Criteria for Use: Drotrecogin Alfa (activated)

VHA Infectious Diseases Program Office, Pulmonary & Critical Care Field Advisory Group, and
Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

*For specific information on dosage, administration, preparation, and details regarding use, please refer to the manufacturer's package insert (**http://pi.lilly.com/us/xigris.pdf**). The package insert provides details regarding this drug as approved by the Food and Drug Administration. .*

A. Criteria for Use

Because of the potentially serious toxicity, lack of information for the wide spread use in high risk patients and the marginal effectiveness demonstrated in some of the groups in the clinical trials, VA clinicians should consider use of drotrecogin alfa (activated) only after the approval of a staff physician or fellow (must be a critical care fellow or an infectious disease / critical care / pulmonary attending). The following recommendations are provided for the use of drotrecogin alfa (activated) in VHA.

1. Patient is within 48 hours of the onset of the first sepsis induced organ dysfunction.

AND

2. Patient is receiving continuous monitoring in the intensive care unit. In general, it is not necessary to begin this medication in the Emergency Room, unless uncontrollable delays are expected to occur prior to movement of the patient to the intensive care setting.

AND

3. Patient has confirmed or suspected infection (positive blood culture, perforated viscus, etc.)

AND

4. Possible sepsis syndrome (modified systemic inflammatory response syndrome-(SIRS), with any 3 of the following signs:

    a. Temperature ≥ 100.4 (38° C) or ≤ 96.8 (36° C)
    b. Heart rate ≥ 90 BPM
    c. Respiratory rate ≥ 20/min or Pa CO_2 < 32mm Hg or the use of mechanical ventilation (not chronic)
    d. WBC ≥ 12,000 or ≤ 4,000 or > 10% immature neutrophils

AND

4. Acute end organ dysfunction (any two of the following five systems):

   a. CARDIOVASCULAR

      (1) An arterial systolic blood pressure of ≤ 90 mm Hg

      OR

      (2) A mean arterial pressure (MAP) ≤ 70 mm Hg for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status

      OR

      (3) The need for vasopressors to maintain systolic blood pressure (SBP) ≥ 90 mm Hg or MAP ≥ 70 mm Hg

   b. RENAL

      Urine output < 0.5 mL/kg/hr for one hour, despite adequate fluid resuscitation

   c. RESPIRATORY

      $PaO_2/FiO_2 \leq 200$

   d. HEMATOLOGY

      Platelet count of < 80,000/mm^3 or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days

   e. METABOLIC ACIDOSIS

      pH ≤ 7.30 or base deficit ≥ 5.0 mEq/L or a plasma lactate level > 1.5 times the upper limit of normal

AND

5. Patient has an Apache II score of greater than 25 and less than 53 (http://www.sfar.org/scores2/apache22.html). Do not delay treatment while gathering data to calculate the Apache II score as long as the patient meets the other criteria in this document. The Apache II score should be completed as soon as possible, however.

B. Contraindications:

In the following situations, the use of drotrecogin alfa (activated) is not recommended.

1. Active internal bleeding
2. Recent (within 3 months) hemorrhagic stroke
3. Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization
4. Trauma patients with increased risk of life-threatening bleeding
5. Patients with an epidural catheter
6. Patients with intracranial neoplasm or mass lesion or evidence of cerebral herniation
7. Patients with known hypersensitivity to drotrecogin alfa (activated) or any component of the product
8. Life expectancy < 1 month or decision not to pursue aggressive medical care (*not in package insert; however, patients in this category were excluded from the pivotal study))*

C. Warnings

In the following conditions, the risks of administration should be weighed against the anticipated benefits.

1. Therapeutic heparin (≥ 15 units/kg/hr)
2. Platelet count < 30,000 X 10^6/L, even if the platelet count is increased after transfusions
3. Prothrombin time – INR > 3
4. Recent (within 6 weeks) gastrointestinal bleeding
5. Recent administration (within 3 days) of thrombolytic therapy
6. Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
7. Recent administration (within 7 days) of aspirin > 650mg per day or other platelet inhibitors
8. Recent (within 3 months) ischemic stroke
9. Patients with intracranial arteriovenous malformation or aneurysm
10. Known bleeding diathesis
11. Chronic sever hepatic disease
12. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
13. For patients who are pregnant or breast-feeding, use only if clearly needed
14. Single organ dysfunction and recent surgery (within 30 days)

D. Exclusions from the Pivotal Study

Since some groups of patients were excluded from the clinical trial by Bernard, appropriateness of use in these patients must be determined on a case-by-case basis, as safety and efficacy data are not currently available. The following are the groups that were excluded from the clinical trial by Bernard:

1. Pregnant or breast-feeding patients
2. Age < 18 years or weight > 135 kg
3. Platelet count < 30,000/mm^3
4. Conditions that increased the risk of bleeding: surgery requiring general or spinal anesthesia within 12 hours before the infusion, the potential need for such surgery during the infusion, or evidence of active bleeding postoperatively; a history of severe head trauma requiring hospitalization, intracranial surgery, or stroke within 3 months before the study or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or mass lesions of the central nervous system; a history of congenital bleeding diatheses; gastrointestinal bleeding within 6 weeks before the study unless corrective surgery had been performed; and trauma considered to increase the risk of bleeding
5. Known hypercoagulable condition, including resistance to activated protein C; hereditary deficiency of protein C, protein S, or antithrombin III; presence of anticardiolipin antibody, antiphospholipid antibody, lupus anticoagulant, or homocysteinemia; or recently documented (within 3 months before the study) or highly suspected deep-vein thrombosis or pulmonary embolism
6. Patient's family, physician, or both not in favor of aggressive treatment of patient or presence of an advanced directive to withhold life-sustaining treatment
7. Patient not expected to survive 28 days because of uncorrectable medical condition, such as poorly controlled neoplasm or other end-stage disease
8. Moribund state in which death was perceived to be imminent
9. Human immunodeficiency virus infection in association with a last known CD4 count of ≤ 50/mm^3
10. History of bone marrow, lung, liver, pancreas, or small-bowel transplantation
11. Chronic renal failure requiring hemodialysis or peritoneal dialysis*
12. Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites
13. Acute pancreatitis with no established source of infection
14. Use of any of the following medications or treatment regimens: unfractionated heparin treatment for an active thrombotic event within 8 hours before the infusion †; low-molecular-weight heparin at a higher dose than recommended for prophylactic use (as specified in the package insert) within 12 hours before the infusion; warfarin (if used within 7 days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution); acetylsalicylic acid at a dose of more than 650 mg/day within 3 days before the study; thrombolytic therapy within 3 days before the study ‡; glycoprotein IIb/IIIa antagonists within 7 days before study entry; antithrombin III at a dose of more

than 10,000 U within 12 hours before the study; or protein C within 24 hours before the study

* Acute renal failure was not an exclusion criterion

† Prophylactic treatment with a dose of unfractionated heparin of up to 15,000 U per day was permitted

‡ Thrombolytic agents were permitted for the treatment of thromboses within a catheter.

References:

1. Bernhard GR, Vincent JV, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Heltebrand JD, Ely W, and Fisher CJ, Jr., for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J of Med*; 344(10):699-709, 2001.

2. Drotrecogin alfa (activated) package insert (http://pi.lilly.com/us/xigris.pdf).

3. Apache II score http://www.sfar.org/scores2/apache22.html.

4. Dhainaut JF, Laterre PF, Janes JM, Bernard GR, et al. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multi-organ dysfunction: data from the PROWESS trial. Intensive Care Med 2003; 29: 894-903.