PRODUCT MONOGRAPH

[Pr]XIGRIS®
drotrecogin alfa (activated)

Sterile Powder for Intravenous Injection 5 mg or 20 mg drotrecogin alfa (activated) per vial

Antithrombotic Profibrinolytic Anti-Inflammatory Enzyme

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Date of Approval:
August 20, 2009

Submission Control No: 128989

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Intravenous injection	5 mg or 20 mg per vial	Sucrose

*For a complete listing, see DOSAGE FORMS, COMPOSITION and PACKAGING section.

DESCRIPTION
XIGRIS [drotrecogin alfa (activated)] is a recombinant form of human Activated Protein C with the same amino acid sequence as human plasma-derived Activated Protein C. Drotrecogin alfa (activated) is secreted into the fermentation medium by an established human cell line modified by recombinant DNA technology. Human Protein C is enzymatically activated by cleavage with thrombin and subsequently purified.

INDICATIONS AND CLINICAL USE
XIGRIS [drotrecogin alfa (activated)] is indicated for 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, or multiple acute organ dysfunctions, see Part II: CLINICAL TRIALS section), when added to current best practice.

Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Xigris should not be used in this category of patients (see Part II: CLINICAL TRIALS section).

This product should be administered under the supervision of a qualified health professional who is experienced in the use of drugs used in the treatment and in the management of severe sepsis. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Geriatrics (> 65 years of age):
In clinical studies evaluating 1821 adult 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 (see ADVERSE REACTIONS, and Part II: CLINICAL TRIALS sections).

Pediatrics (<18 years of age):
Safety and efficacy have not been established in pediatric patients with severe sepsis. Therefore XIGRIS is not recommended for use in pediatric patients. (see PRECAUTIONS, ADVERSE REACTIONS, and Part II: CLINICAL TRIALS sections).

CONTRAINDICATIONS

XIGRIS [drotrecogin alfa (activated)] increases the risk of bleeding. XIGRIS is contraindicated in the following situations:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation.

XIGRIS is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product. (For a complete listing of ingredients, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.)

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Long-term studies in animals to evaluate potential carcinogenicity of XIGRIS [drotrecogin alfa (activated)] 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.

Hematologic

Bleeding is the most common serious adverse event associated with XIGRIS therapy. Serious bleeding includes intracranial hemorrhage (also described as central nervous system [CNS] bleeding), which has been reported in patients receiving XIGRIS in clinical trials (see ADVERSE REACTIONS, Bleeding Events subsection). Each patient being considered for therapy with XIGRIS should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Certain conditions increase the risk of bleeding with XIGRIS therapy. Post-marketing information confirms this possibility (Kanji et al., 2007 and Gentry et al., 2009). 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) (see DRUG INTERACTIONS and Part II: CLINICAL TRIALS sections).
- Heparin doses above those recommended for prophylaxis should not be used.
- Platelet count < 30,000 x 10^6/L, even if the platelet count is increased after transfusions.
- Prothrombin time - International Normalized Ratio (INR) >3.0.
- Recent (within 6 weeks) gastrointestinal bleeding (unless definitive intervention has been performed).
- Recent administration (within 3 days) of thrombolytic therapy.
- Recent administration (within 7 days) of glycoprotein IIb/IIIa inhibitors or oral anticoagulants.
- Recent administration (within 7 days) of aspirin > 650 mg per day or other platelet inhibitors.
- Recent (within 3 months) ischemic stroke (see CONTRAINDICATIONS section)
- Intracranial arteriovenous malformation or aneurysm.

- Raised intracranial pressure.
- Known bleeding diathesis except for acute coagulopathy related to sepsis.
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.
- Chronic severe hepatic disease.

For procedures with an inherent bleeding risk, XIGRIS should be discontinued for 2 hours prior to the start of the procedure. Once adequate hemostasis has been achieved, XIGRIS may be restarted immediately after uncomplicated less invasive procedures and XIGRIS may be restarted 12 hours after major invasive procedures or surgery.

As a component of routine care, measures of hemostasis (e.g., APTT, PT or platelet count) should be obtained during the infusion of XIGRIS. If during the infusion of XIGRIS, routine sequential tests of hemostasis indicate an uncontrolled or worsening coagulopathy that significantly increases the risk of bleeding, the benefits of continuing the infusion must be weighed against the potential increased risk of bleeding for that patient.

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 (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests subsection).

Unless considered medically necessary, prophylactic low-dose heparin should not be discontinued when drotrecogin alfa (activated) is added to the treatment of patients with severe sepsis. In a randomized study of prophylactic low-dose heparin versus placebo in 1935 adult severe sepsis patients treated with drotrecogin alfa (activated), discontinuation of prophylactic low-dose heparin was associated with increased mortality and risk of serious adverse events, including cardiac, gastrointestinal, and venous thrombotic events. The combination of prophylactic low-dose heparin and drotrecogin alfa (activated) did not affect mortality. In addition, the co-administration of prophylactic low-dose heparin and drotrecogin alfa (activated) was associated with a statistically significant increase in nonserious study-drug-related adverse events and in any bleeding events, primarily gastrointestinal or renal bleeding events, which occurred during Study Days 0 through 6 (see DRUG INTERACTIONS, ADVERSE REACTIONS, and Part II: CLINICAL TRIALS)

Hepatic

In patients with severe sepsis, the plasma clearance of XIGRIS was significantly decreased by hepatic dysfunction, but the magnitude of the differences in clearance (< 30%) does not warrant any dosage adjustment (see WARNINGS AND PRECAUTIONS, Special Populations subsection).

Immune

As with all therapeutic proteins, there is a potential for an immune response following treatment with XIGRIS. In patients with severe sepsis, the formation of anti-Activated Protein C antibodies was uncommon (<1%) after a single course of therapy. These antibodies were not capable of neutralizing the effect of either human plasma derived or recombinant human Activated Protein C on the activated partial thromboplastin time (APTT) assay. No anti-Activated Protein C antibody formation was detected in

healthy subjects, even after repeat administration up to 6 times (see DOSAGE AND ADMINISTRATION and ACTIONS AND CLINICAL PHARMACOLOGY sections).

Peri-Operative Considerations

Patients With Single Organ Dysfunction and Recent Surgery

In the randomized, placebo-controlled PROWESS (PROtein C Worldwide Evaluation in Severe Sepsis) trial, analysis showed that among the small number of patients with single organ dysfunction and surgery (within 30 days of study treatment), those treated with XIGRIS had numerically higher 28-day and in-hospital mortality rates than those treated with placebo (non-statistically significant) (see Table 1).

In the randomized, placebo-controlled ADDRESS [ADministration of DRotrecogin alfa (activated) in Early stage Severe Sepsis] trial (see Part II: CLINICAL TRIALS), post-hoc analyses showed that for the surgical subpopulation of the single organ dysfunction subgroup, the 28-day mortality rate was higher in the XIGRIS treatment arm compared to placebo, which was statistically significant (p-value unadjusted for multiple comparisons). For this same subpopulation of patients, those treated with XIGRIS had a numerically higher in-hospital mortality rate than placebo treated patients (non-statistically significant) (see Table 1).

In surgical patients, particularly those with single organ dysfunction, it may be difficult to distinguish between a patient with systemic inflammatory response syndrome (SIRS) and a patient with severe sepsis, thus patients with single organ dysfunction and recent surgery may not be at high risk of death irrespective of APACHE II score, and therefore XIGRIS should not be used in these patients.

Table 1: 28-Day All-Cause Mortality and In-Hospital Mortality for Surgical Patients With Single Organ Dysfunction in PROWESS and ADDRESS

	28-Day Mortality		In-Hospital Mortality	
	XIGRIS	**Placebo**	**XIGRIS**	**Placebo**
PROWESS	10/49	8/49	14/48	8/47
	p=0.60 †		p=0.16 †	
ADDRESS	67/323	44/313	76/325	62/314
	p=0.03 †		p=0.26 †	

† Chi-square test without adjustment for multiple comparisons.

Renal

In patients with severe sepsis, the plasma clearance of XIGRIS was significantly decreased by renal impairment, but the magnitude of the differences in clearance (< 30%) does not warrant any dosage adjustment (see WARNINGS AND PRECAUTIONS, Special Populations subsection).

Sexual Function/Reproduction

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

Special Populations

Pregnant Women:

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

Nursing Women:
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.

Pediatrics (<18 years of age):

Data from a placebo-controlled clinical trial in 477 patients (where the median age of patients enrolled was 2.6 years) did not establish the safety or efficacy of XIGRIS in pediatric patients (see Part II: CLINICAL TRIALS sections). Therefore XIGRIS is not recommended for use in pediatric patients (see INDICATIONS AND CLINICAL USE, ADVERSE REACTIONS).

Analysis of the data from this trial showed that while the rate of serious bleeding events (over the infusion period and over the 28-day study period) between the XIGRIS and placebo groups were similar, the rate of serious bleeding defined as central nervous system (CNS) bleeding was higher in the XIGRIS versus the placebo group. Over the infusion period (study days 0-6) the number of patients experiencing CNS bleeding was 5 versus 1 for the XIGRIS versus placebo groups, with 4 of the 5 events in the XIGRIS group occurring in patients ≤ 60 days or ≤ 3kg. Fatal CNS bleeding events, overall 28-day mortality, serious adverse events, and major amputations were similar in the XIGRIS and placebo groups.

Geriatrics (> 65 years of age):
In clinical studies evaluating 1821 adult 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 (see INDICATIONS AND CLINICAL USE, ADVERSE REACTIONS, and Part II: CLINICAL TRIALS sections).

Monitoring and Laboratory Tests
XIGRIS has minimal effect on the PT. Prolongation of the APTT in patients with severe sepsis receiving XIGRIS may be due to the underlying coagulopathy, the pharmacodynamic effect of XIGRIS, and/or the effect of other concurrent medications. The pharmacodynamic effect of XIGRIS on the APTT assay is dependent on the reagent and instrument used to perform the assay and the time that elapses between sample acquisition and assay performance. XIGRIS present in a plasma sample will be gradually neutralized by endogenous inhibitors. Virtually no measurable activity of XIGRIS is present 2 hours after obtaining the blood sample. Due to these biological and analytical variables, the APTT should not be used to assess the pharmacodynamic effect of XIGRIS. Similarly, approximately 2 hours after terminating the infusion of the drug, there is virtually no measurable activity of XIGRIS remaining in the circulation of the patient; blood samples drawn for APTT determination after this point are no longer affected by the drug. The interpretation of sequential determination of the PT and/or APTT should take these variables into consideration.

Because XIGRIS may affect the APTT assays, 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).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two placebo-controlled trials (the dose-ranging Phase 2 trial and pivotal Phase 3 trial [PROWESS]), 1821 adult patients with severe sepsis were evaluated. Patients ranged in age from 18 to 96 years (mean age of 60.5 years). Women and caucasians comprised 42% and 82% of the patient population, respectively. A total of 940 patients were randomized to and received XIGRIS [drotrecogin alfa (activated)]. Most patients (80%) received a dose of 24 µg/kg/hr administered as a constant rate infusion for 96 hours.

An additional 2378 adult patients with severe sepsis received XIGRIS in the Phase 3b multi-country, single-arm, open-label trial (ENHANCE).

The following adverse events have occurred in patients with severe sepsis who received XIGRIS:

Bleeding Events

Bleeding events are common in patients with severe sepsis. In the placebo-controlled Phase 2 and PROWESS trials, the percentage of patients experiencing at least one bleeding event in the XIGRIS and placebo treatment groups was 23.9% and 17.3%, respectively. In both treatment groups, the majority of bleeding events were gastrointestinal tract bleeding or ecchymosis. Bleeding events were more frequent in the XIGRIS treatment group at all levels of severity, as shown in Table 2.

Table 2: Maximum Severity of Bleeding Events Reported as Treatment-Emergent Adverse Events (One Severity Per Patient) During Infusion or Within Close Proximity to the End of Infusion

Severity of Bleeding	XIGRIS (N=940)	Placebo (N=881)
Mild	95 (10.1%)	65 (7.4%)
Moderate	48 (5.1%)	16 (1.8%)
Severe	25 (2.7%)	11 (1.2%)

Table 3 lists the percentage of patients in clinical trials who experienced serious bleeding events by site of hemorrhage during the study drug infusion period and during the 28-day study period. In the Phase 2, PROWESS and ENHANCE trials, serious bleeding events included any intracranial hemorrhage [also described as central nervous system (CNS) bleeding], 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 serious by the investigator. The difference in the incidence of serious bleeding events between the two treatment groups occurred primarily during study drug administration.

Table 3: Number of Patients Experiencing a Serious Bleeding Event by Site of Hemorrhage During Study Drug Infusion[1] and 28-day Study Period

	Infusion Period			28-day Study Period		
	Phase 2 and PROWESS trials (placebo-controlled)		ENHANCE (single-arm trial)	Phase 2 and PROWESS trials (placebo-controlled)		ENHANCE (single-arm trial)
Site of Hemorrhage	**XIGRIS (N=940)**	**Placebo (N=881)**	**XIGRIS (N=2378)**	**XIGRIS (N=940)**	**Placebo (N=881)**	**XIGRIS (N=2378)**
Gastrointestinal	7 (0.7%)	4 (0.5%)	19 (0.8%)	12 (1.3%)	10 (1.1%)	37 (1.6%)
Intra-abdominal	2 (0.2%)	3 (0.3%)	18 (0.8%)	3 (0.3%)	4 (0.5%)	28 (1.2%)
Intra-thoracic	4 (0.4%)	0	11 (0.5%)	6 (0.6%)	1 (0.1%)	20 (0.8%)
Retroperitoneal	3 (0.3%)	0	4 (0.2%)	4 (0.4%)	0	5 (0.2%)
CNS[2]	2 (0.2%)	0	15 (0.6%)	2 (0.2%)	1 (0.1%)	35 (1.5%)
Genitourinary	2 (0.2%)	0	0	2 (0.2%)	0	0
Skin/soft tissue	2 (0.2%)	0	16 (0.7%)	3 (0.3%)	0	23 (1.0%)
Nasopharyngeal	0	0	4 (0.2%)	0	0	5 (0.2%)
Joint/Bone	0	0	1 (0.04%)	0	0	3 (0.1%)
Site Unknown[3]	1 (0.1%)	1 (0.1%)	6 (0.3%)	2 (0.2%)	2 (0.2%)	10 (0.4%)
Total	23 (2.4%)*	8 (0.9%)	85[4] (3.6%)	34 (3.6%)	18 (2.0%)	155 (6.5%)

[1]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.
[2] CNS bleeding includes any bleed in the central nervous system including the following types of hemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation
[3]Patients requiring the administration of ≥3 units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding.
[4] In ENHANCE six patients experienced multiple serious bleeding events during the study drug infusion period (94 events observed in 85 patients).
* Statistically significantly different from placebo

CNS bleeding includes any bleed in the central nervous system including the following types of hemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation. In the PROWESS study, there was a 0.2% incidence rate of CNS bleeding that occurred during the infusion period for XIGRIS-treated patients. There were no CNS bleeds in the placebo group during the infusion period. The incidence of CNS bleeding during the 28-day study period was 0.2% and 0.1% for XIGRIS-treated and placebo-treated patients, respectively. All cases of CNS bleeds that occurred during infusion and at 28-days were fatal. No CNS bleeds were reported during the Phase 2 study.

In the single-arm trial (ENHANCE), the incidence of CNS bleeding during the infusion period was 0.6% (0.2% fatal) and during the 28-day study period was 1.5% (0.5% fatal).

Although the majority of CNS bleeding occurred in patients with risk factors for bleeding such as severe coagulopathy, severe thrombocytopenia and/or meningitis, the risk of CNS bleeding in **all** patients with these risk factors and treated with XIGRIS is unknown (see WARNINGS AND PRECAUTIONS section). The observed mortality rate for placebo-treated patients who had a platelet count <30,000/mm^3 prior to or during infusion in the Phase 3 PROWESS study was very high (16 of 19 patients died) while similar patients in the XIGRIS treatment arm had a lower mortality rate (5 of 15 died). A thorough risk/benefit

assessment must be performed for patients with severe coagulopathy, severe thrombocytopenia and/or meningitis.

Bleeding Events in ADDRESS Trial

In ADDRESS, the randomized, placebo-controlled trial (see Part II: CLINICAL TRIALS) in adult severe sepsis patients determined to be at low risk of death (the non-indicated population), the percentage of patients experiencing at least one bleeding event in XIGRIS-treated and placebo-treated patients was 10.9% and 6.4%, respectively ($p<0.001$). Bleeding events included serious bleeding events[1], bleeding events assessed as possibly study-drug related by the investigator, bleeding events associated with the need for a red blood cell transfusion, and bleeding events that led to permanent discontinuation of the study drug.

Table 4 lists the percent of patients experiencing serious bleeding events and CNS bleeding events in ADDRESS. The percent of patients experiencing a serious bleeding event by site of hemorrhage was similar to that observed in the Phase 2 and PROWESS trials.

Table 4: Serious Bleeding Event Rates in ADDRESS

	Study drug infusion period[2]		**28-day study period**	
	XIGRIS N=1317	Placebo N=1293	XIGRIS N=1317	Placebo N=1293
Serious bleeding events[1]	31 (2.4%)*	15 (1.2%)	51 (3.9%)*	28 (2.2%)
CNS bleeding events[3]	4 (0.3%)	3 (0.2%)	6 (0.5%)	5 (0.4%)
Fatal CNS bleeding events	0	1 (0.1%)	2 (0.2%)	1(0.1%)

[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] Study drug infusion period is defined as study Day 0 through study Day 6.
[3]CNS bleeding includes any bleed in the central nervous system, including the following types of hemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation.
*Statistically significantly different from placebo.

Bleeding Events in Pediatric Patients

Safety and efficacy have not been established in pediatric patients. In an uncontrolled, safety and pharmacokinetic study of XIGRIS, in pediatric patients with severe sepsis, the percentage of patients experiencing at least one bleeding event was 20.5% (17 of 83). The most common bleeding events were hemorrhage, ecchymosis, hemoptysis, lung hemorrhage, and hematuria. In addition, 4.8% of patients (4 of 83) experienced a serious bleeding event reported as a serious adverse event. The 4 patients each experienced one serious bleeding event (nasopharyngeal hemorrhage caused by the attempted placing of a nasogastric tube [Part 1]; cerebral petechial hemorrhage, gastrointestinal bleeding, and intracranial hemorrhage [Part 2]). The intracranial hemorrhage was considered by the investigator to be possibly related to study drug administration.

The mortality rate for this study was 9.6% (8 of 83); there were no patient deaths in Part 1 (0 of 21 patients) of the study and eight in Part 2 (8 of 62 patients).

Non-Bleeding Events in Pediatric Patients

The safety profile for non-bleeding adverse events in pediatric patients is similar to that seen in adults. Nearly all of the adverse events reported were expected clinical manifestations of severe sepsis (i.e. agitation, edema, oliguria, etc.).

Adverse Events by Body System

Table 5 summarizes adverse events (excluding bleeding events) that occurred at an incidence of ≥5% among XIGRIS-treated patients during infusion and during the 28-day study period.

Table 5: Adverse Events Occurring in ≥5% of XIGRIS-Treated Patients[a]

	Study Drug Infusion Period[b]		28-Day Study Period	
Body System/Adverse Event	**XIGRIS (N=940)**	**Placebo (N=881)**	**XIGRIS (N=940)**	**Placebo (N=881)**
Body as a Whole				
Infection	—	—	99 (10.5%)	99 (11.2%)
Sepsis	—	—	49 (5.2%)	43 (4.9%)
Pain	—	—	50 (5.3%)	40 (4.5%)
Cardiovascular				
Atrial Fibrillation	54 (5.7%)	56 (6.4%)	75 (8.0%)	75 (8.5%)
Digestive System				
Diarrhea	69 (7.3%)	54 (6.1%)	140 (14.9%)	115 (13.1%)
Vomiting	—	—	52 (5.5%)	41 (4.7%)
Nausea	—	—	49 (5.2%)	39 (4.4%)
Hematologic and Lymphatic System				
Anemia	53 (5.6%)	42 (4.8%)	70 (7.4%)	61 (6.9%)
Metabolic				
Generalized edema	—	—	49 (5.2%)	44 (5.0%)
Hypokalemia	—	—	47 (5.0%)	43 (4.9%)
Nervous System				
Confusion	—	—	68 (7.2%)	52 (5.9%)
Agitation	—	—	51 (5.4%)	68 (7.7%)
Respiratory System				
Pleural Effusion	—	—	72 (7.7%)	84 (9.5%)
Pneumonia	—	—	73 (7.8%)	63 (7.2%)
Skin and Appendages				
Rash	—	—	112 (11.9%)	121 (13.7%)
Skin Ulcer	—	—	68 (7.2%)	54 (6.1%)
Urogenital System				
Urinary tract infection	—	—	51 (5.4%)	52 (5.9%)

[a] None of the differences in event rates between XIGRIS and Placebo treatment were statistically significant
[b] There were only three non-bleeding events that occurred in >5% of patients treated with XIGRIS during the study drug infusion period.

Except for increased bleeding events, which may relate to the pharmacologic action of XIGRIS, the incidence of all other adverse events (Table 4-6) was comparable between the XIGRIS and placebo-treated

groups. There were no types of non-bleeding adverse events suggesting a causal association with XIGRIS.

Post-Market Adverse Drug Reactions

Bleeding Events in XPRESS Trial
In a randomized study comparing heparin and placebo in 1935 adult severe sepsis patients treated with drotrecogin alfa (activated) (see WARNINGS AND PRECAUTIONS and Part II: CLINICAL TRIALS sections), prophylactic low-dose heparin did not affect mortality, adversely affect the efficacy of drotrecogin alfa (activated) or increase the risk of serious haemorrhagic events, including central nervous system bleeding. The incidence of nonserious bleeding events was increased by low-dose heparin**.**

Table 6 lists bleeding rates from a randomized study (XPRESS) of low-dose heparin versus placebo in 1935 adult severe sepsis patients treated with drotrecogin alfa (activated). Serious bleeding rates were consistent with those observed in previous studies of drotrecogin alfa (activated). Low-dose heparin did not increase the risk of serious bleeding, including central nervous system bleeding. Low-dose heparin increased the risk of nonserious bleeding compared with placebo over the treatment period of 0-6 days.

Table 6: Bleeding Event Rates in XPRESS

	Study drug infusion period		**28-day study period**	
	Heparin plus Xigris N =976	**Placebo plus Xigris N = 959**	**Heparin plus Xigris N =976**	**Placebo plus Xigris N = 959**
Overall Bleeding (Serious and Non-serious) Events	**105 (10.8%)***	**78 (8.1%)**	**121 (12.4%)**	**105 (10.9%)**
Serious bleeding events[1]	**22 (2.3%)**	**24 (2.5%)**	**38 (3.9%)**	**50 (5.2%)**
CNS bleeding events[2]	**3 (0.3%)**	**3 (0.3%)**	**10 (1.0%)**	**7 (0.7%)**

[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]CNS bleeding includes any bleed in the central nervous system, including the following types of hemorrhage – petechial, parenchymal, subarachnoid, subdural, and stroke with hemorrhagic transformation.
*Statistically significantly different from placebo.

DRUG INTERACTIONS

Drug-Drug Interactions

Caution should be employed when XIGRIS is used with other drugs that affect hemostasis. Low-dose heparin for venous thrombotic event (VTE) prophylaxis may be co-administered with drotrecogin alfa (activated).

In a randomized study comparing heparin and placebo in 1935 adult severe sepsis patients treated with drotrecogin alfa (activated), prophylactic low-dose heparin did not affect mortality, adversely affect the efficacy of drotrecogin alfa (activated) or increase the risk of serious haemorrhagic events, including central nervous system bleeding. The incidence of nonserious bleeding events was increased by

prophylactic low-dose heparin. Prophylactic low-dose heparin, if already used, should not be discontinued when XIGRIS [drotrecogin alfa (activated)] is added to the treatment of patients with severe sepsis (See WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions sections, and Part II: CLINICAL TRIALS).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
For interactions between XIGRIS and laboratory tests, see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests subsection.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- In adult patients with severe sepsis, differences were detected in the plasma clearance of XIGRIS [drotrecogin alfa (activated)] with regard to age, gender, obesity, hepatic and renal dysfunction, or co-administration of low-dose heparin. However, the magnitude of these changes is not considered to be clinically significant and therefore dose adjustment is not required based on these factors alone or in combination.
- The pharmacokinetics of XIGRIS has not been studied in patients with severe sepsis and pre-existing end-stage renal disease or chronic hepatic disease.
- If the infusion is interrupted for any reason, XIGRIS should be restarted at the 24 µg/kg/hr infusion rate and continued to complete the recommended duration of infusion. Dose adjustments or bolus doses of XIGRIS are not recommended.
- **In the event of serious bleeding, immediately stop the infusion.**

Recommended Dose and Dosage Adjustment
XIGRIS should be administered intravenously at an infusion rate of 24 µg/kg/hr (based on actual body weight) for a total duration of infusion of 96 hours.

Administration
XIGRIS must be administered with an IV infusion pump or syringe pump.

Re-administration: There have been no Lilly-sponsored clinical trials in severe sepsis specifically studying drotrecogin alfa (activated) re-administration. There is very limited information regarding re-administration of drotrecogin alfa (activated) in severe sepsis patients. (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY sections).

Reconstitution:
Prior to administration, XIGRIS must be reconstituted with Sterile Water for Injection. The solution of reconstituted XIGRIS must be further diluted into an infusion bag containing sterile 0.9% Sodium Chloride Injection.

Co-administration of XIGRIS solution with other IV crystalloid solutions (0.9% Sodium Chloride Injection (isotonic saline), Lactated Ringer's Injection, or Dextrose and Saline mixtures) is acceptable.

Table 7: Dilution Table for Use with Infusion Pump

Vial Size (mg)	Volume of Sterile Water for Injection to be Added to Vial (mL)	Approximate Available Volume for Withdrawal (mL)	Diluents to be Used for Reconstitution	Solutions Which Can Be Administrated via the Same IV Line	*Recommended Final Concentration per mL
5	2.5	2.5	Sterile Water for Injection	0.9% Sodium Chloride for Injection; Lactated Ringer's Solution; Dextrose; Dextrose-saline mixtures	100-200 µg/mL
20	10	10			

* Refer to steps 8 & 9 for detailed instructions.

Table 8: Dilution Table for Use with Syringe Pump

Vial Size (mg)	Volume of Sterile Water to be Added to Vial (mL)	Approximate Available Volume for Withdrawal (mL)	Diluents to be Used for Reconstitution	Solutions Which Can Be Administrated via the Same IV Line	*Recommended Final Concentration per mL
5	2.5	2.5	Sterile Water for Injection	0.9% Sodium Chloride for Injection; Lactated Ringer's Solution; Dextrose; Dextrose-saline mixtures	100-200 µg/mL
20	10	10			

* Refer to steps 11 & 12 for detailed instructions.

Preparation and administration: 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 delivers 5 mg or 20 mg of XIGRIS. The vial contains an excess XIGRIS to facilitate delivery of the label amount.

3. Prior to administration, 5 mg vials of XIGRIS 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 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. For a summary of the reconstitution and dilution details, refer to the Tables 7 and 8.

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 kept at controlled room temperature 15° to 30°C, but must be used within 3 hours. After preparation in an IV bag, the intravenous solution must be used at controlled room temperature within 12 hours. If the intravenous solution is not administered immediately, the solution should be refrigerated for up to 12 hours; the total in-use time for the intravenous infusion bag solution, including dilution, refrigeration, and administration, should not exceed 24 hours.

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. 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.

9. 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 µg/kg/hr.

   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

   Note: After preparation in an IV bag, the intravenous solution must be used at controlled room temperature within 12 hours.

10. When using a syringe pump to administer the drug, the solution of reconstituted XIGRIS should be diluted with sterile 0.9% Sodium Chloride Injection to a final concentration of between 100 µg/mL and 200 µg/mL. Invert and/or rotate the syringe to obtain a homogeneous solution, but avoid excessive agitation. When administering XIGRIS 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.

11. 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 mg/ml and 0.2 mg/ml, select a different volume and recalculate the final concentration.

12. 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 µg/kg/hr.

13. After preparation in a syringe, the intravenous solution should be used at room temperature (15 to 30C) within 12 hours. If the intravenous solution is not administered immediately, the solution should be refrigerated at 2º to 8 º C 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 dilution, refrigeration, and administration, is 24 hours.

14. 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.

15. 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.

OVERDOSAGE

In the post-marketing experience, accidental overdoses have been reported. Adverse events associated with the overdose have been observed. The observed adverse events were consistent with known effects of the drug and/or sequelae of the underlying condition of sepsis.

There is no known antidote for XIGRIS. In case of overdose, immediately stop the infusion and monitor closely for hemorrhagic complications (see ACTION AND CLINICAL PHARMACOLOGY section).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Drotrecogin alfa (activated) is a recombinant version of Activated Protein C and is produced by genetic engineering from an established human cell line.

Severe sepsis, defined as sepsis associated with acute organ dysfunction, results from the activation of multiple inflammatory pathways recognized clinically as the systemic inflammatory response syndrome (SIRS). More specifically, sepsis induces a procoagulant, inflammatory and antifibrinolytic state; both the procoagulant and antifibrinolytic responses to infection are tightly linked to inflammation; proinflammatory cytokines (e.g., tumour necrosis factor, interleukin-1) are capable of activating coagulation and impairing fibrinolysis.

The specific mechanisms by which Activated Protein C exerts its effect on survival in patients with severe sepsis are not completely understood. Microcirculation is dependent on a homeostatic balance between

procoagulant and anticoagulant pathways, and interactions between leukocytes and the endothelium. It is hypothesized that Activated Protein C adjusts this balance by affecting several pathways. *In vivo*, thrombin binds to endothelial thrombomodulin, which converts Protein C to Activated Protein C. Thrombin is also one of many factors capable of stimulating multiple inflammatory and antifibrinolytic pathways. Activated Protein C exerts an antithrombotic effect by inhibiting Factors Va and VIIIa, key factors in the coagulation cascade. *In vitro* data also indicate that therapeutic concentrations of Activated Protein C exert an anti-inflammatory effect by limiting the chemotactic response of leukocytes to inflammatory cytokines, an inhibitory process mediated by the leukocyte cell surface Activated Protein C receptor. In addition, *in vivo* data using therapeutic doses of Activated Protein C show reduced interactions between leukocytes and the microvascular endothelium while other leukocyte functions, such as bacterial phagocytosis, are not affected. At supra-therapeutic concentrations, *in vitro* data also indicate that Activated Protein C has indirect profibrinolytic activity due to its ability to inhibit plasminogen activator inhibitor-1 (PAI-1). In sepsis, Protein C concentrations decrease rapidly; observational studies have shown that decreased Protein C is associated with increased morbidity and mortality.

Pharmacodynamics

In two placebo-controlled trials by Derhaschnig et al. and Kalil et al. (see Part II: REFERENCES), in a total of 42 healthy subjects receiving a single dose of intravenous endotoxin, drotrecogin alfa (activated) did not inhibit the early cytokine response (as measured by TNF, IL-1, IL-6, IL-8) to endotoxin. In the study by Kalil et al. (n=17), drotrecogin alfa (activated) prevented the development of endotoxin-induced hypotension. In another placebo-controlled trial by Nick et al. (see Part II: REFERENCES), in 16 healthy subjects receiving a single dose of intra-pulmonary endotoxin, drotrecogin alfa (activated) did not inhibit the early cytokine response to endotoxin, but decreased neutrophil accumulation in the alveolar space. Drotrecogin alfa (activated) did not reduce the endotoxin-induced elevation of PAI-1 levels in these three placebo-controlled studies in healthy subjects.

In placebo controlled clinical trials in patients with severe sepsis, drotrecogin alfa (activated) exerted an antithrombotic effect by limiting thrombin generation and improved sepsis-associated coagulopathy, as shown by a more rapid improvement in markers of coagulation and fibrinolysis. Compared to placebo, drotrecogin alfa (activated) caused a more rapid decline in thrombotic markers such as D-dimer, prothrombin F1.2, and thrombin-antithrombin levels and a more rapid increase in Protein C and antithrombin levels. Drotrecogin alfa (activated) also restored endogenous fibrinolytic potential, as evidenced by a more rapid trend toward normalization in plasminogen levels and a more rapid decline in PAI-1 levels. Additionally, patients with severe sepsis treated with drotrecogin alfa (activated) had a more rapid decline in IL-6 levels indicating a reduction in the inflammatory response. Drotrecogin alfa (activated) had no effect on TNF, IL-1, IL-8, and IL-10 levels compared to placebo.

In healthy subjects, administration of drotrecogin alfa (activated) produced a dose-proportional increase in the bedside whole blood activated partial thromboplastin time (APTT). Following cessation of a 24 µg/kg/hr infusion of drotrecogin alfa (activated), the average time for the APTT response to fall to within 25% of the pre-dose (baseline) value was 53 minutes. Administration of drotrecogin alfa (activated) to healthy subjects was associated with a prolongation of less than 3 seconds in the bedside whole blood prothrombin time (PT).

Pharmacokinetics

Drotrecogin alfa (activated) and endogenous human Activated Protein C are inactivated by endogenous plasma protease inhibitors; the mechanism by which these are cleared from plasma is unknown in humans.

Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits and do not influence the pharmacokinetics of drotrecogin alfa (activated).

Absorption and Distribution:
In healthy subjects, greater than 90% of the steady-state plasma concentration is attained within 2 hours following the start of a constant-rate intravenous infusion of drotrecogin alfa (activated). Plasma Activated Protein C steady-state concentrations (C_{ss}) are proportional to the infusion rate over a range of infusion rates from 12 μg/kg/hr to 48 μg/kg/hr. The mean steady-state plasma concentration of drotrecogin alfa (activated) in healthy subjects receiving 24 μg/kg/hr is 72 ng/mL.

In patients with severe sepsis, drotrecogin alfa (activated) infusions of 12 μg/kg/hr to 30 μg/kg/hr rapidly produce steady state concentrations that are proportional to infusion rates. The median C_{ss} of 45 ng/mL (interquartile range of 35 to 62 ng/mL) was attained within 2 hours after starting infusion. The mean C_{ss} (± standard deviation), after censoring of the data to remove abnormally high outlier values, was 53.7 ± 34.1 ng/mL.

Metabolism:
For healthy patients, following the completion of an infusion, the decline in plasma Activated Protein C concentration is biphasic and is comprised of a rapid initial phase ($t_{1/2\alpha}$=13 minutes) and a slower second phase ($t_{1/2\beta}$=1.6 hours). The short half-life of 13 minutes accounts for approximately 80% of the area under the plasma concentration curve and governs the initial rapid accrual of plasma Activated Protein C concentrations towards the steady-state.

Excretion:
In the Phase 3 trial, in patients with severe sepsis (see Part II: CLINICAL TRIALS section), the median clearance of drotrecogin alfa (activated) was 40 L/hr (interquartile range of 27 to 52 L/hr). In the majority of patients, plasma concentrations of drotrecogin alfa (activated) fell below the assay's quantitation limit of 10 ng/mL within 2 hours after stopping the infusion. Plasma clearance of drotrecogin alfa (activated) in patients with severe sepsis is approximately 50% higher than that in healthy subjects. This may reflect the higher levels of endogenous plasma protease inhibitors associated with sepsis, although this has not been confirmed.

Additional Information on Immunogenicity
In adult patients in severe sepsis clinical studies, the frequency of anti-human Activated Protein C IgA/IgG/IgM antibodies or neutralizing antibodies is low and is similar between drotrecogin alfa (activated)- and placebo-treated patients tested. No apparent correlation of antibody development to adverse reactions was observed. There was no evidence that the antibodies detected represented a specific immune response to drotrecogin alfa (activated) therapy.

Samples available from six adult severe sepsis patients who had received a prior course of drotrecogin alfa (activated) were subsequently tested and all were negative for anti-human Activated Protein C antibody (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections).

Special Populations and Conditions
In adult patients with severe sepsis, differences were detected in the plasma clearance of drotrecogin alfa (activated) with regard to age, gender, obesity and hepatic and renal dysfunction. However, the magnitude

of these changes is not considered to be clinically significant and therefore dose adjustment is not required based on these factors alone or in combination (see DOSAGE AND ADMINISTRATION section).

Pediatrics:
Safety and efficacy have not been established in pediatric patients. Therefore XIGRIS is not recommended for use in pediatric patients. The limited data available in pediatric patients indicate that the pharmacokinetics of an infusion of drotrecogin alfa (activated) at a rate of 24 μg/kg/hr appear to be similar to that in adult patients with severe sepsis (see INDICATIONS AND CLINICAL USE, PRECAUTIONS, ADVERSE REACTIONS, and Part II: CLINICAL TRIALS sections).

Geriatrics:
In clinical studies evaluating 1821 adult 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 (see ADVERSE REACTIONS, and Part II: CLINICAL TRIALS sections).

Hepatic Insufficiency:
The pharmacokinetics of drotrecogin alfa (activated) has not been studied in patients with severe sepsis and pre-existing end-stage chronic hepatic disease (see WARNINGS AND PRECAUTIONS, Hepatic subsection).

Renal Insufficiency:
The pharmacokinetics of drotrecogin alfa (activated) has not been studied in patients with severe sepsis and pre-existing end-stage renal disease (see WARNINGS AND PRECAUTIONS, Renal subsection).

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 drotrecogin alfa (activated) administered on non-dialysis days was 30 ± 8 L/hr. Plasma clearance of drotrecogin alfa (activated) 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).

STORAGE AND STABILITY
XIGRIS [drotrecogin alfa (activated)] should be stored in a refrigerator (2° to 8°C). Do not freeze. Protect unreconstituted vials of XIGRIS from light by retaining the vial in the carton until time of use.

SPECIAL HANDLING INSTRUCTIONS
Avoid exposing XIGRIS [drotrecogin alfa (activated)] solutions to heat and/or direct sunlight. Because XIGRIS contains no antibacterial preservatives, the IV 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 stored at room temperature (15 to 30°C), but must be used within 3 hours. After preparation in an IV bag, the intravenous solution must be used at controlled room temperature within 12 hours. If the intravenous solution is not administered immediately, the solution should be stored refrigerated for up to 12 hours; the total in-use time for the infusion bag solution, including dilution, refrigeration, and administration, should not exceed 24 hours. After preparation in a syringe, the intravenous solution must be used at controlled room temperature within 12 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

XIGRIS [drotrecogin alfa (activated)] is supplied as a sterile, lyophilized white to practically-white powder for intravenous infusion and is freely soluble in Water for Injection USP or 0.9% Sodium Chloride Injection USP.

XIGRIS is available in 5 mg and 20 mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated). Each vial of XIGRIS delivers 5 mg or 20 mg of drotrecogin alfa (activated). Other ingredients include sucrose, sodium chloride, citrate (buffer system composed of citric acid, sodium citrate, hydrochloric acid and sodium hydroxide), hydrochloric acid, if necessary, and sodium hydroxide, if necessary.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Drotrecogin alfa (activated)

Chemical name: Drotrecogin alfa (activated) is a recombinant form of human Activated Protein C with the same amino acid sequence as human plasma-derived Activated Protein C.

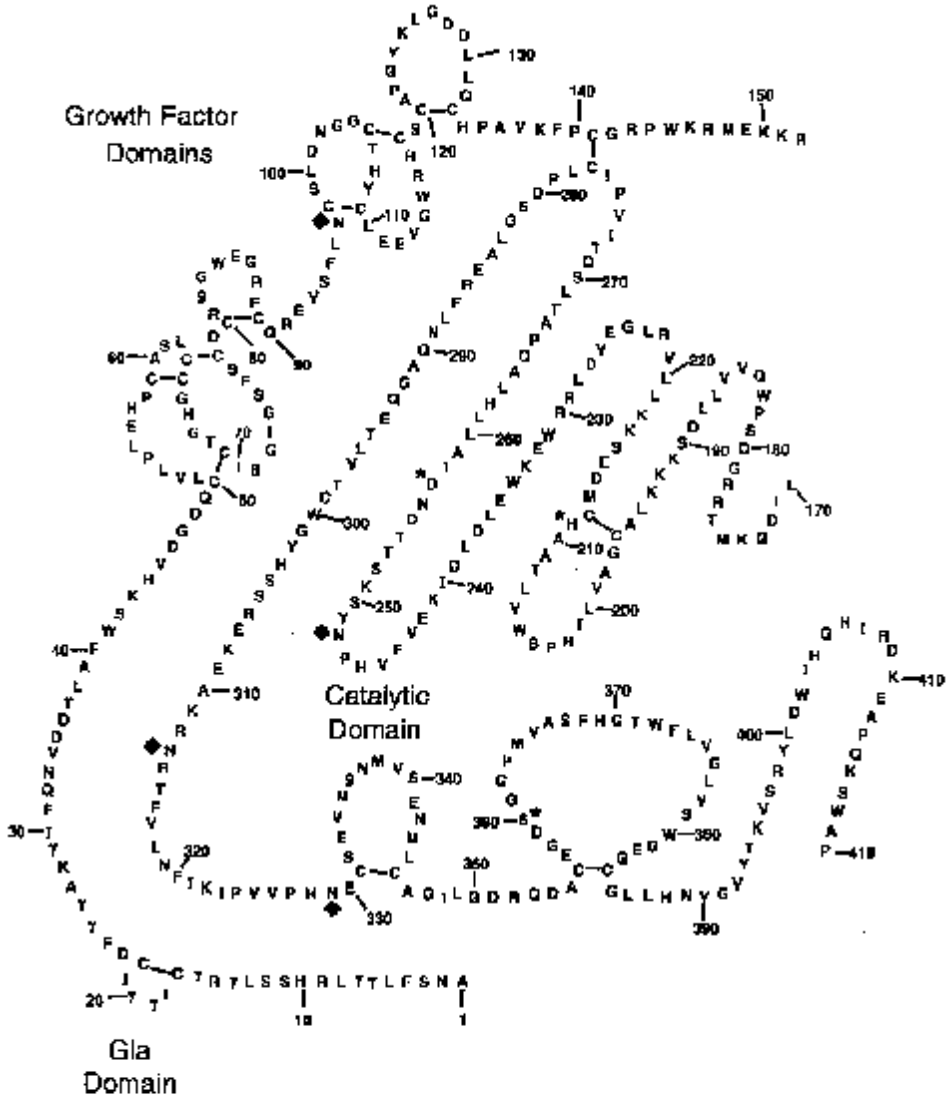
Molecular formula and molecular mass:

Drotrecogin alfa (activated) is comprised of a variety of glycoforms and three major protein variant forms that are due to heterogeneity at the C-terminus of the light chain. The molecular formulas for the protein portion of the three major protein variant forms comprising drotrecogin alfa (activated) are as follows:

Light chain 1-150/Heavy chain 170-419	$C_{1988}H_{3035}N_{553}O_{608}S_{31}$
Light chain 1-151/Heavy chain 170-419	$C_{1994}H_{3047}N_{555}O_{609}S_{31}$
Light chain 1-152/Heavy chain 170-419	$C_{2000}H_{3059}N_{559}O_{610}S_{31}$

Molecular Weight:	Approximately 46 kD excluding carbohydrate. Approximately 55 kD including carbohydrate.

Structural formula:



◆ = Glycosylation sites
* = Catalytic triad
β = β-hydroxyaspartic acid
γ = γ-carboxyglutamic acid

Physicochemical properties:

Description:	The drug substance is a bulk frozen solution containing approximately 10 mg drotrecogin alfa (activated) per mL in 20 mM citrate buffer (~ pH 6.0) and 350 mM sodium chloride.
pH:	The drug substance solution is approximately pH 6.0 in 20 mM citrate buffer.
Isoelectric point:	4.5-5.2 (range due to variable amounts of sialic acid).
Solubility Profile:	Drotrecogin alfa (activated) has a solubility of at least 25 mg/mL in 20 mM citrate buffer with 350 mM sodium chloride at a pH of approximately 6.0.
Process Related Impurities	Process related impurities include HEK293 host cell proteins, predominantly human Protein S, and thrombin of bovine origin. The levels are monitored via product testing, and, if present, are detected in minute quantities.

Product Characteristics

Drotrecogin alfa (activated) is secreted into the fermentation medium by an established human cell line modified by recombinant DNA technology. Human Protein C is enzymatically activated by cleavage with thrombin and subsequently purified.

CLINICAL TRIALS

The effects of XIGRIS in patients with severe sepsis have been studied during five clinical studies. Three of these trials (a Phase 2 and two Phase 3, PROWESS and ENHANCE) evaluated the effect of XIGRIS in adult patients with sepsis associated with acute organ dysfunction (severe sepsis) while another Phase 3 trial (ADDRESS) was conducted in the non-indicated population of adult patients with severe sepsis associated with a lower risk of death. A Phase 1B study evaluated XIGRIS's effects in pediatric patients with severe sepsis. As specified in the inclusion criteria for these above mentioned studies, the presence of one or more sepsis induced acute organ dysfunction was defined as the need for vasoactive support or oliguria despite adequate fluid resuscitation; relative hypoxemia (PaO_2/FiO_2 ratio ≤ 250); marked reduction in platelet counts or (in the adult population only) unexplained metabolic acidosis (pH ≤ 7.30 or base deficit ≥ 5.0 mEq/L and an elevated plasma lactate acid concentration).

The Phase 2 clinical trial was a multi-centre, randomized, double-blind, placebo controlled trial, which evaluated multiple infusion rates and infusion durations of XIGRIS. One hundred and thirty one patients with severe sepsis received placebo or XIGRIS for 48 hours or 96 hours at infusion rates ranging between 12 µg/kg/hr to 30 µg/kg/hr. Infusion of XIGRIS from 12 µg/kg/hr to 30 µg/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. XIGRIS produced dose-dependent declines in D-dimer and IL-6 levels indicating a decrease in sepsis-induced coagulopathy and inflammation, respectively. Based on the results of the dose ranging Phase 2 study, a 96-hour administration at 24 µg/kg/hr dose was established for Phase 3 study.

XIGRIS was studied in a Phase 3 international, multi-centre, randomized, double-blind, placebo controlled trial in which 1690 patients with severe sepsis received XIGRIS (n=850) or placebo (n=840). This study was given the acronym PROWESS, recombinant human Activated **Pro**tein C **W**orldwide **E**valuation in **S**evere **S**epsis. Patients received XIGRIS or placebo within 48 hours of onset of the first sepsis-induced organ dysfunction. The mean duration from first organ dysfunction to treatment was 17.4 hours. In this study, the pharmacokinetics of XIGRIS were evaluated in 342 patients with severe sepsis administered a 96-hour continuous infusion at 24 µg/kg/hr. The pharmacokinetics of XIGRIS were characterized by a steady-state plasma concentration within 2 hours following the start of the infusion. In the majority of patients, measurements of Activated Protein C beyond 2 hours after termination of the infusion were below the quantifiable limit (<10 ng/mL), suggesting rapid elimination of XIGRIS from the systemic circulation.

Patients treated with XIGRIS in PROWESS experienced improved 28-day survival compared to those treated with placebo. At 28 days, the overall mortality rates were 24.7% for the XIGRIS-treated group and 30.8% for the placebo-treated group, an absolute mortality reduction of 6.1% (p=0.005 see Figure 1).

In a Phase 3b multi-country, single-arm, open-label trial ENHANCE, (Extended Evaluation of Recombinant Human Activated Protein C), 2378 adult patients with severe sepsis received XIGRIS. The entry criteria were similar to those employed in PROWESS including the fact that patients received XIGRIS within 48 hours of onset of the first sepsis-induced organ dysfunction. The mean duration from first organ dysfunction to treatment was 26 hours. At 28 days, the overall mortality rate was 25.3% (see Figure 1). The mortality rate was lower for patients treated within 24 hours of the first sepsis induced organ failure compared to those treated after 24 hours (23.0% versus 27.4% (P=0.014), respectively) even after adjustment for differences in disease severity.

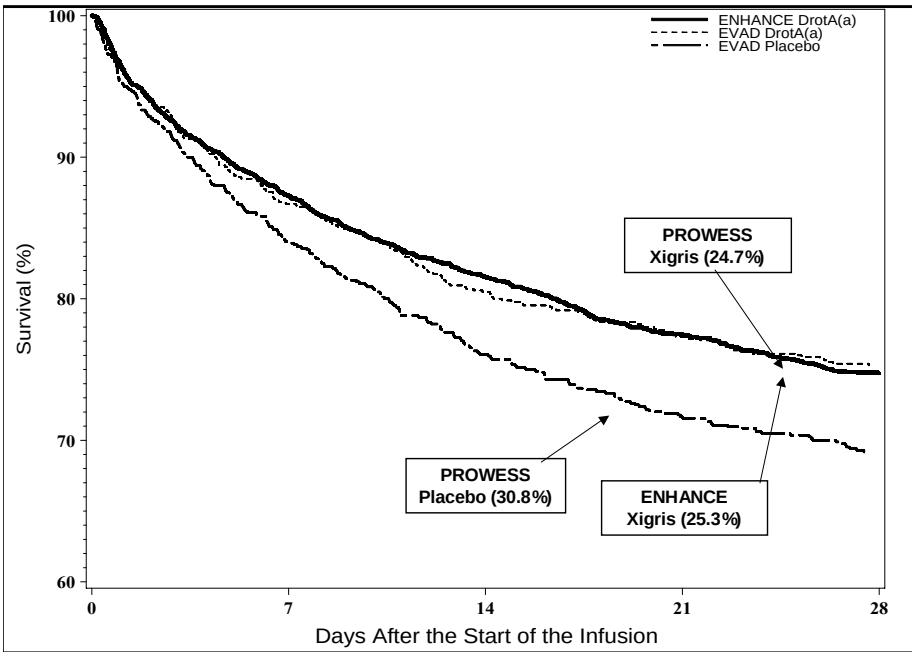


Figure 1: Kaplan-Meier Survival Curve for Intent-to-Treat Patients from PROWESS and ENHANCE

A statistically significant reduction in mortality with XIGRIS, compared to placebo, was observed in more severely ill adult patients as defined by APACHE II score > 24 (see Table 9). A statistically significant treatment-by-APACHE II-quartile interaction was observed based on the Breslow-Day test for homogeneity of odds ratios across strata (p=0.0899).

Other important indicators which supported an association between disease severity and likelihood of benefit with XIGRIS included number of organ dysfunctions and presence of severe community-acquired pneumonia (CAP). 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. Mortality in the placebo groups with 1,2,3 and 4 or more organ dysfunctions was 21%, 26%, 34%, and 47%, respectively. In the subgroup of patients with at least 2 acute organ dysfunctions at baseline, the mortality was 26.5% in the XIGRIS group (168 out of 634) and 33.9% in the placebo group (216 out of 637). No significant reduction in mortality was observed in the subgroup of patients with less than 2 acute organ dysfunctions at baseline (see Table 9).

Community-acquired pneumonia (CAP) represented a high percentage of patients with severe sepsis in the PROWESS trial as the lung was the most common site of infection. In this subgroup, the relative risk of mortality in patients treated with XIGRIS versus placebo was 0.72 (0.55 – 0.94) with an absolute risk reduction of 9%. Many of these patients had indicators of high risk of death, which included CAP associated with a high Pneumonia Severity Index score, bacteremia, or intense coagulation and inflammatory response requiring intensive care unit care. The relative risk reduction in the severe CAP subpopulation was consistent with the overall CAP population[19].

Table 9: 28-day All-Cause Mortality for All Patients and for Subgroups defined by APACHE II score or No. of Organ Dysfunctions at Baseline

	XIGRIS Total N[a] N[b] (%)	**Placebo** Total N[a] N[b] (%)	Absolute Mortality Difference (%)	Relative Risk (RR)	95% CI for RR
Overall	850 210 (24.7)	840 259 (30.8)	-6.1	0.81	0.70, 0.93
APACHE II quartile (score)					
1st (3-19)	218 33 (15)	215 26 (12)	3	1.25	0.78, 2.02
2nd (20-24)	218 49 (23)	222 57 (26)	-3	0.88	0.63, 1.22
3rd (25-29)	204 48 (24)	162 58 (36)	-12	0.66	0.48, 0.91
4th (30-53)	210 80 (38)	241 118 (49)	-11	0.78	0.63, 0.97
# of Organ Dysfunctions					
≤1	216 42 (19)	203 43 (21)	-2	0.92	0.63, 1.35
2	270 56 (21)	273 71 (26)	-5	0.79	0.59, 1.08
3	214 56 (26)	218 75 (34)	-8	0.76	0.57, 1.02
4	119 46 (39)	116 54 (47)	-8	0.83	0.62, 1.12
5	31 10 (32)	30 16 (53)	-21	0.60	0.33, 1.11

[a]Total N = Total number of patients in group
[b]N = Number of deaths in group

Most patients (55%) with only one organ dysfunction at baseline had respiratory failure. Certain organ dysfunctions were under-represented, particularly hematologic failure which was present at baseline in only 16% of all patients, compared to 75% for respiratory and 72% for cardiovascular (see Table 10).

Table 10: Patient Population by Type of Organ Dysfunction at Baseline

	XIGRIS		**Placebo**		**All Patients**
# Organ Dysfunctions	**1**	**2 or more**	**1**	**2 or more**	
Evaluable Patients:	215	635	203	637	1690
Organ Dysfunction	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Respiratory	113 (53)	519 (82)	118 (58)	522 (82)	1272 (75)
Cardiovascular	66 (31)	536 (84)	58 (29)	554 (87)	1214 (72)
Renal	19 (9)	338 (53)	14 (7)	339 (53)	710 (42)
Metabolic Acidosis	11 (5)	288 (45)	7 (3)	275 (43)	581 (34)
Hematology	6 (3)	132 (21)	6 (3)	124 (19)	268 (16)

A consistent treatment effect on mortality with XIGRIS administration was observed in patients with normal Protein C levels and those with low Protein C levels at study entry. Patients were classified as acquired Protein C deficient at baseline if their Protein C activity level, measured within 24 hours prior to the start of study drug infusion, was below the lower limit of normal (81%). There was no statistically significant treatment-by-subgroup interaction observed based on subgroups defined by baseline Protein C deficiency status (p=0.3338).

In addition to the reduction in the relative risk of death, XIGRIS-treated patients experienced significantly more days alive without the need for vasopressor support or mechanical ventilation as compared to placebo-treated patients. XIGRIS-treated survivors did not require additional days in the intensive care unit or in the hospital, and had similar functional capacity as placebo-treated survivors.

Post-hoc analysis conducted on the PROWESS data has shown that the reduction in hospital mortality in

the majority of subgroups of PROWESS is consistent with reduction in 28-day mortality and hospital mortality observed in the overall PROWESS population. With XIGRIS treatment, significantly more severe sepsis subjects survive to hospital discharge and more of these survivors were discharged to home[20].

Although PROWESS was not powered or designed to do so, longer term mortality was evaluated to a maximum of 3.6 years. The acute survival benefit observed in subjects with severe sepsis who received XIGRIS persists to hospital discharge. The survival benefit loses statistical significance thereafter. Post-hoc analysis suggests the effect of XIGRIS varies by APACHE II score with improved long-term survival in subjects with APACHE II scores ≥25 but no benefit in those with lower scores[3].

ADDRESS Trial

The ADDRESS study was designed and conducted to investigate the benefit/risk profile of XIGRIS, in addition to best standard of care, as treatment for patients with severe sepsis considered at lower risk of death (e.g. as determined by APACHE II or single organ dysfunction). Based on an interim review of data from approximately 13% of the targeted enrollment, the independent Data Monitoring Committee recommended the study be discontinued because of a low likelihood that the trial would meet the prospectively defined objective of demonstrating a significant reduction in the risk of 28-day all-cause mortality with XIGRIS. As a consequence, the study did not enrol a sufficient number of patients to yield a precise estimate of the effect of XIGRIS in this population. However, for the population of patients enrolled, no beneficial treatment effect associated with the administration of Xigris was observed[2]. While there were no statistically significant differences between the baseline characteristics of the treatment groups, the XIGRIS treated patients had numerically higher values for a number of baseline disease characteristics associated with disease severity (e.g. APACHE II score, multiple organ failure, respiratory dysfunction).

For all enrolled patients in ADDRESS (N=2640), overall 28-day mortality rate was 18.5% for XIGRIS patients and 17.0% for placebo patients (p=0.34). In-hospital mortality was 20.6% for the XIGRIS patients and 20.5% for placebo patients (p=0.98). The number of hemorrhage-related deaths was small; however, a greater number of XIGRIS patients died of hemorrhage compared to placebo patients (9 patients versus 3 patients, respectively). For the subgroup of patients with a baseline APACHE II score <25, no differences between XIGRIS and placebo patients were observed for 28-day mortality (16.9% versus 16.0%, respectively) or in-hospital morality (18.9% versus 18.8%, respectively).

Pediatric Trials

An open label, Phase 1B study was conducted to investigate the safety, pharmacokinetics and pharmacodynamics of XIGRIS in pediatric patients with severe sepsis. This study was comprised of two parts. Part 1 was an open-label, dose-escalation, safety and pharmacokinetic study in three separate age groups (newborn to <1 year [N=6], 1 year to <8 years [N=8], and 8 years to <18 years [N=7]). Part 2 was an open-label, safety, pharmacokinetic, and pharmacodynamic study in the three separate age-groups (newborn to <1 year [N=19], 1 year to <8 years [N=26], and 8 years to <18 years [N=17]).

In Part 1 of the study, XIGRIS was administered as a 6-hour constant rate infusion once daily on 4 consecutive days. Four doses were investigated: 6, 12, 24 and 36 µg/kg/hr. The limited pharmacokinetic data available in pediatric patients from Part 1 suggested that an infusion rate of 24 µg/kg/hr was appropriate for Part 2 of the study.

In Part 2 of the study, XIGRIS was administered as a continuous intravenous infusion at a rate of 24

μg/kg/hr for 96 hours ±1 hour to patients in the three age groups. The mean elimination half-life ($t_{½}$) for Part 2 was approximately 30 minutes and the mean sampling time of the last quantifiable plasma concentration (t_{last}) was approximately 45 minutes. Mean $t_{½}$ and t_{last} increased with increasing age-group, but were less than 45 minutes and 1.5 hours, respectively, in all age-groups. These estimates indicate rapid elimination of XIGRIS consistent with that observed in healthy adult subjects and adult patients with severe sepsis.

The limited pharmacokinetic data available in pediatric patients suggest that the plasma clearance (CL_p) and the concentration at steady state (C_{ss}) were similar to those observed in adult sepsis patients.

The pediatric trial, F1K-MC- EVBP, was a multi-country, randomized, double-blind, placebo-controlled Phase 3 study designed to evaluate the safety and efficacy of drotrecogin alfa (activated) in pediatric severe sepsis. This study was stopped for futility after a planned interim analysis showed that drotrecogin alfa (activated) was highly unlikely to show an improvement over placebo in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" over 14 days. Of the targeted 600 patients, 477 were enrolled before the study was stopped. The median age of patients enrolled was 2.6 years.

There was a higher rate of central nervous system (CNS) bleeding in the drotrecogin alfa (activated) versus the placebo group. During the infusion period (study days 0-6), 5 CNS bleeding events occurred in the drotrecogin alfa (activated) group and 1 in the placebo group Four of the 5 events in the drotrecogin alfa (activated) group occurred in patients ≤60 days or ≤3kg.

Overall 28-day mortality was similar between the drotrecogin alfa (activated) and placebo groups (41 versus 41), with 2 deaths in the drotrecogin alfa (activated) group and 5 deaths in the placebo group attributed to bleeding events. Fatal CNS bleeding events, serious bleeding events (over the infusion period and over the 28-day study period), serious adverse events, and major amputations were similar in the drotrecogin alfa (activated) and placebo groups.

XPRESS Trial

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 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.

There was no significant difference in 28-day all-cause mortality between the treatment groups (individual heparin groups combined 28.3%, placebo 31.9%, p=0.081). There were also no significant differences between the heparin and placebo groups in the rate of either venous thrombotic or serious bleeding events, including intracranial hemorrhage. There were no statistically significant differences between heparin and placebo patients in the occurrence of fatal bleeds, nonfatal serious bleeds, and heparin-induced thrombocytopenia during both Study Days 0 through 6 and Study Days 0 through 28. Prophylactic heparin increased the risk of non-serious bleeding compared with placebo over the treatment period of 0-6 days.

The rate of ischemic stroke was significantly lower in the heparin group over days 0-6 (heparin 0.3 versus placebo 1.3%, p=0.018) and 0-28 (heparin 0.5 versus placebo 1.8%, p=0.009).

In the subgroup of 889 patients receiving commercially available heparin at study entry, those patients randomized to placebo had an increased risk of mortality (35.6% versus 26.9%, p=0.05) and serious adverse events (18.0% versus 11.6%, p=0.008) compared to patients in whom commercial heparin was replaced by study heparin (see WARNINGS and PRECAUTIONS, and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions sections). 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 the heparin and placebo groups.

DETAILED PHARMACOLOGY

Drotrecogin alfa (activated), produced recombinantly, is a homologue of the endogenous human plasma-derived Activated Protein C. The recombinant molecule is identical to plasma-derived Activated Protein C in its primary amino acid sequence. It is distinguished only by unique oligosaccharides in the carbohydrate portion of the molecule. Although the unique oligosaccharides in drotrecogin alfa (activated) are not found in endogenous Activated Protein C, they are found in other endogenous human proteins.

A profound species specificity has been demonstrated for plasma-derived Activated Protein C. This was also demonstrated for the recombinant molecule, drotrecogin alfa (activated), in the non-clinical pharmacology studies conducted.

The order of activity of human plasma-derived Activated Protein C in various species is human>monkey>dog> rabbit>guinea pig>mouse>rat. Similar species specificity was also observed in vitro for drotrecogin alfa (activated). Relative to human plasma, the concentration of drotrecogin alfa (activated) required to prolong the activated partial thromboplastin time (APTT) by 50% was approximately four-fold higher in guinea pig and almost 12-fold higher in rat plasma. Both human plasma-derived Activated Protein C and drotrecogin alfa (activated) have the highest activity in plasma from human and non-human primates. Due to these species effects, increasing doses of drotrecogin alfa (activated) were required to obtain the desired effects moving from non-human primates through the range of species to the rat.

Efficacious doses in antithrombotic models, for example, (comparing infusions) in non-clinical pharmacology studies ranged from 15 μg/kg/hr in the rhesus monkey to 5000 μg/kg/hr in the guinea pig. To demonstrate an antithrombotic effect in rats, an i.v. bolus dose of 10,000 μg/kg was required.

Due to these observed differences that are species specific, it is not feasible to exactly predict an efficacious or safe dose of drotrecogin alfa (activated) based on animal studies. However, from the animal data, important insights and partial support for the mechanism of action of drotrecogin alfa (activated) may be construed (see Part I: ACTION AND CLINICAL PHARMACOLOGY section).

TOXICOLOGY

Acute, subchronic, and ocular toxicity studies as well as genotoxicity, immunogenicity, and blood compatibility studies with drotrecogin alfa (activated) have been conducted.

Inherent toxicity of drotrecogin alfa (activated), apart from its antithrombotic pharmacologic properties,

has not been identified in acute and subchronic studies in rhesus monkeys. Effects consistent with pharmacological activity include prolongation of activated partial thromboplastin (APTT) and prothrombin (PT) times; systemic effects in animals are secondary to these antithrombotic properties. At higher doses, hemorrhaging and vascular inflammation with thrombosis and embolism at the injection site occurred and sometimes progressed to death. Anti-drotrecogin alfa (activated) IgG antibodies were induced in rhesus monkeys following challenge and re-challenge with drotrecogin alfa (activated); no hypersensitivity reactions were associated with the antibody responses. Addition of the drotrecogin alfa (activated) to whole blood from rhesus monkeys or humans did not cause hemolysis. The no-observed-adverse-event dose for drotrecogin alfa (activated) in monkeys for a 96-hour infusion dosing was established as 2 $mg/m^2/hr$ (equivalent to approximately 48 μg/kg/hr for humans). When evaluated for genotoxic potential, drotrecogin alfa (activated) did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei in bone marrow erythrocytes of mice.

The commercial formulation of drotrecogin alfa (activated) was not an ocular irritant when tested in rabbits.

REFERENCES

1. Abraham E, Glauser MP, et al. 1997. p55 tumor necrosis factor receptor fusion protein in the treatment of patients with severe sepsis and septic shock: a randomized, controlled multicenter trial. JAMA 277:1531-1538.

2. Abraham E, Laterre PF, Garg R, et al. 2005. Drotrecogin Alfa (Activated) for adults with Severe Sepsis and Low risk of Death. New Eng J Med 353: 1332-1341.

3. Angus DC, Laterre P-F, Helterbrand J, Ely EW, Ball DE, Garg R, et al. 2004. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. Crit Care Med 32:2199-2206

4. Bernard GR, Vincent JL, Laterre PF et al. 2001. Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. New Eng J Med 344: 699-709.

5. Brun-Buisson C, Doyon F, Carlet J, et al. 1995. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. JAMA 274:968-974.

6. Derhaschnig U, Reiter R, Knobl P, Baumgartner M, Keen P, Jilma B. 2003. Recombinant human activated protein C (rhAPC, drotrecogin alfa activated) has minimal effect on markers of coagulation, fibrinolysis and inflammation in acute human endotoxemia. Blood 102(6): 2093-2098.

7. Ely EW, Angus DC, Williams MD, Bates B, Qualy R, Bernard GR. Drotrecogin Alfa (Activated) Treatment of Older Patients with Severe Sepsis. Clinical Infectious Diseases 2003: 37:187–195

8. Esmon CT. 1998. Inflammation and thrombosis: mutual regulation by protein C. Immunologist 6:84-89.

9. Fourrier F, Chopin C, Goudemand J, et al. 1992. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest 101:816-823.

10. Friedman G, Silva E, Vincent J-L. 1998. Has the mortality of septic shock changed with time? Crit Care Med 26:2078-2086.

11. Grinnell BW, Hermann RB, Yan SB. 1994. Human protein C inhibits selectin-mediated cell

adhesion: role of unique fucosylated oligosaccharide. Glycobiology 4:221-225.

12. Hancock WW, Bach FH. 1997. Immunobiology and therapeutic applications of protein C/protein S/thrombomodulin in human and experimental allotransplantation and xenotransplantation. Trends Cardiovasc Med 7:174-183.

13. Hartman DL, Bernard GR, Helterbrand JD et al. 1998b. Recombinant activated protein C (rhAPC) improves coagulation abnormalities associated with severe sepsis [abstract]. Intensive Care Med 24:S77.

14. Hartman DL, Bernard GR, Stacek JE, et al. 1998a. Protein C activity at baseline predicts development of shock and 28-day mortality in patients with severe sepsis [abstract]. Intensive Care Med 24:S138.

15. Hesselvik JF, Malm J, Dählback B, et al. 1991. Protein C, protein S and C4b-binding protein in severe infection and septic shock. Thromb Haemost 65:126-129.

16. Iba T, Kidokoro A, Yagi Y. 1998. The role of the endothelium in changes in procoagulant activity in sepsis. J Am Coll Surg 187:321-329.

17. Kalil A, Coyle SM, Um JY, Larosa SP, Turlo MA, Calvano SE, et al. 2004. Effects of drotrecogin alfa (activated) in human endotoxemia. Shock 21(3): 222-229.

18. Kidokoro A, Iba T, Fukunaga M, et al. 1996. Alterations in coagulation and fibrinolysis during sepsis. Shock 5:223-228.

19. Laterre PF, Garber G, Levy H, et al. Severe community-acquired pneumonia as a cause of severe sepsis: Data from the PROWESS study. Critical Care Medicine 2005; 33(5): 952-961.

20. Laterre PF, Levy H, Clermont G, Ball DE, Garg R, Nelson DR, Dhainaut JF, Angus DC. Hospital mortality and resource use in subgroups of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. Critical Care Medicine 2004; 23(11): 2207-2218.

21. Levi M, Ten Cate H. 1999. Disseminated intravascular coagulation. N Engl J Med 341:586-592.

22. Linde-Zwirble WT, Angus DC, Carcillo J, et al. 1999. Age-specific incidence and outcome of sepsis in the US [abstract]. Crit Care Med 27:A33.

23. Lorente JA, Garcia-Frade LJ, Landin L, et al. 1993. Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest 103:1536-1542.

24. Lynn WA, Cohen J. 1995. Adjunctive therapy for septic shock: a review of experimental approaches. Clin Infect Dis 20:143-158.

25. Macias WL, Dhainaut JF, Yan SCB, et al. 2002. Pharmacokinetic-pharmacodynamic analysis of drotrecogin alfa (activated) in patients with severe sepsis. Clin Pharmacol Ther 72:391-402.

26. Marlar RA, Endros-Brooks J, Miller C. 1985. Serial studies of protein C and its plasma inhibitor in patients with disseminated intravascular coagulation. Blood 66:59-63.

27. McGilvray ID, Rotstein OD. 1998. Role of the coagulation system in the local and systemic inflammatory response. World J Surg 22:179-186.

28. Natanson C, Esposito CJ, Banks SM. 1998. The sirens' songs of confirmatory sepsis trials: selection bias and sampling error. Crit Care Med 26:1927-1931.

29. Nick JA, Coldren C, Geraci M, Poch KR, Fouty B, O'Brien J, et al. 2004. Recombinant human activated protein C reduces human endotoxin-induced pulmonary inflammation via inhibition of neutrophil chemostaxis. Blood 104(13):3878-3885.

30. Opal SM. 1998. The uncertain value of the definition of SIRS [editorial]. Chest 113:1442-1443.

31. Opal SM, Cohen J. 1999. Clinical gram-positive sepsis: does it fundamentally differ from gram-negative bacterial sepsis? Crit Care Med 27:1608-1616.

32. Rivard GE, David M, Farrell C, Schwarz HP. 1995. Treatment of purpura fulminans in meningococcemia with protein C concentrate. J. Pediatr 126:646-652.

33. Sands KE, Bates DW, Lanken PN, et al. 1997. Epidemiology of sepsis syndrome in 8 academic medical centres. JAMA 278:234-240.

34. Smith OP, White B, Vaughan D, et al. 1997. Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. Lancet 350:1590-1593.

35. Vervloet MG, Thijs LG, Hack CE. 1998. Derangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. Semin Thromb Hemost 24:33-44.

36. Vincent JL, Angus DC, Artigas A. Kalil A, Basson BR, Jamal HH, Johnson G, Bernard GR. Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial. Critical Care Medicine 2003; 31(3): 834-840.

37. Zeni F, Freeman B, Natanson C. 1997. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit Care Med 25:1095-1100.

38. Kanji Salmaan, et al. 2007. Evaluating the use of Drotrecogin alfa (activated) in adult severe sepsis: a Canadian multicenter observational study. Intensive Care Med, Brief Report.

39. Gentry Chris A., et al. 2009. Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precautions. Crit Care Med 37:1-7.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr XIGRIS®
drotrecogin alfa (activated)

This new leaflet is part III of a three-part "Product Monograph" published when XIGRIS was approved for sale in Canada and is designed specifically for patients and/or their extended families. This leaflet is a summary and will not tell you everything about XIGRIS. Contact your doctor or pharmacist if you have any questions about XIGRIS.

ABOUT THIS MEDICATION

What XIGRIS is used for:
XIGRIS is used to treat adult patients with severe sepsis who are at high risk of death.

When a patient has a severe infection, clots can form inappropriately in their blood. These clots can block the blood supply to important parts of the body such as kidneys and lungs. This causes an illness called severe sepsis, which can make the patient very ill. Some people will die from this illness.

What XIGRIS does:
XIGRIS helps to control blood clotting and inflammation. When a patient's body has a severe infection, clots can form in the patient's blood. These clots can block the blood supply to important parts of the body such as kidneys and lungs. This causes an illness called severe sepsis, which can make the patient very ill. Some people will die from this illness. XIGRIS helps the patient's body with severe sepsis to stop clots from forming, get rid of the existing clots and also reduces the inflammation caused by the infection.

When it should not be used:
A patient should not be treated with XIGRIS if they have an allergy to drotrecogin alfa (activated) or any of the other ingredients of XIGRIS listed in the "Nonmedicinal Ingredients" section of this leaflet, or bovine (cattle-derived) thrombin (protein).

They should not receive XIGRIS:
- If they have internal bleeding
- If they have had a bleed in their brain called a haemorrhagic stroke within the last 3 months
- If they have had surgery on their brain or spine or have been in hospital with severe injury to their head within the last 2 months
- If they have had a major accident and are at risk of dying from bleeding
- If they have an epidural catheter (a tube in their spine)
- If they have a brain tumour or similar mass in their head

What the medicinal ingredient is:
XIGRIS contains the active ingredient drotrecogin alfa (activated). Drotrecogin alfa (activated) is very similar to a protein that occurs naturally in the blood.

What the important nonmedicinal ingredients are:
XIGRIS contains the following inactive ingredients: sucrose, sodium chloride, citrate (buffer system composed of citric acid, sodium citrate, and hydrochloric acid and sodium hydroxide). It may also contain hydrochloric acid and/or sodium hydroxide, if necessary.

What dosage forms it comes in:
XIGRIS is supplied to the hospital as a powder in 5 mg and 20 mg vials. A hospital pharmacist, nurse or doctor will dissolve the XIGRIS powder in water for injection and sodium chloride solution.

WARNINGS AND PRECAUTIONS

All medicines have risks and benefits. If a patient is being considered for therapy with XIGRIS, their doctor will carefully evaluate the potential benefits against potential risks associated with this therapy. There may be some patients with certain characteristics that may not benefit or may be harmed with this therapy. Certain conditions increase the risk of bleeding with XIGRIS therapy. Therefore, before starting XIGRIS, your doctor will examine and evaluate the need for a patient to be treated with XIGRIS.

When low dose heparin is given for prophylaxis of venous thrombotic events with Xigris, prophylactic heparin should not be discontinued unless considered medically necessary.

The doctor should be told if a patient has an increased risk of bleeding, for example:
- they have a known problem with bleeding or condition in which significant bleeding is likely or hard to control
- they are taking other drugs which affect how their blood clots
- their platelet (a type of cell in the blood) count is low
- they have bled from their stomach/intestines within the last 6 weeks
- they have had a stroke caused by a blood clot within the last 3 months
- they have abnormal blood vessels in their brain or increased pressure on the brain
- they have a long-standing, severe problem with their liver

Pregnant women: Tell the doctor or health care professional if the patient is pregnant or planned to become pregnant or is breast-feeding. XIGRIS is not recommended for use in pregnancy. The doctor can discuss the risks and benefits involved.

INTERACTIONS WITH THIS MEDICATION

Tell the doctor or health care professional if a patient is taking any other medicines, including any that are purchased without a prescription from your pharmacy, supermarket or health food shop. Some medicines and XIGRIS may interfere with each other. These include:

- Medicines that affect blood clotting, such as warfarin, heparin and aspirin

When low dose heparin is given for prophylaxis of venous thrombotic events with Xigris, prophylactic heparin should not be discontinued unless considered medically necessary.

These medications may be affected by XIGRIS or may affect how well it works. The patient may need different amount of their medicines or may need to take different medicines.

The health care professional has more information on medicines to be careful with or avoid while receiving XIGRIS.

PROPER USE OF THIS MEDICATION

How much will be given:
The recommended dose of XIGRIS is 24 micrograms per kilogram of body weight each hour for 96 hours.

How will it be given:
A hospital pharmacist, nurse or doctor will dissolve the XIGRIS powder in water for injection and sodium chloride solution. This liquid will then be injected from a bag or pump into a patient's veins.

XIGRIS will be given for 96 hours. If there is an interruption during the time XIGRIS is given, it may be restarted and given for a total of 96 hours.

The doctor may want to stop this therapy based on the risk involved with certain procedures or surgery. In most cases, this can be safely restarted at the discretion of the doctor.

Overdose:
As XIGRIS will be given under the supervision of a doctor, it is unlikely that too much will be given. However, if a patient experiences any side effects after having XIGRIS, tell the doctor or nurse immediately. There is no known antidote for XIGRIS. In case of overdose, the infusion should be stopped immediately, and the doctor should monitor the patient closely.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, XIGRIS can have side effects. As noted previously, XIGRIS may increase the risk of bleeding which can be serious or life threatening.
The doctor should be notified immediately if any side effects are noticed that are not mentioned in this leaflet.

This is not a complete list of side effects. For any unexpected effects while taking XIGRIS, contact the doctor or health care professional.

HOW TO STORE IT

XIGRIS is stored in hospitals under the following conditions:

- Kept in a refrigerator, between 2° to 8 °C in its original package (unreconstituted).
- Do not freeze XIGRIS. Do not use XIGRIS if it has been frozen.
- Unreconstituted vial must be protected from exposure to light by keeping the vial in carton until it is time for it to be used.
- Keep where children cannot reach.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972, or visit the website at: www.lilly.ca

This leaflet was prepared by Eli Lilly Canada Inc., Toronto Ontario, M1N 2E8

Last revised: TBD