Criteria for Non-Formulary Use
Drotrecogin alfa [activated] (Xigris®)
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VHA Pharmacy Benefits Management Services and Medical Advisory Panel

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

Because of the potentially serious toxicity, lack of information for the wide spread use in high risk patients and the marginal efficacy 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 pulmonary, critical care, or infectious disease attending physician or other designee determined locally (e.g., critical care fellow). The following recommendations are provided for the use of drotrecogin alfa (activated) in VHA.

EXCLUSION CRITERIA (If one is selected, patient is NOT eligible)

Contraindications

- ❑ Active internal bleeding
- ❑ Recent (within 3 months) hemorrhagic stroke
- ❑ Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization
- ❑ Trauma with an increased risk of life-threatening bleeding
- ❑ Presence of an epidural catheter
- ❑ Intracranial neoplasm or mass lesion or evidence of cerebral herniation
- ❑ Known hypersensitivity to drotrecogin alfa (activated) or any component of the product
- ❑ Life expectancy < 1 month or decision not to pursue aggressive medical care

Bleeding-related warnings which led to exclusion from the phase III trial. Mortality and serious bleeding event rates were higher in patients with one of the following baseline bleeding-related warnings in a subsequent retrospective study.

- ❑ Concurrent therapeutic heparin at doses to treat an active thrombotic or embolic event
- ❑ Platelet count <30,000, even if the platelet count is increased after transfusions
- ❑ Recent (within 7 days) warfarin therapy and/or prothrombin time-INR >3.0, even if the INR is reversed (with fresh frozen plasma or vitamin K)
- ❑ Recent (within 6 weeks) gastrointestinal bleeding (unless corrective surgery had been performed)
- ❑ Recent administration (within 3 days) of thrombolytic therapy (except for treatment of thrombosed catheters)
- ❑ Recent administration (within 7 days) of aspirin (>650 mg/day) or other platelet inhibitors
- ❑ Recent administration (within 7 days) of glycoprotein IIb/IIIa inhibitors
- ❑ Recent administration (within 12 hours) of greater than 10,000 U of antithrombin III
- ❑ Recent (within 3 months) ischemic stroke
- ❑ Intracranial arterio-venous malformation or aneurysm
- ❑ Known bleeding diathesis
- ❑ Chronic severe hepatic disease (portal hypertension, cirrhosis, chronic jaundice or ascites)

INCLUSION CRITERIA

Suspected or proven infection (One of the following must be present for patient to be eligible)

Patient has known or suspected infection defined as:

- ❑ Positive culture (indicating infection rather than colonization or contamination)
- ❑ Abnormal number of neutrophils in a normally sterile body fluid
- ❑ Perforated viscus
- ❑ Radiological and clinical evidence of pneumonia
- ❑ Other syndrome with high probability of infection (e.g., ascending cholangitis)

Monitoring (The following must be selected for patient to be eligible)

- ❑ Patient is receiving continuous monitoring in the intensive care unit

SIRS (At least 3 of the 4 following criteria must be present for patient to be eligible)

Patient has three or more signs of systemic inflammatory response syndrome (SIRS) as defined as:

- ❑ Core temp of ≥ 100.4 F (38°C) or ≤ 96.8 F (36°C)
- ❑ HR of ≥90 beats/minute
- ❑ RR ≥ 20 breaths/min or $PaCO_2 \leq 32$ mmHg or mechanical ventilation for acute (not chronic) respiratory process
- ❑ WBC ≥ 12,000/mm^3 or ≤ 4,000/mm^3 or ≥ 10% immature neutrophils

Organ system dysfunction (At least 2 of the following must be present for patient to be eligible)

Patient has dysfunction of 2 or more organs or systems defined as:

- ❑ CARDIOVASCULAR: Arterial systolic BP ≤ 90mmHg **OR** a mean arterial pressure (MAP) ≤70mmHg for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status, **OR** the need for vasopressors to maintain systolic blood pressure (SBP) ≥ 90 mm HG or MAP ≥ 70 mm Hg
- ❑ RENAL: Urine output < 0.5 ml/kg/hr for > 1 hour, despite adequate fluid resuscitation
- ❑ RESPIRATORY: $PaO_2/FiO_2 \leq 200$
- ❑ HEMATOLOGIC: Platelet count < 80,000/mm^3 or decreased by 50% from highest value in the previous 72 hours
- ❑ METABOLIC: PH ≤ 7.30 or base deficit ≥ 5 mEq/L with plasma lactate > 1.5 times the upper limit of normal

APACHE II Score (must be selected for patient to be eligible)

Acute Physiology and Chronic Health Evaluation (APACHE) II Score:

- ❑ APACHE II ≥ 25 and < 53 as calculated on basis of physiologic and laboratory data obtained within the immediately preceding 24 hour period (http://www.sfar.org/scores2/apache22.html).
  No benefit of drotrecogin alfa has been demonstrated in patients with severe sepsis and low risk of death (e.g., APACHE score <25 or single organ dysfunction)

Acuity (must be selected for the patient to be eligible)

- ❑ Less than 48 hours after the onset of the first sepsis induced organ dysfunction

OTHER PRECAUTIONS

Warnings which did not lead to exclusion from the phase III trial

- ➢ Patients with single organ dysfunction and recent surgery (within 30 days) (all-cause mortality was higher in patients receiving drotrecogin compared to the placebo group)
- ➢ Any other condition in which bleeding is a significant hazard or would be particularly difficult to manage

The effectiveness of drotrecogin has not been established in patients with the following conditions, all of which led to exclusion from the phase 3 trial.

- ➢ Age < 18 years or weight > 135 kg (298 pounds)
- ➢ Patients who are pregnant or breastfeeding
- ➢ Surgery requiring general or spinal anesthesia within the preceding 12 hours, active post-operative bleeding, intra-cranial surgery within 3 months, or anticipated surgery requiring general or spinal anesthesia during the infusion
- ➢ Hypercoagulable condition
- ➢ Highly suspected deep venous thrombosis or pulmonary embolism
- ➢ Acute pancreatitis with no established source of infection
- ➢ HIV+ with ≤ 50 $CD4^+$ cells or status-post bone marrow, lung, liver, pancreas or small bowel transplant
- ➢ Chronic renal failure requiring hemodialysis or peritoneal dialysis (acute renal failure was not an exclusion)
- ➢ Recent (within 3 months) documented or highly suspected DVT or pulmonary embolism

Patient meets ***all*** inclusion criteria and does not have any exclusion criteria

- ❑ Yes

❑ No

INTRODUCTION
Drotrecogin alfa (activated) is a recombinant form of human activated protein C and is indicated to reduce mortality in adult patients with severe sepsis who have a high risk of death. The specific mechanism of drotrecogin alfa (activated) in improving survival in patients with severe sepsis is not completely understood. Severe sepsis is associated with a generalized inflammatory and procoagulant response to infection. Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. The most common adverse event with drotrecogin is an increased risk of bleeding.

CLINICAL STUDIES
The efficacy of Drotrecogin was studied in an international, multi-center, randomized, double-blind, placebo-controlled trial of 1690 patients with severe sepsis. Entry criteria included a systemic inflammatory response presumed due to infection and at least one associated acute organ dysfunction. Acute organ dysfunction was defined as one of the following: cardiovascular dysfunction (shock, hypotension, or the need for vasopressor support despite adequate fluid resuscitation); respiratory dysfunction (relative hypoxemia (PaO_2/FiO_2 ratio <250)); renal dysfunction (oliguria despite adequate fluid resuscitation); thrombocytopenia (platelet count < 80,000/mm3 or 50% decrease from the highest value the previous 3 days); or metabolic acidosis with elevated lactic acid concentrations. Patients received a 96 hour infusion of Drotrecogin at 24 µg/kg/hr or placebo starting within 48 hours after the onset of the first sepsis induced organ dysfunction. Exclusion criteria encompassed patients at high risk for bleeding (*see* **CONTRAINDICATIONS** and **WARNINGS**), patients who were not expected to survive for 28 days due to a pre-existing, non-sepsis related medical condition. The primary efficacy endpoint was all-cause mortality assessed 28 days after the start of study drug administration. Prospectively defined subsets for mortality analyses included groups defined by APACHE II Score. The APACHE II score was calculated from physiologic and laboratory data obtained within the 24-hour period immediately preceding the start of study drug administration irrespective of the preceding length of stay in the Intensive Care Unit. Baseline APACHE II score was correlated with risk of death; among patients receiving placebo, those with the lowest APACHE II scores had a 12% mortality rate, while those in the 2nd, 3rd, and 4th APACHE quartiles had mortality rates of 26%, 36% and 49%, respectively. The observed mortality difference between Drotrecogin and placebo was limited to the half of patients with higher risk of death, i.e., APACHE II score =25, the 3rd and 4th quartile APACHE II scores (Table 1).

Table : 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score

	Drotrecogin N (mortality%)	**Placebo N (mortality%)**	**Absolute mortality difference (%)**	**Relative Risk (RR)**	**95% CI for RR**
Overall	850 (25%)	840 (31%)	-6	0.81	0.70 – 0.93
APACHE II quartile (score)					
1st + 2nd (3 – 24)	436 (19%)	437 (19%)	0	0.99	0.75 – 1.30
3rd and 4th (25 – 53)	414 (31%)	403 (44%)	-13	0.71	0.59 – 0.85

CONTRAINDICATIONS and **WARNINGS** (see checklist for contra-indications and additional warnings)
Bleeding is the most common serious adverse effect associated with Drotrecogin therapy. Each patient being considered for therapy with Drotrecogin should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Should clinically important bleeding occur, immediately stop the infusion of Drotrecogin. Continued use of other agents affecting the coagulation system should be carefully assessed. Once adequate hemostasis has been achieved, continued use of Drotrecogin may be reconsidered. Drotrecogin should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedures with an inherent risk of bleeding. Once adequate hemostasis has been achieved,

initiation of Drotrecogin may be reconsidered 12 hours after major invasive procedures or surgery or restarted immediately after uncomplicated less invasive procedures.

In a separate analysis of the PROWESS data, all-cause mortality was higher with drotrecogin in patients with single organ dysfunction and recent surgery (within 30 days) compared to placebo. For drotrecogin, the 28-day and in-hospital mortality was 10/49 (20.4%) and 14/48 (29.2%) respectively compared to 8/49 (16.3%) and 8/47 (17.0%) respectively for the placebo group. The higher risk of all-cause mortality was also seen in a preliminary analysis of results from the ADDRESS study. In the subgroup with single organ dysfunction AND recent surgery, the 28-day and in-hospital mortality rate was 67/323 (20.7%) and 76/325 (23.4%) respectively in the drotrecogin group compared to 44/313 (14.1%) and 62/314(19.8%) respectively the placebo group.

The efficacy of drotrecogin alfa in patients with severe sepsis at a low risk of death (defined by an APACHE II score <25 or single organ dysfunction) was further evaluated in the randomized, double-blind, placebo-controlled ADDRESS trial. Based on an interim analysis (n=2613), drotrecogin alfa failed to demonstrate a mortality benefit in this population, with 28-day and in-hospital mortality rates of 18.5% and 20.6% respectively in the drotrecogin group compared to 17% and 20.5% respectively in the placebo group. Similar results were seen in the sub-group of patients with an APACHE II score <25 (n=2315; 88% of the population) with 28-day and in-hospital mortality rates of 16.9% and 18.9% respectively in the drotrecogin group compared to 16% and 18.7% respectively in the placebo group. Serious bleeding events occurred more frequently in patients treated with drotrecogin alfa (51/1317 (3.9%) vs. 28/1293 (2.2%). The study was terminated early due to no observed benefit.

In a retrospective chart review analysis of 73 patients with severe sepsis who received drotrecogin alfa, serious bleeding event and 30-day mortality rates were higher in patients with baseline bleeding-related warnings, as defined in the PROWESS trial and in the product labeling. Nearly half of the study population was comprised of veterans. Serious bleeding events occurred in 7/20 (35%) of patients with baseline bleeding-related warnings vs. 2/53 (3.8%) with no bleeding-related warnings ($p < 0.05$). Mortality at 30 days was 13/20 (65%) in patients with bleeding precautions, compared to 13/53 (24.5%) in patients without bleeding precautions ($p < 0.05$). FDA issued an Early Communication on February 4, 2009 about an ongoing safety review being conducted with the manufacturer to determine whether this information warrants any regulatory action.

PRECAUTIONS

Laboratory Tests

Most patients with severe sepsis have a coagulopathy that is commonly associated with prolongation of the activated partial thromboplastin time (APTT) and the prothrombin time (PT). Drotrecogin may variably prolong the APTT. Therefore, the APTT cannot be reliably used to assess the status of the coagulopathy during Drotrecogin infusion. Drotrecogin has minimal effect on the PT and the PT can be used to monitor the status of the coagulopathy in these patients.

REFERENCES

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2. Drotrecogin alfa (activated) package insert (http://pi.lilly.com/us/xigris.pdf).
3. Apache II score http://www.sfar.org/scores2/apache22.html.
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6. Gentry CA, Grosse KB, Sud B, et al. Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precautions. Crit Care Med. 2009;37(1):19-25.

7. Early communication about an ongoing safety review Xigris (drotrecogin alfa [activated]). February 4, 2009. http://www.fda.gov/CDER/drug/early_comm/drotrecogin_alfa.html (accessed February 25, 2009).

FURTHER DETAILS

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.

More details regarding drotrecogin are available in the presentation to the FDA Advisory Board (see http://www.fda.gov/ohrms/dockets/ac/01/slides/3797s1_01_Lilly-CORE/ and http://www.fda.gov/ohrms/dockets/ac/01/slides/3797s1_02_Forsyth/) and the formula for calculating APACHE II scores (http://www.sfar.org/scores2/apache22.html).

FDA Early Communication issued on February 4, 2009:
http://www.fda.gov/CDER/drug/early_comm/drotrecogin_alfa.html

The criteria checklist was initially prepared by VISN 22 and Greater Los Angeles VA Medical Center clinical staff. The VHA Infectious Diseases Program Office, Pulmonary & Critical Care Field Advisory Group, and Pharmacy Benefits Management - Medical Advisory Panel clinical staff assisted in its review.

VHA PBM Services Contact Person: Lisa Longo, PharmD, BCPS