PV 5652 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 may have indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and may exert an anti-inflammatory effect by limiting the chemotactic response of leukocytes to inflammatory cytokines, an inhibitory process mediated by leukocyte cell surface Activated Protein C receptor. In addition, *in vivo* data suggest Activated Protein C may reduce interactions between leukocytes and the microvascular endothelium. *In vitro* bacterial phagocytosis by neutrophils and monocytes is not affected.

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 with 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 mcg/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 mcg/kg/hr to 30 mcg/kg/hr rapidly produce steady-state concentrations (C_{ss}) that are proportional to infusion rates. In Study 1 (*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, renal dysfunction, or obesity. Dose adjustment is not required based on these factors alone or in combination (*see* **WARNINGS** *and* **PRECAUTIONS**).

End Stage Renal Disease — Patients with end stage renal disease requiring chronic renal replacement therapy were excluded from Study 1. 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 — Data from a placebo-controlled clinical trial in pediatric patients did not establish efficacy of Xigris (*see* **PRECAUTIONS** *and* **CLINICAL STUDIES**), therefore no dosage recommendation can be made for pediatric patients with severe sepsis.

Drug-Drug Interactions — In a randomized, double-blind, placebo-controlled trial in adult patients with severe sepsis (XPRESS), co-administration of Xigris (24 mcg/kg/hr for 96 hours) and prophylactic heparin (enoxaparin 40 mg every 24 hours or unfractionated sodium heparin 5000 U every 12 hours administered subcutaneously) did not alter the clearance and steady-state concentrations of Xigris. No dosage adjustment of Xigris is recommended when co-administered with prophylactic heparin.

CLINICAL STUDIES

Study 1

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 mcg/kg/hr or placebo starting within 48 hours after the onset of the first sepsis induced organ dysfunction. The median duration of organ dysfunction prior to treatment was 18 hours, and 89% of patients received study drug within 24 hours after onset of the first organ dysfunction. Exclusion criteria encompassed patients at high risk for bleeding (*see* **CONTRAINDICATIONS** *and* **WARNINGS: Bleeding**), 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 ≤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% versus 259/840, 31% p=0.005, see Table 1).

Baseline APACHE II score, as measured in Study 1, 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[b]	N[c] (%)	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 within 28 days 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.

Long-Term Follow-Up (Study 1)

The one-year survival status was provided for 93% of the 1690 Study 1 subjects. For patients with APACHE II score ≥25, mortality was lower for the Xigris group compared with the placebo group through 90-days (41% versus 52%; RR: 0.72, 95% CI: 0.59-0.88) and through 1 year (48% versus 59%; RR: 0.73, 95% CI: 0.60-0.88).

However, for patients with APACHE II score <25, mortality was higher for the Xigris group compared with the placebo group through 90-days (27% versus 25%; RR: 1.09, 95% CI: 0.84-1.42) and through 1 year (35% versus 28%; RR: 1.24, 95% CI: 0.97-1.58).

Study 2

A randomized, double-blind, placebo-controlled trial (ADDRESS) of Xigris (96-hour infusion of Xigris at 24 mcg/kg/hr) was performed in adult patients with severe sepsis who were not at high risk of death. Most patients had APACHE II score <25 or only one sepsis-induced organ failure. The study was stopped at an interim analysis after enrollment of 2640 patients due to futility. All-cause mortality at 28 days after randomization was 18% (243/1333) in patients randomized to Xigris and 17% (221/1307) in patients randomized to placebo (RR: 1.08, 95% CI: 0.91-1.27).

The results of Studies 1 and 2 do not provide evidence of benefit of Xigris in patients with severe sepsis who are not at high risk of death (e.g., patients with single-organ dysfunction or APACHE II score <25). Xigris is not indicated for such patients.

Study 3 (Pediatric Study)

A randomized, double-blind, placebo-controlled trial of Xigris (96-hour infusion at 24 mcg/kg/hr) was conducted in 477 pediatric patients with severe sepsis (age limits ≥38 weeks corrected gestational age to <18 years). Patients were required to have both sepsis-induced cardiovascular and respiratory organ dysfunction (defined as treatment with vasoactive agents despite adequate fluid resuscitation and invasive mechanical ventilation).

The study was stopped after a planned interim analysis showed Xigris was unlikely to show statistically significant improvement over placebo in the primary efficacy measure, a composite endpoint based on time to resolution of organ dysfunction (cardiovascular, respiratory, and renal), incorporating also unresolved organ dysfunction and mortality.

Central nervous system bleeding occurred in a greater number of Xigris-treated patients during the 28-day study period; this difference was most pronounced in patients aged 60 days or younger (≤60 days: 4/24 Xigris-treated patients versus 0/26 placebo-treated patients; >60 days: 7/216 Xigris-treated patients versus 5/211 placebo-treated patients).

All-cause mortality at 28 days, all serious bleeding events, all serious adverse events, fatal CNS bleeding events, and major amputations were similar in the Xigris and placebo groups.

The results of this study do not provide evidence of benefit of Xigris in pediatric patients with severe sepsis.

Study 4 (Heparin Study)

A randomized, double-blind, placebo-controlled trial (XPRESS) investigated the safety of prophylactic heparin when concomitantly administered with Xigris (96-hour infusion at 24 mcg/kg/hr) in adult patients with severe sepsis who were at high risk of death (n=1935).

Patients were randomized 1:1:2 to receive low molecular weight heparin enoxaparin (40 mg every 24 hours), unfractionated sodium heparin (5000 U every 12 hours), or placebo administered concomitantly with the Xigris infusion. Outside the Xigris treatment period (prior

to study entry and following Xigris infusion), the use of commercially available heparin was left to the discretion of the investigator.

The 28-day all-cause mortality was similar between heparin and placebo groups: individual heparin groups combined 28.2% (275/976), placebo 31.8% (305/959) (RR: 0.89, 95% CI: 0.77-1.02). There were no significant differences between the heparin and placebo groups in the rate of either venous thrombotic or serious bleeding events, including intracranial hemorrhage. Prophylactic heparin increased the risk of non-serious bleeding compared with placebo over the treatment period of 0-6 days.

In the subgroup of 889 patients receiving commercially available heparin at study entry, those patients randomized to placebo had higher mortality (placebo 35.5% (154/434) versus heparin 26.8% (122/455) and higher rate of serious adverse events (placebo 18.0% (78/434) versus heparin 11.6% (53/455) compared with patients in whom commercial heparin was replaced by study heparin (*see* **WARNINGS**). Increased serious adverse events in this subgroup included cardiac, gastrointestinal, and venous thrombotic events. In patients not receiving commercial heparin at study entry, mortality and the rate of serious adverse events were similar between heparin and placebo groups.

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**).

Xigris is not indicated in adult patients with severe sepsis and lower risk of death (*see* **CLINICAL STUDIES**). Xigris is not indicated in pediatric patients with severe sepsis (*see* **CLINICAL STUDIES**).

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

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 Study 1, are likely to increase the risk of bleeding with Xigris therapy. For individuals with 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 (*see* **PRECAUTIONS: Drug Interactions**)
- 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.

Invasive procedures increase the risk for bleeding among patients receiving Xigris. 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.

Mortality in Patients with Single Organ Dysfunction and Recent Surgery

Among the small number of patients enrolled in Study 1 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 a separate, randomized, placebo-controlled study (ADDRESS) of 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). Patients with single organ dysfunction and recent surgery may not be at high risk of death irrespective of APACHE II score and therefore not among the indicated population.

Clinicians should consider continuing prophylactic heparin when initiating Xigris therapy, unless discontinuation is considered 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 low-dose heparin was stopped on study entry by randomization to placebo. This finding was based on prospectively defined exploratory subgroup analyses; however, the explanation for the finding is unclear (*see* **CLINICAL STUDIES**).

PRECAUTIONS

General

Invasive procedures, including arterial and central venous punctures, should be minimized in order to decrease the risk for serious bleeding. Noncompressible puncture sites should be

avoided. Xigris should be discontinued prior to the performance of invasive surgical procedures or other procedures associated with special risks for bleeding (*see* **WARNINGS: Bleeding**).

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 Study 1 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

Since there is an increased risk of bleeding with Xigris, caution should be employed when Xigris is used with other drugs that affect hemostasis (*see* **CLINICAL PHARMACOLOGY** *and* **WARNINGS: Bleeding**).

Low-dose heparin for VTE prophylaxis may be co-administered with Xigris (*see* **WARNINGS** *and* **CLINICAL STUDIES**).

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

A placebo-controlled trial in pediatric patients did not establish the safety and effectiveness of Xigris in the pediatric patient population (*see* **CLINICAL STUDIES**).

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 Study 1, 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 included any intracranial hemorrhage, any life-threatening or fatal 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 Study 1[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 Study 1, two 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: Bleeding**).

In Study 1, 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.

Additional information on adverse events has been obtained in the controlled study of patients not at high risk of death (Study 2) and an open label, uncontrolled study of 2378 adult patients with severe sepsis that enrolled both patients at high risk of death and not at high risk of death. The incidence rates and nature of treatment-associated adverse events in Study 2 were generally similar to that seen on Study 1. In the open label, uncontrolled study, serious bleeding occurred in 3.6% of patients during the infusion period, and 6.5% during the 28 day study period. Intracranial hemorrhage occurred among 0.6% of patients during the infusion period and 1.5% within 28 days. Most of the post-infusion ICH events occurred within 1 week of the Xigris infusion, the relationship of these events to Xigris is uncertain.

In Study 4, a randomized trial (XPRESS) of low-dose heparin versus placebo in Xigris-treated severe sepsis patients, rates of serious bleeding, including ICH, were consistent with rates observed in previous studies. Low-dose heparin did not increase the risk of serious bleeding, including ICH. Low-dose heparin increased the risk of non-serious bleeding compared with placebo over the treatment period of 0-6 days (see Table 3). The rate of ischemic stroke was lower in the heparin group over days 0-6 (heparin 0.3% versus placebo 1.3%) and days 0-28 (heparin 0.5% versus placebo 1.8%).

Table 3: Bleeding Event Rates in Study 4

	Heparin plus Xigris N=976	**Placebo plus Xigris N=959**
Serious Bleeding Events[1] (%)		
Days 0-6	22 (2.3%)	24 (2.5%)
Days 0-28	38 (3.9%)	50 (5.2%)
ICH[2] (%)		
Days 0-6	3 (0.3%)	3 (0.3%)
Days 0-28	10 (1.0%)	7 (0.7%)
Overall Bleeding (Serious and Non-serious) Events (%)		
Days 0-6	105 (10.8%)	78 (8.1%)
Days 0-28	121 (12.4%)	105 (10.9%)

[1] Serious bleeding events included any fatal bleed, any life-threatening bleed, any CNS bleed, or any bleeding event assessed as serious by the investigator.

[2] ICH includes any bleed in the central nervous system, including the following types of hemorrhage — petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation.

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* **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**).

In postmarketing experience there have been a limited number of medication error reports of excessive rate of Xigris infusion for short periods of time (median 2 hours). No unexpected adverse events were observed during the overdose period. However, this information is insufficient to assess whether Xigris overdose is associated with an increased hemorrhage risk beyond that observed with Xigris administered at the recommended dose.

DOSAGE AND ADMINISTRATION

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

If the infusion is interrupted, Xigris should be restarted at the 24 mcg/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: Bleeding**).

Preparation and Administration Instructions:

1. Use appropriate aseptic technique during the preparation of Xigris for intravenous administration.
2. Calculate the approximate amount of Xigris needed based upon the patient's actual body weight and duration of this infusion period. The maximum duration of infusion from one preparation step is 12 hours. Multiple infusion periods will be needed to cover the entire 96-hour duration of administration.

   mg of Xigris = (patient weight, kg) X 24 mcg/kg/hr X (hours of infusion) ÷ 1000

   Round the actual amount of Xigris to be prepared to the nearest 5 mg increment to avoid discarding reconstituted Xigris.
3. Determine the number of vials of Xigris needed to make up this amount.
4. Reconstitute each vial of Xigris with Sterile Water for Injection, USP. The 5 mg vials must be reconstituted with 2.5 mL; the 20 mg vials with 10 mL. 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. The resulting Xigris concentration of the solution is 2 mg/mL.
5. Xigris contains no antibacterial preservatives; the intravenous solution should be prepared immediately after 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 20° to 25°C (68° to 77°F), but must be used within 3 hours.
6. Inspect the reconstituted Xigris in the vials for particulate matter and discoloration before further dilution. Do not use vials if particulate matter is visible or the solution is discolored.
7. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; Dextrose Injection, USP; and Dextrose and Sodium Chloride Injection, USP.
8. Avoid exposing Xigris solutions to heat and/or direct sunlight. Studies conducted at the recommended concentrations indicate the Xigris intravenous solution to be compatible with glass infusion bottles, and infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

Dilution and Administration Instructions for an Intravenous Infusion Pump Using an Infusion Bag:

1. Complete Preparation and Administration steps 1-8, then complete the next 6 steps.
2. The solution of reconstituted Xigris must be further diluted into an infusion bag containing 0.9% Sodium Chloride Injection, USP to a final concentration of between 0.1 mg/mL and 0.2 mg/mL. Bag volumes between 50 mL and 250 mL are typical.
3. Confirm that the intended bag volume will result in an acceptable final concentration.

   Final concentration, mg/mL = (actual Xigris amount, mg) ÷ (bag volume, mL)

   If the calculated final concentration is not between 0.1 mg/mL and 0.2 mg/mL select a different bag volume and recalculate the final concentration.
4. Slowly withdraw the reconstituted Xigris solution from the vial(s) and add the reconstituted Xigris into the infusion bag of 0.9% Sodium Chloride Injection, USP. When injecting 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 using mechanical transport systems such as pneumatic-tube systems that may cause vigorous agitation of the solution.
5. Calculate the actual duration of the infusion period for the diluted Xigris.

   Infusion period, hours = (actual Xigris amount, mg) X 1000 ÷ (patient weight, kg) ÷ 24 mcg/kg/hr

6. Account for the added volume of reconstituted Xigris (0.5 mL per mg of Xigris used) and the volume of bag saline solution removed (if saline solution is removed prior to adding the reconstituted Xigris).

   Final bag volume, mL = starting bag volume, mL + reconstituted Xigris volume, mL - saline volume removed (if any), mL

   Calculate the actual infusion rate of the diluted Xigris.

   Infusion rate, mL/hr = final bag volume, mL ÷ infusion period, hours

7. After preparation, the intravenous solution should be used at controlled room temperature 20° to 25°C (68° to 77°F) within 14 hours. If the intravenous solution is not administered immediately, the solution may be stored refrigerated 2° to 8°C (36° to 46°F) for up to 12 hours. If the prepared solution is refrigerated prior to administration, **the maximum time limit for use of the intravenous solution, including preparation, refrigeration, and administration, is 24 hours.**

Dilution and Administration Instructions for a Syringe Pump:

1. Complete Preparation and Administration steps 1-8, then complete the next 7 steps.
2. The solution of reconstituted Xigris must be further diluted with 0.9% Sodium Chloride Injection, USP to a final concentration of between 0.1 mg/mL and 1.0 mg/mL.
3. Confirm that the intended solution volume will result in an acceptable final concentration.

   Final concentration, mg/mL = (actual Xigris amount, mg) ÷ (solution volume, mL)

   If the calculated final concentration is not between 0.1 to 1.0 mg/mL select a different volume and recalculate the final concentration.

4. Slowly withdraw the reconstituted Xigris solution from the vial(s) into a syringe that will be used in the syringe pump. Into the same syringe, slowly withdraw 0.9% Sodium Chloride Injection, USP to obtain the desired final volume of diluted Xigris. Gently invert and/or rotate the syringe to obtain a homogeneous solution.
5. Calculate the actual duration of the infusion period for the diluted Xigris.

Infusion period, hours = (actual Xigris amount, mg) X 1000 ÷ (patient weight, kg) ÷ 24 mcg/kg/hr

6. Calculate the actual infusion rate of the diluted Xigris.

Infusion rate, mL/hr = (solution volume, mL) ÷ (infusion period, hours)

7. When administering Xigris using a syringe pump at low concentrations (less than approximately 0.2 mg/mL) with 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.
8. After preparation, the intravenous solution should be used at controlled room temperature 20° to 25°C (68° to 77°F) within 12 hours. **The maximum time limit for use of the intravenous solution, including preparation and administration, is 12 hours.**

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;13:818-829.

Literature revised April 27, 2007

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