
<td>• Active internal bleeding</td>
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<tr>
<td>• Recent (within three months) hemorrhagic stroke</td>
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<tr>
<td>• Recent (within two months) intracranial or intraspinal surgery, or severe head trauma</td>
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<tr>
<td>• Trauma with an increased risk of life-threatening bleeding</td>
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<tr>
<td>• Presence of an epidural catheter</td>
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<td>• Intracranial neoplasm or mass lesion or evidence of cerebral herniation</td>
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<table>
<thead>
<tr>
<th>Warnings</th>
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<tbody>
<tr>
<td>• Concurrent therapeutic heparin (&gt;15 units/kg/hr)</td>
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<tr>
<td>• Platelet count &lt; 30,000 x 10^6/L, even if the platelet count is increased after transfusions</td>
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<tr>
<td>• Prothrombin time-INR &gt;3</td>
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<tr>
<td>• Recent (within six weeks) gastrointestinal bleeding</td>
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<tr>
<td>• Recent administration (within three days) of thrombolytic therapy</td>
</tr>
<tr>
<td>• Recent administration (within seven days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>• Recent administration (within seven days) of aspirin &gt;650 mg per day or other platelet inhibitors</td>
</tr>
<tr>
<td>• Recent (within three months) ischemic stroke</td>
</tr>
<tr>
<td>• Intracranial arteriovenous malformation or aneurysm</td>
</tr>
<tr>
<td>• Known bleeding diathesis</td>
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<tr>
<td>• Chronic severe hepatic disease</td>
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<tr>
<td>• Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location</td>
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<table>
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<tr>
<th>Precautions</th>
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<tbody>
<tr>
<td>• Lab tests – APTT might be prolonged, therefore APTT cannot be reliably used to assess the status of the coagulopathy during rhAPC infusion</td>
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<tr>
<td>• Immunogenicity – Incidence of antibody development in patients receiving rhAPC has not been adequately determined.</td>
</tr>
</tbody>
</table>

MEDICATION SAFETY 1

Following reconstitution with sterile water for injection, rhAPC must only be further diluted with 0.9% sodium chloride for injection. Because of the lack of a preservative, infusions of rhAPC must be completed within 14 hours of preparation if kept continuously at room temperature; or infusions may be stored in the refrigerator for up to 12 hours, then kept at room temperature for 12 hours. 8 The agent should be administered via a dedicated intravenous line or a dedicated lumen of a multi-lumen central venous catheter. The only other solutions that can be administered through the same line with drotrecogin alfa are sodium chloride injection, lactated ringer’s injection, dextrose or dextrose and saline mixtures. Because of its protein nature, rhAPC should not be exposed to heat or direct sunlight.

MONITORING PARAMETERS

Although their role is still unclear, prothrombin time (PT), international normalized ratio (INR), and platelet count appear to be essential monitoring components of the agent. In addition, signs and symptoms of infection (fever, tachycardia) and of organ function serum creatinine (SCR), liver function tests (LFTs), complete blood count (CBC), neurological status, and signs and symptoms of bleeding should be monitored.

Place in Therapy

Patients with sepsis at low risk of death, patients with severe sepsis for greater than 24 hours, and patients with severe sepsis not
Recombinant Human Activated Protein C

Table 2 Clinical Efficacy and Safety of Drotrecogin Alfa (Activated)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Drug/Dose</th>
<th>N</th>
<th>Study Parameters</th>
<th>Efficacy Results</th>
<th>Tolerability Results (%)</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, R, DB, PC</td>
<td>D=24mg/kg/hr continuous infusion for 96 hours or PL</td>
<td>840</td>
<td>-28 day all-cause mortality</td>
<td>IL-6 significantly greater in D v. PL</td>
<td>PL D P-value</td>
<td>At least one serious event: 12.1 12.5 0.84</td>
</tr>
</tbody>
</table>
| MC | | | | Day | P-value | Bernard, Vincent, Laterre, et al.

| P, R, DB, PC | LD=12 or 18 µg/kg/hr HD= 24 or 30mg/kg/hr continuous infusion for 48 or 96 hours or PL | 118 | -Morbidity (organ failure-free days) | D-dimer significantly greater in D vs. PL | PL HD P-value | Serious bleeding event: 2.0 3.5 0.06 |
| Phase II abstract | | | | Day | P-value | Bernard, Ely, Wright, et al.

| P, R, DB, PC | D=850 PL=840 | 120 | Serial measurements of protein C, AT, D-dimer, PT, APTT, IL-6 | Patients in treatment arm exhibited significantly greater decreases in D-dimer and IL-6 levels and greater increases in protein C activity compared with placebo. APTT and PT significantly increased in treatment vs. placebo arm. | AT levels increased in both groups. | Kinasewitz, Marolis, Freebairn, et al.

Dosage Formulation

Drotrecogin alpha (activated) is supplied as 5- and 20-mg vials. A 70-kg adult treated for 96 hours with an infusion of 24 mcg/kg/hr would receive a total of 161.28 mg.

Cost Evaluation

The cost of drotrecogin alfa (activated) is approximately $8,000 per treatment course for a 70-kg adult. If an estimated 100 patients were treated annually with rhAPC for four days duration, the resultant incremental expenditure would be $800,000.

Recommendation

Although safety data and efficacy data are currently limited, drotrecogin alfa (activated) is a promising drug for the treatment of severe sepsis. The reduction in mortality with the agent is significant, and the lack of other agents for severe sepsis necessitates the addition of the agent to hospital formularies. However, safety and cost issues prompted the development of specific criteria for defining appropriate patients to be initiated on therapy as well as the development of institutional ordering forms for the agent (see following pages).

REFERENCES

2. Yan SH; Heterbrand JD; Hartman DL; Wright TJ; Bernard GR. Low levels of protein C are associated with a poor outcome in severe sepsis. Chest 2001; 120(3): 915–922.
UMHHC ORDER FORM FOR THE USE OF DROTRECOGIN ALFA (ACTIVATED) (XIGRIS®; RECOMBINANT HUMAN ACTIVATED PROTEIN C)

IN ADULT PATIENTS

This order form MUST be used to order drotrecogin alfa (activated) (Xigris®). Signature of an ICU ATTENDING PHYSICIAN is REQUIRED.

INCLUSION CRITERIA: The patient must meet all of the following criteria (numbered 1 through 6 on the left) to be eligible to receive drotrecogin alfa (activated). All six boxes on the left must be checked "yes".

1. The patient must have a known or suspected infection as evidenced by one or more of the following (check all that apply):
   - A. Microbiologically-confirmed infection
   - B. White cells in a normally sterile body fluid
   - C. Perforated viscus
   - D. Radiographic evidence of pneumonia in association with production of purulent sputum
   - E. A syndrome associated with a high risk of infection

2. The patient must have the systemic inflammatory response syndrome (SIRS) as evidenced by the following criteria (must have at least 3 of 4; check all that apply):
   - A. Core temperature of ≥ 38°C or ≤ 36°C
   - B. A heart rate of ≥ 90 beats/minute (except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia)
   - C. A respiratory rate of ≥ 20 breaths per minute or a PaCO2 of ≤ 32 mm Hg or the use of mechanical ventilation for an acute respiratory process
   - D. A white-cell count of ≥ 12,000/mm³ or ≤ 4,000/mm³ or a differential count showing > 10% immature neutrophils

3. The patient must have evidence of at least two dysfunctional organs or systems (must meet at least 2 of the following 5 criteria; check all that apply):
   - A. Arterial systolic blood pressure ≤ 90 mm Hg or the mean arterial pressure ≤ 70 mm Hg for at least one hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in attempt to maintain a systolic blood pressure ≥ 90 mm Hg or a mean arterial pressure of ≥ 70 mm Hg
   - B. Urine output less than 0.5mL/kg of body weight/hour for 1 hour, despite adequate fluid resuscitation
   - C. PaO2 to FiO2 ratio must be ≤ 250 in the presence of other dysfunctional organs or systems or ≤ 200 if the lung is the only dysfunctional organ
   - D. Platelet count must be < 80,000/mm³ or have decreased by 50% in the 3 days prior to infusion
   - E. In case of unexplained metabolic acidosis, the pH must be ≤ 7.30 or the base deficit must be ≥ 5.0 mmol/L in association with a plasma lactate level that is > 1.5 times the upper limit of normal

4. The patient has NOT met all criteria for GREATER THAN 24 hours

5. The patient has a reasonable expectation of survival

6. The patient is in an ICU, all life support measures are being undertaken and the underlying infection is being aggressively treated

EXCLUSION CRITERIA: The patient must NOT meet any of the exclusion criteria listed on the reverse side of this form, otherwise he/she is NOT eligible to receive drotrecogin alfa (activated). The box on the left must be checked "no", indicating the attending physician has examined the patient and the patient does not meet any of the criteria.

NO. THE PATIENT DOES NOT MEET ANY OF THE EXCLUSION CRITERIA

WARNINGS AND PRECAUTIONS: Drotrecogin alfa (activated) should be used cautiously in the following patients:

1. Patients who are pregnant or breast feeding
2. Patients with chronic renal failure requiring hemodialysis or peritoneal dialysis
3. Patients with cirrhosis with a potential for bleeding
4. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage

If the patient meets ALL of the above criteria and ALL boxes in the left column are checked, begin drotrecogin alfa (activated) continuous infusion at 24 mcg/kg/hr x 96 hours of total infusion time.

Patient actual body weight (dry) = ____________ kg

Nurse: Monitor patient as described on the Nurse Monitoring Protocol for Patients on Xigris®

Signature of
ICU Fellow: Print name of authorizing ICU
Attending Physician (required): Date: Time:
ICU Attending Physician Signature (required within 24 hrs of original order): Doctor #: Date: Time:

UMHHC EXCLUSION CRITERIA FOR DROTRECOGIN ALFA (ACTIVATED) (XIGRIS®; RECOMBINANT HUMAN ACTIVATED PROTEIN C)

FOR ADULT PATIENTS

If the patient meets any of the following exclusion criteria, he/she is NOT eligible to receive drotrecogin alfa (activated) (Xigris®; recombinant human Activated Protein C). The box in the left column on the front of this form must be checked "no" indicating the attending physician has examined the patient and the patient does NOT meet any of the following criteria:

1. The patient’s platelet count is ≤ 30,000.
2. The patient has an increased risk of bleeding as evidenced by one or more of the following:
   - A. Surgery requiring general or spinal anesthesia within 12 hours before infusion or the potential need for surgery during the infusion
   - B. Evidence of active bleeding
   - C. A history of severe head trauma requiring hospitalization, intracranial surgery or stroke within 3 months before the infusion
   - D. A history of uncorrected intracranial arteriovenous malformation, cerebral aneurysm, or mass lesion of central nervous system
   - E. A history of congenital bleeding diathesis
   - F. Gastrointestinal bleeding within 6 weeks of infusion, unless corrective surgery performed
   - G. Trauma considered to increase the risk of bleeding
3. The patient has a known hypercoagulable condition:
   - A. Resistance to activated protein C
   - B. Hereditary deficiency of protein C, protein S, or antithrombin III
   - C. Presence of antiphospholipid antibody, antiphospholipid antibody, lupus anticoagulant or homocysteinemia
   - D. Recently documented (within 3 months of infusion) or highly suspected deep-vein thrombosis or pulmonary embolism
4. The patient has a "do not resuscitate" order in chart
5. The patient is in a moribund state in which death is perceived to be inevitable
6. The patient has received any of the following medications or treatment regimens:
   - A. Unfractionated heparin to treat an active thrombotic event within 8 hours before infusion
   - B. Low molecular weight heparin at higher doses than those recommended for prophylaxis with 12 hours before infusion
   - C. Warfarin if used within 7 days of before infusion and if the prothrombin time exceeds the upper limit of normal
   - D. Aspirin use at a dose of more than 650 mg per day, or use of other platelet inhibitors, within 3 days before infusion
   - E. Thrombolytic therapy within 3 days before infusion (use other than catheter clearance)
   - F. Glycoprotein IIb/IIIa antagonists used within 7 days before infusion
   - G. Antithrombin III at a dose of more than 10,000 units within 12 hours of infusion
7. The patient has an epidural catheter in place
8. The patient has a known hypersensitivity to drotrecogin alfa (activated) (Xigris®; recombinant human Activated Protein C) or any component of the preparation

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UNIVERSITY OF MICHIGAN HOSPITALS AND HEALTH CENTERS CRITERIA FOR THE USE OF DROTRECOGIN ALFA (ACTIVATED) (XIGRIS®; RECOMBINANT HUMAN ACTIVATED PROTEIN C) IN ADULT PATIENTS

INCLUSION CRITERIA
1. Known or suspected infection as evidenced by one or more of the following
   A. Microbiologically-confirmed infection
   B. White cells in a normally sterile body fluid
   C. Perforated viscus
   D. Radiographic evidence of pneumonia in association with production of purulent sputum
   E. A syndrome associated with a high risk of infection

2. Modified SIRS: patient must meet at least 3 of following 4 criteria:
   A. Core temperature of ≤ 38°C or ≥ 36°C
   B. A heart rate of ≥ 90 beats/minute (except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia)
   C. A respiratory rate of ≥ 20 breaths per minute or a PaCO2 of ≤ 32 mm Hg or the use of mechanical ventilation for an acute respiratory process
   D. A white-cell count of ≤ 12,000/mm³ or ≤ 4,000/mm³ or a differential count showing > 10% immature neutrophils

3. Criteria for dysfunctional organs or systems: patient must meet at least 2 of the following 5 criteria:
   A. Arterial systolic blood pressure ≤ 90 mm Hg or the mean arterial pressure ≤ 70 mm Hg for at least one hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in attempt to maintain a systolic blood pressure ≥ 90 mm Hg or a mean arterial pressure of ≥ 70 mm Hg
   B. Urine output less than 0.5 mL/kg of body weight/hour for 1 hour, despite adequate fluid resuscitation
   C. PaO2 to FiO2 ratio must be ≤ 250 in the presence of other dysfunctional organs or systems or ≤ 200 if the lung is the only dysfunctional organ
   D. Platelet count must be < 80,000/mm³ or have decreased by 50% in the 3 days prior to infusion
   E. In case of unexplained metabolic acidosis, the pH must be ≤ 7.30 or the base deficit must be ≥ 5.0 mmol/L in association with a plasma lactate level that is > 1.5 times the upper limit of normal

4. The patient has NOT met all criteria for GREATER than 24 hours

5. The patient has a reasonable expectation of survival

6. The patient is in an ICU, all life support measures are being undertaken and the underlying infection is being aggressively treated

EXCLUSION CRITERIA
1. Platelet count < 30,000
2. Patient with increased risk of bleeding
   A. Surgery requiring general or spinal anesthesia within 12 hours before infusion or the potential need for surgery during the infusion
   B. Evidence of active bleeding
   C. A history of severe head trauma requiring hospitalization, intracranial or intraspinal surgery or stroke within 3 months before the infusion
   D. A history of uncorrected intracerebral arteriovenous malformation, cerebral aneurysm, neoplasm or mass lesion of the central nervous system
   E. A history of congenital bleeding diathesis
   F. Gastrointestinal bleeding within 6 weeks of infusion, unless corrective surgery performed
   G. Trauma considered to increase the risk of bleeding

3. Known hypercoagulable condition
   A. Resistance to activated protein C
   B. Hereditary deficiency of protein C, protein S, or antithrombin III
   C. Presence of anticardiolipin antibody, antiphospholipid antibody, lupus anticoagulant or homocysteinemia
   D. Recently documented (within 3 months of infusion) or highly suspected deep-vein thrombosis or pulmonary embolism

4. Do not resuscitate order in chart

5. Moribund state in which death is perceived to be inevitable

6. Use of any of the following medications or treatment regimens:
   A. Unfractionated heparin to treat an active thrombotic event within 8 hours before infusion
   B. Low molecular weight heparin at higher doses than those recommended for prophylaxis with 12 hours before infusion
   C. Warfarin if used within 7 days of before infusion and if the prothrombin time exceeds the upper limit of normal
   D. Aspirin use at a dose of more than 650 mg per day, or use of other platelet inhibitors, within 5 days before infusion
   E. Thrombolytic therapy within 3 days before infusion (use other than catheter clearance)
   F. Glycoprotein IIb/IIIa antagonists used within 7 days before infusion
   G. Antithrombin III at a dose of more than 10,000 units within 12 hours of infusion

7. Presence of an epidural catheter

8. Known hypersensitivity to drotrecogin alfa (activated) (Xigris®; recombinant human Activated Protein C) or any component of the preparation

WARNINGS AND PRECAUTIONS
1. Pregnant or breast feeding
2. Chronic renal failure requiring hemodialysis or peritoneal dialysis
3. Presence of cirrhosis with a potential for bleeding
4. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage
5. Immediately stop the infusion if any clinically important bleeding occurs; once adequate hemostasis has been achieved, initiation of the infusion may be considered

6. Drotrecogin alfa (activated) (Xigris®) infusion should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedure with an inherent risk of bleeding; once adequate hemostasis has been achieved, initiation of the infusion may be considered 12 hours after major invasive procedures or surgery, or may be restarted immediately after uncomplicated less invasive procedures

ALL OF THE FOLLOWING MUST BE FULLFILLED FOR THE PATIENT TO BE ELIGIBLE TO RECEIVE DROTRECOGIN ALFA (ACTIVATED) (XIGRIS®):
- The patient meets ALL inclusion criteria
- The patient does NOT meet any of the exclusion criteria
- The patient has been evaluated by an ICU attending physician or ICU fellow
- The appropriate UMHC drotrecogin alfa (activated) (Xigris®) order form has been properly filled out
- The appropriate UMHC drotrecogin alfa (activated) (Xigris®) order form has been signed by an ICU attending physician or an ICU fellow has taken a verbal or telephone order from an attending physician
- The attending physician must sign, date and time the order within 24 hours