

# Xigris<sup>®</sup>

## Drotrecogin alfa (activated)

### DESCRIPTION

Xigris<sup>®</sup> (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 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 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

48 of Xigris fell below the assay's quantitation limit of 10 ng/mL within 2 hours after stopping  
49 infusion. Plasma clearance of Xigris in patients with severe sepsis is approximately 50% higher  
50 than that in healthy subjects.

### 51 **Special Populations**

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

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

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

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

## 66 **CLINICAL STUDIES**

### 67 **Study 1**

68 The efficacy of Xigris was studied in an international, multi-center, randomized, double-blind,  
69 placebo-controlled trial (PROWESS) of 1690 patients with severe sepsis.<sup>1</sup> Entry criteria included  
70 a systemic inflammatory response presumed due to infection and at least one associated acute  
71 organ dysfunction. Acute organ dysfunction was defined as one of the following: cardiovascular  
72 dysfunction (shock, hypotension, or the need for vasopressor support despite adequate fluid  
73 resuscitation); respiratory dysfunction (relative hypoxemia ( $\text{PaO}_2/\text{FiO}_2$  ratio  $<250$ ));  
74 renal dysfunction (oliguria despite adequate fluid resuscitation); thrombocytopenia (platelet  
75 count  $<80,000/\text{mm}^3$  or 50% decrease from the highest value the previous 3 days); or metabolic  
76 acidosis with elevated lactic acid concentrations. Patients received a 96-hour infusion of Xigris  
77 at 24 mcg/kg/hr or placebo starting within 48 hours after the onset of the first sepsis induced  
78 organ dysfunction. Exclusion criteria encompassed patients at high risk for bleeding (*see*  
79 **CONTRAINDICATIONS and WARNINGS**), patients who were not expected to survive for  
80 28 days due to a pre-existing, non-sepsis related medical condition, HIV positive patients whose  
81 most recent CD<sub>4</sub> count was  $\leq 50/\text{mm}^3$ , patients on chronic dialysis, and patients who had  
82 undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.

83 The primary efficacy endpoint was all-cause mortality assessed 28 days after the start of study  
84 drug administration. Prospectively defined subsets for mortality analyses included groups  
85 defined by APACHE II score<sup>2</sup> (a score designed to assess risk of mortality based on acute  
86 physiology and chronic health evaluation, see <http://www.sfar.org/scores2/scores2.html>),  
87 protein C activity, and the number of acute organ dysfunctions at baseline. The APACHE II  
88 score was calculated from physiologic and laboratory data obtained within the 24-hour period  
89 immediately preceding the start of study drug administration irrespective of the preceding length  
90 of stay in the Intensive Care Unit.

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

94 Baseline APACHE II score, as measured in PROWESS, was correlated with risk of death;  
95 among patients receiving placebo, those with the lowest APACHE II scores had a 12% mortality  
96 rate, while those in the 2nd, 3rd, and 4th APACHE quartiles had mortality rates of 26%, 36%,

97 and 49%, respectively. The observed mortality difference between Xigris and placebo was  
 98 limited to the half of patients with higher risk of death, i.e., APACHE II score  $\geq 25$ , the 3rd and  
 99 4th quartile APACHE II scores (Table 1). The efficacy of Xigris has not been established in  
 100 patients with lower risk of death, e.g., APACHE II score  $< 25$ .  
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**Table 1: 28-Day All-Cause Mortality for All Patients and for Subgroups Defined by APACHE II Score<sup>a</sup>**

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

<sup>a</sup> For more information on calculating the APACHE II score, see: <http://www.sfar.org/scores2/scores2.html>

<sup>b</sup> Total N=Total number of patients in group.

<sup>c</sup> N=Number of deaths in group.

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106 Of measures used, the APACHE II score was most effective in classifying patients by risk of  
 107 death within 28 days and by likelihood of benefit from Xigris, but other important indicators of  
 108 risk or severity also supported an association between likelihood of Xigris benefit and risk of  
 109 death. Absolute reductions in mortality of 2%, 5%, 8%, and 11% with Xigris were observed for  
 110 patients with 1, 2, 3, and 4 or more organ dysfunctions, respectively. Similarly, each of the  
 111 three major components of the APACHE II score (acute physiology score, chronic health score,  
 112 age score) identified a higher risk population with larger mortality differences associated with  
 113 treatment. That is, the reduction in mortality was greater in patients with more severe  
 114 physiologic disturbances, in patients with serious underlying disease predating sepsis, and in  
 115 older patients.

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

119 **Long-Term Follow-Up (Study 1)**

120 The one-year survival status was provided for 93% of the 1690 PROWESS subjects. For  
 121 patients with APACHE II score  $\geq 25$ , mortality was lower for the Xigris group compared to the  
 122 placebo group through 90-days (41% versus 52%; RR: 0.72, 95% CI: 0.59-0.88) and through  
 123 1 year (48% versus 59%; RR: 0.73, 95% CI: 0.60-0.88).

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

127 **Study 2**

128 A randomized, double-blind, placebo-controlled trial (ADDRESS) of Xigris (96-hour infusion  
 129 of Xigris at 24 mcg/kg/hr) was performed in adult patients with severe sepsis who were not at  
 130 high risk of death. Most patients had APACHE II score  $< 25$  or only one sepsis-induced organ  
 131 failure. The study was stopped at an interim analysis after enrollment of 2640 patients due to  
 132 futility. All-cause mortality at 28 days after randomization was 18% (243/1333) in patients  
 133 randomized to Xigris and 17% (221/1307) in patients randomized to placebo (RR: 1.08, 95% CI:  
 134 0.91-1.27).

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

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## INDICATIONS AND USAGE

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

142 Xigris is not indicated in adult patients with severe sepsis and lower risk of death (*see*  
143 **CLINICAL STUDIES**). Safety and efficacy have not been established in pediatric patients with  
144 severe sepsis.

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## CONTRAINDICATIONS

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

- 149 • Active internal bleeding
- 150 • Recent (within 3 months) hemorrhagic stroke
- 151 • Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- 152 • Trauma with an increased risk of life-threatening bleeding
- 153 • Presence of an epidural catheter
- 154 • Intracranial neoplasm or mass lesion or evidence of cerebral herniation

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

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## WARNINGS

### Bleeding

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

162 Certain conditions, many of which led to exclusion from the Phase 3 trial, are likely to increase  
163 the risk of bleeding with Xigris therapy. For individuals with one or more of the following  
164 conditions, the increased risk of bleeding should be carefully considered when deciding whether  
165 to use Xigris therapy:

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

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

184 Xigris should be discontinued 2 hours prior to undergoing an invasive surgical procedure or  
185 procedures with an inherent risk of bleeding. Once adequate hemostasis has been achieved,

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

### 188 **Mortality in Patients with Single Organ Dysfunction and Recent Surgery**

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

193 In an analysis of the subset of patients with single organ dysfunction and recent surgery from a  
194 separate, randomized, placebo-controlled study (ADDRESS) of septic patients not at high risk of  
195 death, all-cause mortality was also higher in the Xigris group (28-day: 67/323; in-hospital:  
196 76/325) compared to the placebo group (28-day: 44/313; in-hospital: 62/314). Patients with  
197 single organ dysfunction and recent surgery may not be at high risk of death irrespective of  
198 APACHE II score and therefore not among the indicated population.

## 199 **PRECAUTIONS**

### 200 **Laboratory Tests**

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

### 206 **Immunogenicity**

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

214 Xigris has not been readministered to patients with severe sepsis.

### 215 **Drug Interactions**

216 Drug interaction studies with Xigris have not been performed in patients with severe sepsis.  
217 However, since there is an increased risk of bleeding with Xigris, caution should be employed  
218 when Xigris is used with other drugs that affect hemostasis (*see* **CLINICAL**  
219 **PHARMACOLOGY, WARNINGS**). Approximately 2/3 of the patients in the Phase 3 study  
220 received either prophylactic low dose heparin (unfractionated heparin up to 15,000 units/day) or  
221 prophylactic doses of low molecular weight heparins as indicated in the prescribing information  
222 for the specific products. Concomitant use of prophylactic low dose heparin did not appear to  
223 affect safety, however, its effects on the efficacy of Xigris have not been evaluated in an  
224 adequate and well-controlled clinical trial.

### 225 **Drug/Laboratory Test Interaction**

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

231 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

238 **Pregnancy Category C**

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

242 **Nursing Mothers**

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

247 **Pediatric Use**

248 The safety and effectiveness of Xigris have not been established in the age group newborn  
249 (38 weeks gestational age) to 18 years. The efficacy of Xigris in adult patients with severe sepsis  
250 and high risk of death cannot be extrapolated to pediatric patients with severe sepsis.

251 **Geriatric Use**

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

255 **ADVERSE REACTIONS**

256 **Bleeding**

257 Bleeding is the most common adverse reaction associated with Xigris.

258 In the Phase 3 study, serious bleeding events were observed during the 28-day study period in  
259 3.5% of Xigris-treated and 2.0% of placebo-treated patients, respectively. The difference in  
260 serious bleeding between Xigris and placebo occurred primarily during the infusion period and is  
261 shown in Table 2.<sup>1</sup> Serious bleeding events were defined as any intracranial hemorrhage, any  
262 life-threatening bleed, any bleeding event requiring the administration of  $\geq 3$  units of packed red  
263 blood cells per day for 2 consecutive days, or any bleeding event assessed as a serious adverse  
264 event.

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**Table 2: Number of Patients Experiencing a Serious Bleeding Event by Site of Hemorrhage During the Study Drug Infusion Period<sup>a</sup> In PROWESS<sup>1</sup>**

	<b>Xigris N=850</b>	<b>Placebo N=840</b>
<b>Total</b>	<b>20 (2.4%)</b>	<b>8 (1.0%)</b>
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 <sup>b</sup>	1	1

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<sup>a</sup> 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.  
<sup>b</sup> Patients requiring the administration of  $\geq 3$  units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding.

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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.

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**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.

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**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**).

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.

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**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**).

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

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

302 **Preparation and Administration Instructions:**

- 303 1. Use appropriate aseptic technique during the preparation of Xigris for intravenous  
304 administration.  
305 2. Calculate the approximate amount of Xigris needed based upon the patient's actual body  
306 weight and duration of this infusion period. The maximum duration of infusion from one  
307 preparation step is 12 hours. Multiple infusion periods will be needed to cover the entire  
308 96-hour duration of administration.

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$$\text{mg of Xigris} = (\text{patient weight, kg}) \times 24 \text{ mcg/kg/hr} \times (\text{hours of infusion}) \div 1000$$

311 Round the actual amount of Xigris to be prepared to the nearest 5 mg increment to avoid  
312 discarding reconstituted Xigris.

- 313 3. Determine the number of vials of Xigris needed to make up this amount.  
314 4. Reconstitute each vial of Xigris with Sterile Water for Injection, USP. The 5 mg vials must  
315 be reconstituted with 2.5 mL; the 20 mg vials with 10 mL. Slowly add the Sterile Water  
316 for Injection, USP to the vial and avoid inverting or shaking the vial. Gently swirl each  
317 vial until the powder is completely dissolved. The resulting Xigris concentration of the  
318 solution is 2 mg/mL.  
319 5. Xigris contains no antibacterial preservatives; the intravenous solution should be prepared  
320 immediately after reconstitution of the Xigris in the vial(s). If the vial of reconstituted  
321 Xigris is not used immediately, it may be held at controlled room temperature 20° to 25°C  
322 (68° to 77°F), but must be used within 3 hours.  
323 6. Inspect the reconstituted Xigris in the vials for particulate matter and discoloration before  
324 further dilution. Do not use vials if particulate matter is visible or the solution is  
325 discolored.  
326 7. Xigris should be administered via a dedicated intravenous line or a dedicated lumen of a  
327 multilumen venous catheter. The **ONLY** other solutions that can be administered through  
328 the same line are 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP;  
329 Dextrose Injection, USP; and Dextrose and Sodium Chloride Injection, USP.  
330 8. Avoid exposing Xigris solutions to heat and/or direct sunlight. Studies conducted at the  
331 recommended concentrations indicate the Xigris intravenous solution to be compatible  
332 with glass infusion bottles, and infusion bags and syringes made of polyvinylchloride,  
333 polyethylene, polypropylene, or polyolefin.  
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335 **Dilution and Administration Instructions for an Intravenous Infusion Pump Using**  
336 **an Infusion Bag:**

- 337 1. Complete Preparation and Administration steps 1-8, then complete the next 6 steps.  
338 2. The solution of reconstituted Xigris must be further diluted into an infusion bag containing  
339 0.9% Sodium Chloride Injection, USP to a final concentration of between 0.1 mg/mL and  
340 0.2 mg/mL. Bag volumes between 50 mL and 250 mL are typical.  
341 3. Confirm that the intended bag volume will result in an acceptable final concentration.  
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$$\text{Final concentration, mg/mL} = (\text{actual Xigris amount, mg}) \div (\text{bag volume, mL})$$

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345 If the calculated final concentration is not between 0.1 mg/mL and 0.2 mg/mL select a  
346 different bag volume and recalculate the final concentration.

- 347 4. Slowly withdraw the reconstituted Xigris solution from the vial(s) and add the  
348 reconstituted Xigris into the infusion bag of 0.9% Sodium Chloride Injection, USP. When  
349 injecting the Xigris into the infusion bag, direct the stream to the side of the bag to  
350 minimize the agitation of the solution. Gently invert the infusion bag to obtain a  
351 homogeneous solution. Do not transport the infusion bag using mechanical transport  
352 systems such as pneumatic-tube systems that may cause vigorous agitation of the solution.

- 353 5. Calculate the actual duration of the infusion period for the diluted Xigris.

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$$\text{Infusion period, hours} = (\text{actual Xigris amount, mg}) \times 1000 \div (\text{patient weight, kg}) \div$$
  
356 
$$24 \text{ mcg/kg/hr}$$

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

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$$\text{Final bag volume, mL} = \text{starting bag volume, mL} + \text{reconstituted Xigris volume, mL} -$$
  
363 
$$\text{saline volume removed (if any), mL}$$

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365 Calculate the actual infusion rate of the diluted Xigris.

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$$\text{Infusion rate, mL/hr} = \text{final bag volume, mL} \div \text{infusion period, hours}$$

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- 369 7. After preparation, the intravenous solution should be used at controlled room temperature  
370 20° to 25°C (68° to 77°F) within 14 hours. If the intravenous solution is not administered  
371 immediately, the solution may be stored refrigerated 2° to 8°C (36° to 46°F) for up to  
372 12 hours. If the prepared solution is refrigerated prior to administration, **the maximum**  
373 **time limit for use of the intravenous solution, including preparation, refrigeration,**  
374 **and administration, is 24 hours.**

375 **Dilution and Administration Instructions for a Syringe Pump:**

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

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$$\text{Final concentration, mg/mL} = (\text{actual Xigris amount, mg}) \div (\text{solution volume, mL})$$

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

- 385 4. Slowly withdraw the reconstituted Xigris solution from the vial(s) into a syringe that will  
386 be used in the syringe pump. Into the same syringe, slowly withdraw 0.9% Sodium  
387 Chloride Injection, USP to obtain the desired final volume of diluted Xigris. Gently invert  
388 and/or rotate the syringe to obtain a homogenous solution.

- 389 5. Calculate the actual duration of the infusion period for the diluted Xigris.

390

391 
$$\text{Infusion period, hours} = (\text{actual Xigris amount, mg}) \times 1000 \div (\text{patient weight, kg}) \div$$
  
392 
$$24 \text{ mcg/kg/hr}$$

393

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

395

396 
$$\text{Infusion rate, mL/hr} = (\text{solution volume, mL}) \div (\text{infusion period, hours})$$

- 397  
398 7. When administering Xigris using a syringe pump at low concentrations (less than  
399 approximately 0.2 mg/mL) with low flow rates (less than approximately 5 mL/hr), the  
400 infusion set must be primed for approximately 15 minutes at a flow rate of approximately  
401 5 mL/hr.  
402 8. After preparation, the intravenous solution should be used at controlled room temperature  
403 20° to 25°C (68° to 77°F) within 12 hours. **The maximum time limit for use of the**  
404 **intravenous solution, including preparation and administration, is 12 hours.**

405 **HOW SUPPLIED**

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

408 **Vials:**

- 409 5 mg Vials  
410 NDC 0002-7559-01  
411 20 mg Vials  
412 NDC 0002-7561-01

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

416 **REFERENCES**

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421 Literature revised ~~December 17, 2004~~Month dd, yyyy

422 **Eli Lilly and Company**  
423 **Indianapolis, IN 46285, USA**

424 **www.lilly.com**

425 **0.02 NL 3426 AMP**

PRINTED IN USA

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