



## Lilly Announces Withdrawal of Xigris® Following Recent Clinical Trial Results

INDIANAPOLIS, October 25, 2011 /PRNewswire/ --

Eli Lilly and Company announces withdrawal of its Xigris(R) [drotrecogin alfa (activated)] product in all markets following results of the PROWESS-SHOCK study, which showed the study did not meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients with septic shock. The company is working with regulatory agencies on this withdrawal, and is in the process of notifying health care professionals and clinical trial investigators.

"While there were no new safety findings, the study failed to demonstrate that Xigris improved patient survival and thus calls into question the benefit-risk profile of Xigris and its continued use," said Timothy Garnett, M.D., Lilly's Senior Vice President and Chief Medical Officer. "Patients currently receiving treatment with Xigris should have treatment discontinued, and Xigris treatment should not be initiated for new patients."

"We believe the original Xigris approval was appropriate and these recent results were quite unexpected," Garnett added. "A contributing factor to these study results could be advances in the standard of care for treating severe sepsis over the past 10 years."

Xigris was approved in the United States by the Food and Drug Administration (FDA) in November 2001, and was licensed in the European Union in 2002. The PROWESS-SHOCK study was initiated in March of 2008 as a condition for continued market authorization in Europe. Lilly committed to conduct a new placebo-controlled clinical trial to help refine appropriate patient identification for treatment with Xigris and to confirm the benefit-risk profile of the product.

BioCritica, Inc. has sales and marketing rights for Xigris in the United States and Puerto Rico, and Lilly sells and markets Xigris in other countries.

Patients, physicians, pharmacists, or other healthcare professionals with additional questions about Xigris should contact The Lilly Answer Center at 1-800-LillyRx or visit [www.Lilly.com](http://www.Lilly.com).

### About Severe Sepsis

Sepsis is a common and deadly disease(1). Severe sepsis can develop as a complication after common illnesses such as pneumonia and bacterial infections, and is characterized by an overwhelming systemic response to infection which can rapidly lead to organ failure and ultimately death.

### About Xigris

Xigris (drotrecogin alfa [activated]) is a recombinant form of human Activated Protein C. It is administered by intravenous infusion. Based on the results of the PROWESS study the U.S. Food and Drug Administration approved Xigris in November 2001 for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (e.g., as determined by APACHE II). Xigris is not indicated in adult patients with severe sepsis and a lower risk of death (e.g., APACHE II score <25). Xigris is not indicated in pediatric patients. In 2002, the EMA licensed Xigris for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care.

### IMPORTANT SAFETY INFORMATION

#### CONTRAINDICATIONS

Xigris increases the risk of bleeding. Xigris is contraindicated in the following clinical situations where bleeding could lead to significant morbidity or death:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke

- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

## WARNINGS and PRECAUTIONS

Bleeding is the most common serious adverse effect associated with Xigris therapy. Each patient being considered for therapy with Xigris should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Certain conditions, many of which led to exclusion from the Phase 3 trial (PROWESS), are likely to increase the risk of bleeding with Xigris therapy. Therefore, for patients with severe sepsis who have one or more of the following conditions, the increased risk of bleeding should be carefully considered when deciding whether to use Xigris therapy:

- Concurrent therapeutic dosing of heparin to treat an active thrombotic or embolic event
- Platelet count  $<30,000 \times 10^6/L$ , even if the platelet count is increased after transfusions
- Prothrombin time-INR  $>3.0$
- Recent (within 6 weeks) gastrointestinal bleeding
- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
- Recent administration (within 7 days) of aspirin  $>650$  mg per day or other platelet inhibitors
- Recent (within 3 months) ischemic stroke
- Intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis
- Chronic severe hepatic disease
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Should clinically important bleeding occur, immediately stop the infusion of Xigris. Continued use of other agents affecting the coagulation system should be carefully assessed. Once adequate hemostasis has been achieved, continued use of Xigris may be reconsidered.

## Mortality In Patients with Single Organ Dysfunction and Recent Surgery

Among the small number of patients in PROWESS, with single organ dysfunction and recent surgery (surgery within 30 days prior to study treatment), all-cause mortality was numerically higher in the Xigris group (28 day: 10/49; in hospital: 14/48) compared with the placebo group (28 day: 8/49; in hospital: 8/47).

In an analysis of the subset of patients with single organ dysfunction and recent surgery from the ADDRESS study, which enrolled septic patients not at high risk of death, all cause mortality was also higher in the Xigris group (28 day: 67/323; in hospital: 76/325) compared with the placebo group (28 day: 44/313; in hospital: 62/314). Single organ dysfunction patients with recent surgery may not be at high risk of death irrespective of APACHE II score. Therefore, these patients may not be among the indicated population.

#### Patients on Prophylactic Heparin when Xigris is Initiated

Clinicians should consider continuing heparin for venous thromboembolism (VTE) prophylaxis when initiating Xigris, unless discontinuation is medically necessary. In a randomized study of prophylactic heparin versus placebo in 1935 adult severe sepsis patients treated with Xigris, mortality and the rate of serious adverse events were increased in the subgroup of 434 patients whose heparin was stopped on study entry by randomization to placebo plus Xigris. This finding was based on prospectively defined exploratory subgroup analyses; however, the explanation for the finding is unclear. The safety of prophylactic heparin when concomitantly administered with Xigris in adult patients with severe sepsis was evaluated with low molecular weight heparin enoxaparin (40 mg every 24 hours) and unfractionated sodium heparin (5000 U every 12 hours), but was not evaluated with unfractionated sodium heparin 5000 U when dosed every 8 hours.

#### Invasive Procedures

Invasive procedures increase the risk for bleeding with Xigris. Such procedures, including arterial and central venous punctures, should be minimized during the Xigris infusion. Puncture of a noncompressible site should be avoided during the infusion. Xigris 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, Xigris may be restarted 12 hours after surgery and major invasive procedures or immediately after uncomplicated less invasive procedures.

#### ADVERSE REACTIONS

Bleeding is the most commonly reported adverse reaction in patients receiving Xigris therapy. Patients administered Xigris as treatment for severe sepsis experience many events which are potential sequelae of severe sepsis and may or may not be attributable to Xigris therapy. In severe sepsis clinical trials, there were no types of non-bleeding adverse events suggesting a causal association with Xigris. In the PROWESS study, serious bleeding events were observed during the 28-day study period in 3.5% of Xigris-treated and 2.0% of placebo-treated patients. The difference in serious bleeding occurred primarily during infusion.

The incidence of intracranial hemorrhage (ICH) during the study period was 0.2% for Xigris treated patients and 0.1% for placebo treated patients. ICH has been reported in patients receiving Xigris in non-placebo controlled trials with an incidence of approximately 1% during the infusion period. The risk of ICH may be increased in patients with risk factors for bleeding such as severe coagulopathy and severe thrombocytopenia.

\*APACHE (Acute Physiology And Chronic Health Evaluation).

DR HCP ISI 091010

For more information, see full prescribing information at <http://pi.lilly.com/us/xigris.pdf>.

#### About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at [www.lilly.com](http://www.lilly.com).

This press release contains forward-looking statements about Xigris and reflects Lilly's current beliefs. As with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Xigris(R) (drotrecogin alfa [activated]) is a registered trademark of Eli Lilly and Company

(1) Angus DC et al. Crit Care Med 2001; 29,: 1303-10

P-LLY

(Logo: <http://photos.prnewswire.com/prnh/20031219/LLYLOGO> )

CONTACT: Tina Gaines, +1-317-651-5567, Lilly Bio-Medicines Communications;  
Phil Johnson, +1-317-655-6874, Investor Relations

News Provided by Acquire Media