PV 3420 AMP

# Xigris™
# Drotrecogin alfa (activated)

## DESCRIPTION

Xigris™ (drotrecogin alfa (activated)) is a recombinant form of human Activated Protein C. An established human cell line possessing the complementary DNA for the inactive human Protein C zymogen secretes the protein into the fermentation medium. Fermentation is carried out in a nutrient medium containing the antibiotic geneticin sulfate. Geneticin sulfate is not detectable in the final product. Human Protein C is enzymatically activated by cleavage with thrombin and subsequently purified.

Drotrecogin alfa (activated) is a serine protease with the same amino acid sequence as human plasma-derived Activated Protein C. Drotrecogin alfa (activated) is a glycoprotein of approximately 55 kilodalton molecular weight, consisting of a heavy chain and a light chain linked by a disulfide bond. Drotrecogin alfa (activated) and human plasma-derived Activated Protein C have the same sites of glycosylation, although some differences in the glycosylation structures exist.

Xigris is supplied as a sterile, lyophilized, white to off-white powder for intravenous infusion. The 5 and 20 mg vials of Xigris contain 5.3 mg and 20.8 mg of drotrecogin alfa (activated), respectively. The 5 and 20 mg vials of Xigris also contain 40.3 and 158.1 mg of sodium chloride, 10.9 and 42.9 mg of sodium citrate, and 31.8 and 124.9 mg of sucrose, respectively.

## CLINICAL PHARMACOLOGY

### General Pharmacology

Activated Protein C exerts an antithrombotic effect by inhibiting Factors Va and VIIIa. *In vitro* data indicate that Activated Protein C has indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin-activatable-fibrinolysis-inhibitor. Additionally, *in vitro* data indicate that Activated Protein C may exert an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory responses within the microvascular endothelium.

### Pharmacodynamics

The specific mechanisms by which Xigris exerts its effect on survival in patients with severe sepsis are not completely understood. In patients with severe sepsis, Xigris infusions of 48 or 96 hours produced dose dependent declines in D-dimer and IL-6. Compared to placebo, Xigris treated patients experienced more rapid declines in D-dimer, PAI-1 levels, thrombin-antithrombin levels, prothrombin F1.2, IL-6, more rapid increases in protein C and antithrombin levels, and normalization of plasminogen. As assessed by infusion duration, the maximum observed pharmacodynamic effect of drotrecogin alfa (activated) on D-dimer levels occurred at the end of 96 hours of infusion for the 24 μg/kg/hr treatment group.

## Human Pharmacokinetics

Xigris and endogenous Activated Protein C are inactivated by endogenous plasma protease inhibitors. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits.

In patients with severe sepsis, Xigris infusions of 12 μg/kg/hr to 30 μg/kg/hr rapidly produce steady state concentrations ($C_{ss}$) that are proportional to infusion rates. In the phase 3 trial (*see* **CLINICAL STUDIES**), the median clearance of Xigris was 40 L/hr (interquartile range of 27 to 52 L/hr). The median $C_{ss}$ of 45 ng/mL (interquartile range of 35 to 62 ng/mL) was attained within 2 hours after starting infusion. In the majority of patients, plasma concentrations of Xigris fell below the assay's quantitation limit of 10 ng/mL within 2 hours after stopping infusion. Plasma clearance of Xigris in patients with severe sepsis is approximately 50% higher than that in healthy subjects.

## Special Populations

In adult patients with severe sepsis, small differences were detected in the plasma clearance of Xigris with regard to age, gender, hepatic dysfunction or renal dysfunction. Dose adjustment is not required based on these factors alone or in combination (*see* **PRECAUTIONS**).

*End stage renal disease*—Patients with end stage renal disease requiring chronic renal replacement therapy were excluded from the Phase 3 study. In patients without sepsis undergoing hemodialysis (n=6), plasma clearance (mean ± SD) of Xigris administered on non-dialysis days was 30 ± 8 L/hr. Plasma clearance of Xigris was 23 ± 4 L/hr in patients without sepsis undergoing peritoneal dialysis (n=5). These clearance rates did not meaningfully differ from those in normal healthy subjects (28 ± 9 L/hr) (n=190).

*Pediatrics*—Safety and efficacy have not been established in pediatric patients with severe sepsis (*see* **INDICATIONS AND USAGE**), therefore no dosage recommendation can be made. The pharmacokinetics of a dose of 24 μg/kg/hr of Xigris appear to be similar in pediatric and adult patients with severe sepsis.

*Drug-Drug Interactions*—Formal drug interactions studies have not been conducted.

## CLINICAL STUDIES

The efficacy of Xigris was studied in an international, multi-center, randomized, double-blind, placebo-controlled trial (PROWESS) of 1690 patients with severe sepsis.[1] 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 $< 80{,}000/mm^3$ 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 Xigris 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, HIV positive patients whose most recent $CD_4$ count was $\leq 50/mm^3$, patients on chronic dialysis, and patients who had undergone bone marrow, lung, liver, pancreas or small bowel transplantation.

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[2] (a score designed to assess risk of mortality based on acute physiology and chronic health evaluation, see http://www.sfar.org/scores2/scores2.html), protein C activity, and the number of acute organ dysfunctions at baseline. 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.

The study was terminated after a planned interim analysis due to significantly lower mortality in patients on Xigris than in patients on placebo (210/850, 25% vs. 259/840, 31% p=0.005, see Table 1).

Baseline APACHE II score, as measured in PROWESS, 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 Xigris 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). The efficacy of Xigris has not been established in patients with lower risk of death, e.g., APACHE II score < 25.

**Table 1: 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score[a]**

| | Xigris Total N[b] N[c] (%) | Placebo Total N N (%) | Absolute Mortality Difference (%) | Relative Risk (RR) | 95% CI for RR |
|---|---|---|---|---|---|
| **Overall** | 850 210 (25) | 840 259 (31) | -6 | 0.81 | 0.70, 0.93 |
| APACHE II quartile (score) | | | | | |
| **1st + 2nd (3-24)** | 436 82 (19) | 437 83 (19) | 0 | 0.99 | 0.75, 1.30 |
| **3rd + 4th (25-53)** | 414 128 (31) | 403 176 (44) | -13 | 0.71 | 0.59, 0.85 |

[a]For more information on calculating the APACHE II Score, see: http://www.sfar.org/scores2/scores2.html
[b]Total N = Total number of patients in group
[c]N = Number of deaths in group

Of measures used, the APACHE II score was most effective in classifying patients by risk of death and by likelihood of benefit from Xigris, but other important indicators of risk or severity also supported an association between likelihood of Xigris benefit and risk of death. Absolute reductions in mortality of 2%, 5%, 8% and 11% with Xigris were observed for patients with 1, 2, 3, and 4 or more organ dysfunctions, respectively. Similarly, each of the three major components of the APACHE II score (acute physiology score, chronic health score, age score) identified a higher risk population with larger mortality differences associated with treatment. That is, the

reduction in mortality was greater in patients with more severe physiologic disturbances, in patients with serious underlying disease predating sepsis, and in older patients.

Treatment-associated reductions in mortality were observed in patients with normal protein C levels and those with low protein C levels. No substantial differences in Xigris treatment effects were observed in subgroups defined by gender, ethnic origin, or infectious agent.

## INDICATIONS AND USAGE

Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II, *see* **CLINICAL STUDIES**).

Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

## CONTRAINDICATIONS

Xigris increases the risk of bleeding. Xigris is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- 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

Xigris is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product.

## WARNINGS

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, 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 heparin (≥15 units/kg/hr)
- Platelet count <30,000 x $10^6$/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 (*see* **CONTRAINDICATIONS**)
- 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.

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

## 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). Xigris may variably prolong the APTT. Therefore, the APTT cannot be reliably used to assess the status of the coagulopathy during Xigris infusion. Xigris has minimal effect on the PT and the PT can be used to monitor the status of the coagulopathy in these patients.

### Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Xigris has not been adequately determined, as the assay sensitivity is inadequate to reliably detect all potential antibody responses. One patient in the phase 2 trial developed antibodies to Xigris without clinical sequelae. One patient in the phase 3 trial who developed antibodies to Xigris developed superficial and deep vein thrombi during the study, and died of multi-organ failure on day 36 post-treatment but the relationship of this event to antibody is not clear.

Xigris has not been readministered to patients with severe sepsis.

### Drug Interactions

Drug interactions with Xigris have not been studied in patients with severe sepsis. Caution should be employed when Xigris is used with other drugs that affect hemostasis (*see* **CLINICAL PHARMACOLOGY**, **WARNINGS**). Approximately 2/3 of the patients in the phase 3 study received prophylactic low dose heparin. Concomitant use of prophylactic low dose heparin did not appear to affect safety. Its effect on the efficacy of Xigris has not been evaluated in a randomized controlled clinical trial.

### Drug/Laboratory Test Interaction

Because Xigris may affect the APTT assay, Xigris present in plasma samples may interfere with one-stage coagulation assays based on the APTT (such as factor VIII, IX, and XI assays). This interference may result in an apparent factor concentration that is lower than the true concentration. Xigris present in plasma samples does not interfere with one-stage factor assays based on the PT (such as factor II, V, VII, and X assays).

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate potential carcinogenicity of Xigris have not been performed.

Xigris was not mutagenic in an *in vivo* micronucleus study in mice or in an *in vitro* chromosomal aberration study in human peripheral blood lymphocytes with or without rat liver metabolic activation.

The potential of Xigris to impair fertility has not been evaluated in male or female animals.

### Pregnancy Category C

Animal reproductive studies have not been conducted with Xigris. It is not known whether Xigris can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xigris should be given to pregnant women only if clearly needed.

### Nursing Mothers

It is not known whether Xigris is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

The safety and effectiveness of Xigris have not been established in the age group newborn (38 weeks gestational age) to 18 years. The efficacy of Xigris in adult patients with severe sepsis and high risk of death cannot be extrapolated to pediatric patients with severe sepsis.

### Geriatric Use

In clinical studies evaluating 1821 patients with severe sepsis, approximately 50% of the patients were 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

## ADVERSE REACTIONS

### Bleeding

Bleeding is the most common adverse reaction associated with Xigris.

In the phase 3 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, respectively. The difference in serious bleeding between Xigris and placebo occurred primarily during the infusion period and is shown in Table 2.[1] Serious bleeding events were defined as any intracranial hemorrhage, any

life-threatening bleed, any bleeding event requiring the administration of ≥3 units of packed red blood cells per day for 2 consecutive days, or any bleeding event assessed as a serious adverse event.

**Table 2: Number of Patients Experiencing a Serious Bleeding Event by Site of Hemorrhage During the Study Drug Infusion Period[a] in PROWESS[1]**

| | Xigris N=850 | Placebo N=840 |
|---|---|---|
| **Total** | **20 (2.4%)** | **8 (1.0%)** |
| Site of Hemorrhage | | |
| Gastrointestinal | 5 | 4 |
| Intra-abdominal | 2 | 3 |
| Intra-thoracic | 4 | 0 |
| Retroperitoneal | 3 | 0 |
| Intracranial | 2 | 0 |
| Genitourinary | 2 | 0 |
| Skin/soft tissue | 1 | 0 |
| Other[b] | 1 | 1 |

[a]Study drug infusion period is defined as the date of initiation of study drug to the date of study drug discontinuation plus the next calendar day.

[b]Patients requiring the administration of ≥3 units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding.

In PROWESS, 2 cases of intracranial hemorrhage (ICH) occurred during the infusion period for Xigris treated patients and no cases were reported in the placebo patients. The incidence of ICH during the 28-day 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 (*see* **WARNINGS**).

In PROWESS, 25% of the Xigris-treated patients and 18% of the placebo-treated patients experienced at least one bleeding event during the 28-day study period. In both treatment groups, the majority of bleeding events were ecchymoses or gastrointestinal tract bleeding.

### Other Adverse Reactions

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 clinical trials, there were no types of non-bleeding adverse events suggesting a causal association with Xigris.

## OVERDOSAGE

There is no known antidote for Xigris. In case of overdose, immediately stop the infusion and monitor closely for hemorrhagic complications (*see* **Human Pharmacokinetics**).

## DOSAGE AND ADMINISTRATION

Xigris should be administered intravenously at an infusion rate of 24 μg/kg/hr for a total duration of infusion of 96 hours. Dose adjustment based on clinical or laboratory parameters is not recommended (*see* **PRECAUTIONS**).

If the infusion is interrupted, Xigris should be restarted at the 24 μg/kg/hr infusion rate. Dose escalation or bolus doses of Xigris are not recommended.

In the event of clinically important bleeding, immediately stop the infusion (*see* **WARNINGS**).

**Preparation and administration instructions: Use aseptic technique.**

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.
2. Calculate the dose and the number of Xigris vials needed. Each Xigris vial contains 5 mg or 20 mg of Xigris. The vial contains an excess of Xigris to facilitate delivery of the label amount.
3. Prior to administration, 5 mg vials must be reconstituted with 2.5 mL Sterile Water for Injection, USP, and 20 mg vials of Xigris must be reconstituted with 10 mL of Sterile Water for Injection, USP. The resulting concentration of the solution is approximately 2 mg/mL of Xigris. Slowly add the Sterile Water for Injection, USP to the vial and avoid inverting or shaking the vial. Gently swirl each vial until the powder is completely dissolved.
4. The solution of reconstituted Xigris must be further diluted with sterile 0.9% Sodium Chloride Injection. Slowly withdraw the appropriate amount of reconstituted Xigris solution from the vial. Add the reconstituted Xigris into a prepared infusion bag of sterile 0.9% Sodium Chloride Injection. When adding the Xigris into the infusion bag, direct the stream to the side of the bag to minimize the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag between locations using mechanical delivery systems.
5. Because Xigris contains no antibacterial preservatives, the intravenous solution should be prepared immediately upon reconstitution of the Xigris in the vial(s). If the vial of reconstituted Xigris is not used immediately, it may be held at controlled room temperature 15° to 30°C (59° to 86°F), but must be used within 3 hours. Intravenous administration must be completed within 12 hours after the intravenous solution is prepared.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
7. When using an intravenous infusion pump to administer the drug, the solution of reconstituted Xigris is typically diluted into an infusion bag containing sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 μg/mL and 200 μg/mL.

8. When using a syringe pump to administer the drug, the solution of reconstituted Xigris is typically diluted with sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 μg/mL and 1000 μg/mL. When administering Xigris at low concentrations (less than approximately 200 μg/mL) at low flow rates (less than approximately 5 mL/hr), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 mL/hr.
9. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen central venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Dextrose, or Dextrose and Saline mixtures.
10. Avoid exposing Xigris solutions to heat and/or direct sunlight. No incompatibilities have been observed between Xigris and glass infusion bottles or infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

## HOW SUPPLIED

Xigris is available in 5 mg and 20 mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated).

**Vials:**

5 mg Vials
NDC 0002-7559-01
20 mg Vials
NDC 0002-7561-01

Xigris should be stored in a refrigerator 2° to 8°C (36° to 46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

## REFERENCES

1. Bernard GR, et al. Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. *N Engl J Med*. 2001;344:699-709

2. Knaus WA, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29

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